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Canadian Intellectual Property Office

CA 3002220 C 2021/07/20

(11)(21) 3 002 220

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2016/10/17
(87) Date publication PCT/PCT Publication Date: 2017/04/20
(45) Date de délivrance/Issue Date: 2021/07/20
(85) Entrée phase nationale/National Entry: 2018/04/16
(86) N° demande PCT/PCT Application No.: US 2016/057372
(87) N° publication PCT/PCT Publication No.: 2017/066775
(30) Priorités/Priorities: 2015/10/16 (US62/242,797); 2015/12/15 (US62/267,672); 2016/02/29 (US62/301,537); 2016/06/20 (US62/352,380)

(51) Cl.Int./Int.Cl. *C07D 487/14* (2006.01), *A61P 35/00* (2006.01)

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(54) Titre : PROCEDE DE PREPARATION DE (3S,4R)-3-ETHYL-4-(3H-IMIDAZO[1,2-A]PYRROLO[2,3-E]-PYRAZIN-8-YL)-N-(2,2,2-TRIFLUOROETHYL)PYRROLIDINE-1-CARBOXAMIDE ET DE SES FORMES A L'ETAT SOLIDE

(54) Title: PROCESSES FOR THE PREPARATION OF (3S,4R)-3-ETHYL-4-(3H-IMIDAZO[1,2-A]PYRROLO[2,3-E]-PYRAZIN-8-YL)-N-(2,2,2-TRIFLUOROETHYL)PYRROLIDINE-1-CARBOXAMIDE AND SOLID STATE FORMS THEREOF

(57) Abrégé/Abstract:
The present disclosure relates to processes for preparing (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, solid state forms thereof, and corresponding pharmaceutical compositions, methods of treatment (including treatment of rheumatoid arthritis), kits, methods of synthesis, and products-by-process.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 April 2017 (20.04.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/066775 A1

(51) International Patent Classification:
C07D 487/14 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US2016/057372

(22) International Filing Date:
17 October 2016 (17.10.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/242,797	16 October 2015 (16.10.2015)	US
62/267,672	15 December 2015 (15.12.2015)	US
62/301,537	29 February 2016 (29.02.2016)	US
62/352,380	20 June 2016 (20.06.2016)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2017/066775 A1

(54) Title: PROCESSES FOR THE PREPARATION OF (3S,4R)-3-ETHYL-4-(3H-IMIDAZO[1,2-a]PYRROLO[2,3-e]-PYRAZIN-8-YL)-N-(2,2,2-TRIFLUOROETHYL)PYRROLIDINE-1-CARBOXAMIDE AND SOLID STATE FORMS THEREOF

(57) Abstract: The present disclosure relates to processes for preparing (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, solid state forms thereof, and corresponding pharmaceutical compositions, methods of treatment (including treatment of rheumatoid arthritis), kits, methods of synthesis, and products-by-process.

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __2___

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PROCESSES FOR THE PREPARATION OF (3S,4R)-3-ETHYL-4-(3*H*-IMIDAZO[1,2-*a*]PYRROLO[2,3-*e*]-PYRAZIN-8-YL)-N-(2,2,2-TRIFLUOROETHYL)PYRROLIDINE-1-CARBOXAMIDE AND SOLID STATE FORMS THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/242,797, filed October 16, 2015; and claims the benefit of U.S. Provisional Application No. 62/267,672, filed December 15, 2015; and claims the benefit of U.S. Provisional Application No. 62/301,537, filed February 29, 2016; and claims the benefit of U.S. Provisional Application No. 62/352,380, filed June 20, 2016 .

FIELD OF THE INVENTION

[0002] The present disclosure relates to: (a) processes for the preparation of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (referred to herein as "Compound 1"), (b) intermediates used in the preparation of Compound 1 and processes for preparing the intermediates; (c) solid state forms of Compound 1, (d) pharmaceutical compositions comprising one or more solid state forms of Compound 1, and, optionally, one or more additional therapeutic agents; (e) methods of treating Janus kinase-associated conditions (including rheumatoid arthritis) by administering one or more solid state forms of Compound 1 to a subject in need thereof; (f) kits comprising a first pharmaceutical composition comprising a solid state form of Compound 1, and, optionally, a second pharmaceutical composition comprising one or more additional therapeutic agents; (g) methods for the preparation of solid state forms of Compound 1; and (h) solid state forms of Compound 1 prepared in accordance with such methods.

BACKGROUND OF THE INVENTION

[0003] (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide ("Compound 1") was first disclosed in International Application WO2011/068881A1 . The compound has activity as a Janus kinase ("JAK") inhibitor, particularly as a JAK-1 inhibitor. Clinical trials are ongoing to evaluate the use of the compound to treat rheumatoid arthritis.

[0004] The isolation and commercial-scale preparation of a solid state form of Compound 1 and corresponding pharmaceutical formulations having acceptable solid state

properties (including chemical stability, thermal stability, solubility, hygroscopicity, and/or particle size), compound manufacturability (including yield, impurity rejection during crystallization, filtration properties, drying properties, and milling properties), and formulation feasibility (including stability with respect to pressure or compression forces during tableting) present a number of challenges that are discussed in greater detail below. Accordingly, there is a current need for one or more solid state forms of Compound 1 that have an acceptable balance of these properties and can be used in the preparation of pharmaceutically acceptable solid dosage forms.

[0005] Additionally, currently known processes for the preparation of Compound 1 involve the use of particularly hazardous reagents, such as trimethylsilyldiazomethane or diazomethane, and do not produce a crystalline product. There is thus also a need for a process for preparing Compound 1, and pharmaceutically acceptable salts thereof, that avoids the use of particularly hazardous reagents, and can produce a crystalline product and crystalline intermediates.

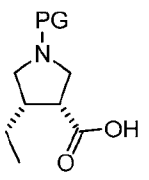
[0006] Additionally, sustained peak plasma concentrations can theoretically be achieved by means of sustained release matrix systems. However, when such systems are made of hydrophilic polymers, such as HPMC, they seldom provide pH independent drug release of pH-dependent soluble drugs, and they are normally incapable of attaining zero-order release except for practically insoluble drugs. Unexpectedly, is has been discovered that when tartaric acid is used as a pH- modifier in such a system, it allows Compound 1 to be released at a steady rate regardless of the pH of the environment.

[0007] In an unexpected finding, it was discovered that as a tablet containing the hydrophilic polymer matrix system erodes, Compound 1 reacts with the HPMC, creating a thicker gel layer which slows the release of Compound 1 from the tablet. The resulting gel layer provided an environment suitable for Compound 1 to dissolve.

SUMMARY OF THE INVENTION

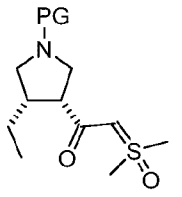
[0008] In one aspect, the present disclosure relates to a process for preparing Compound 1, or a pharmaceutically acceptable salt thereof. The process comprises:

a) reacting a compound of formula (I)



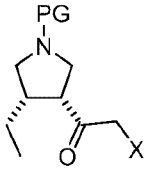
(I)

or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride to form a compound of formula (II)


(II)

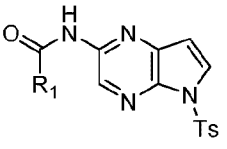
wherein PG is a protecting group;

b) contacting the compound of formula (II) with LiX and a sulfonic acid to form a compound of formula (III)

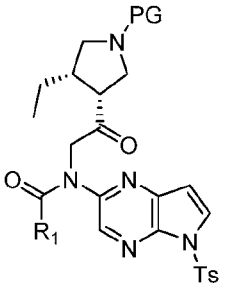

(III)

wherein X is Br or Cl;

c) reacting the compound of formula (III) with a compound of formula (IV)

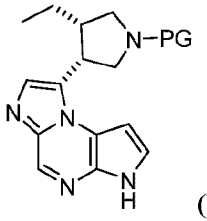

(IV)

to produce a compound of formula (V)


(V)

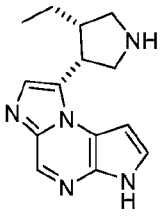
wherein R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$; R_2 is alkyl; and Ts is tosyl;

d) contacting the compound of formula (V) with a perfluoro acid anhydride and an organic base to form a compound of formula (VI)



(VI)

e) deprotecting the compound of formula (VI) and forming a pharmaceutically acceptable salt of the compound of formula (VII):

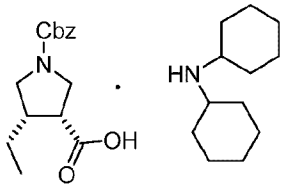


(VII)

f) reacting the pharmaceutically acceptable salt of the compound of formula (VII) with 2,2,2-trifluoroethylamine to produce Compound 1.

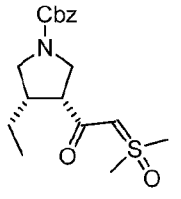
[0009] In another aspect, the present disclosure relates to a process for preparing Compound 1, or a pharmaceutically acceptable salt thereof. The process comprises:

a) reacting a compound of formula (Ib)



(Ib)

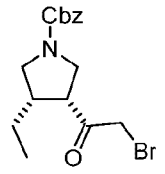
with trimethylsulfoxonium chloride in the presence of carbonyldiimidazole and a strong base to form a compound of formula (IIa)



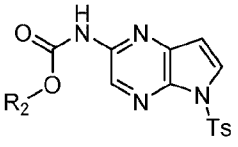
(IIa)

wherein Cbz is carboxybenzyl;

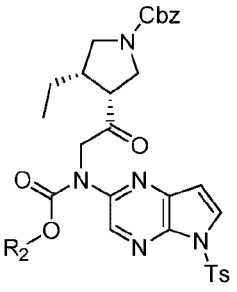
b) contacting the compound of formula (IIa) with lithium bromide and a sulfonic acid to form a compound of formula (IIIa)


(IIIa)

c) reacting the compound of formula (IIIa) with a compound of formula (IVa)

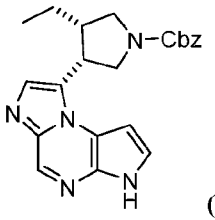

(IVa)

in the presence of lithium *tert*-butoxide to produce a compound of formula (Va)

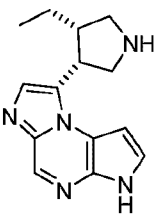

(Va)

wherein R_2 is methyl or ethyl; and Ts is tosyl;

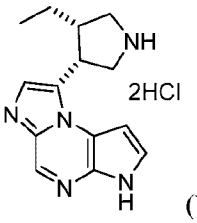
d) contacting the compound of formula (Va) with a perfluoro acid anhydride and an organic base to form a compound of formula (VIa)


(VIa)

e) deprotecting the compound of formula (VIa) to form a compound of formula (VII)


(VII)

f) contacting the compound of formula (VII) with hydrochloric acid to form a compound of formula (VIIa)

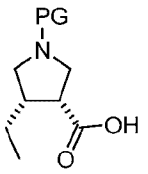


(VIIa)

g) reacting the compound of formula (VIIa) with 2,2,2-trifluoroethylamine in the presence of carbonyldiimidazole to produce Compound 1.

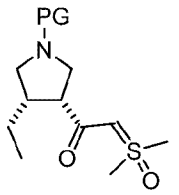
[0010] In another aspect, the present disclosure relates to a process for preparing Compound 1. The process comprises:

a) reacting a compound of formula (I)



(I)

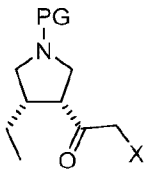
or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride to form a compound of formula (II)



(II)

wherein PG is a protecting group;

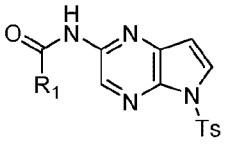
b) contacting the compound of formula (II) with LiX and a sulfonic acid to form a compound of formula (III)



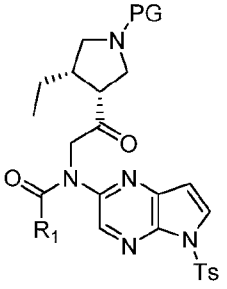
(III)

wherein X is Br or Cl;

c) reacting the compound of formula (III) with a compound of formula (IV)

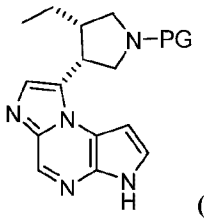

(IV)

to produce a compound of formula (V)

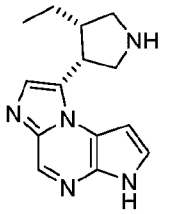

(V)

wherein R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$; R_2 is alkyl; and Ts is tosyl;

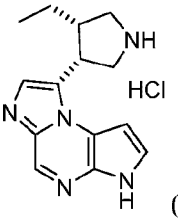
d) contacting the compound of formula (V) with a perfluoro acid anhydride and an organic base to produce a compound of formula (VI)


(VI)

e) deprotecting the compound of formula (VI) to form a compound of formula (VII)


(VII)

and contacting the compound of formula (VII) with hydrochloric acid to form the compound of formula (VIIb)



(VIIb)

f) contacting the compound of formula (VIIb) with a base to form the compound of formula (VII);

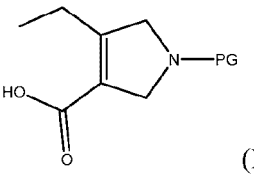
g) reacting the compound of formula (VII) with 2,2,2-trifluoroethylamine to produce Compound 1;

h) contacting Compound 1 with L-tartaric acid to produce a tartrate salt of Compound 1; and

i) contacting the tartrate salt with sodium carbonate and sodium bicarbonate to produce Compound 1.

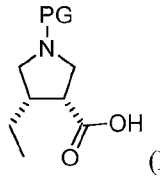
[0011] In another aspect, the present disclosure relates to a process for preparing Compound 1, or a pharmaceutically acceptable salt thereof. The process comprises:

a) converting a compound of formula (XIa):



(XIa)

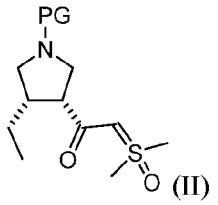
to a compound of formula (I):



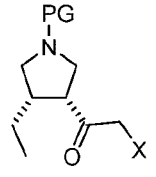
(I)

wherein PG is a protecting group;

b) reacting the compound of formula (I) with trimethylsulfoxonium chloride to form a compound of formula (II)

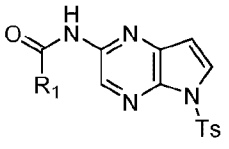

(II)

c) contacting the compound of formula (II) with an anhydrous source of HBr or HCl to form a compound of formula (III)

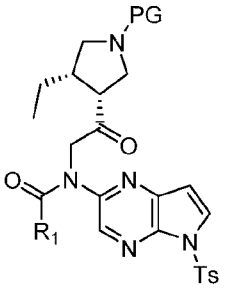

(III)

wherein X is Br or Cl;

d) reacting the compound of formula (III) with a compound of formula (IV)

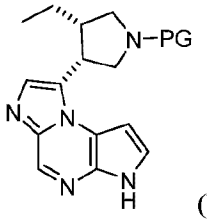

(IV)

to produce a compound of formula (V)


(V)

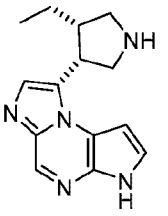
wherein R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$; R_2 is alkyl; and Ts is tosyl;

e) contacting the compound of formula (V) with a perfluoro acid anhydride and an organic base to form a compound of formula (VI)



(VI)

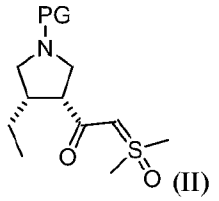
f) deprotecting the compound of formula (VI) and forming a pharmaceutically acceptable salt of the compound of formula (VII):



(VII); and

g) reacting the pharmaceutically acceptable salt of the compound of formula (VII) with 2,2,2-trifluoroethylamine to produce Compound 1.

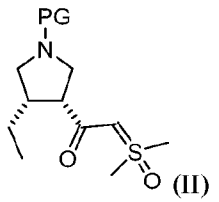
[0012] In another aspect, the present disclosure relates to a compound of formula (II):



(II)

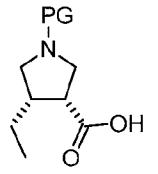
wherein PG is a protecting group.

[0013] In another aspect, the disclosure relates to a process for preparing a compound of formula (II):



(II)

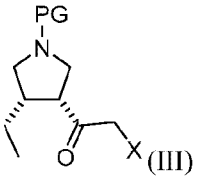
wherein PG is a protecting group, the process comprising reacting a compound of formula (I)



(I)

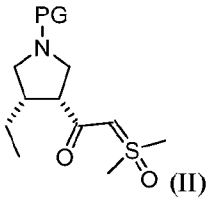
or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride to form the compound of formula (II).

[0014] In another aspect, the present disclosure is directed to a process for the preparation of a compound of formula (III):



(III)

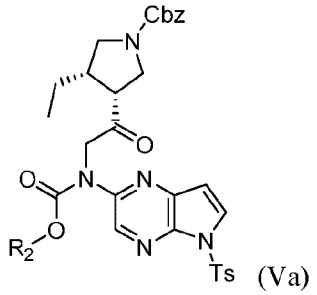
the process comprising contacting a compound of formula (II)



(II)

with LiX and a sulfonic acid to form the compound of formula (III); wherein PG is a protecting group; and X is Br or Cl.

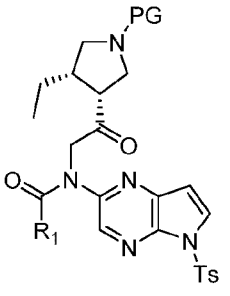
[0015] In another aspect, the present disclosure relates to a compound of formula (Va)



(Va)

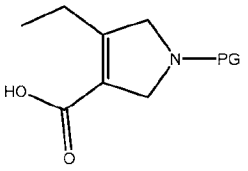
wherein R_2 is methyl or ethyl; and Ts is tosyl.

[0016] In another aspect, the present disclosure relates to a process for preparing a compound of formula (V)

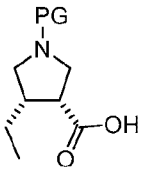

(V)

the process comprising:

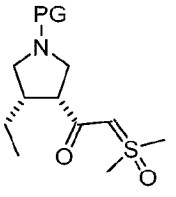
a) converting a compound of formula (XIa):


(XIa)

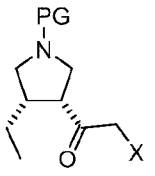
to a compound of formula (I)


(I);

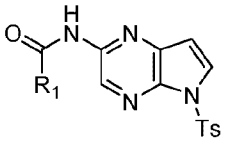
b) reacting the compound of formula (I) with trimethylsulfoxonium chloride to form a compound of formula (II)


(II)

c) contacting the compound of formula (II) with an anhydrous source of HBr or HCl to form a compound of formula (III)


(III)

d) reacting the compound of formula (III) with a compound of formula (IV)



(IV)

to produce the compound of formula (V);

wherein:

PG is a protecting group;

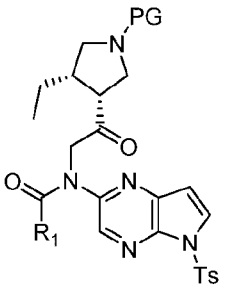
X is Br or Cl;

R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$;

R_2 is alkyl; and

Ts is tosyl.

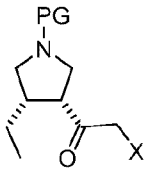
[0017] In another aspect, the disclosure is directed to a process for preparing a crystalline compound of formula (V)



(V)

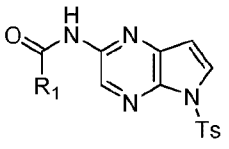
the process comprising:

a) reacting a compound of formula (III)



(III)

with a compound of formula (IV):


(IV)

to produce the compound of formula (V);

wherein:

PG is a protecting group;

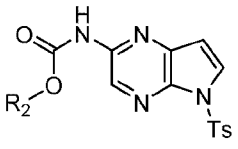
X is Br or Cl;

R_1 is $-OR_2$;

R_2 is methyl or ethyl; and

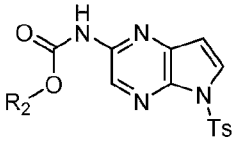
Ts is tosyl.

[0018] In another aspect, the present disclosure relates to a compound of formula (IVa):


(IVa)

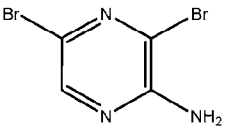
wherein R_2 is methyl or ethyl, and Ts is tosyl.

[0019] In another aspect, the present disclosure relates to a process for preparing a compound of formula (IVa):

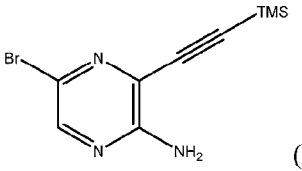

(IVa)

wherein R_2 is methyl or ethyl, and Ts is tosyl, the process comprising:

a) reacting a compound of formula (XVII)


(XVII)

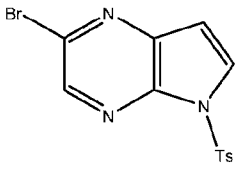
with trimethylsilylacetylene in the presence of a catalyst to form a compound of formula (XVIII):



(XVIII)

wherein TMS is trimethylsilyl;

b) contacting the compound of formula (XVIII) with p-toluenesulfonyl chloride in the presence of a base to form a compound of formula (XIX)

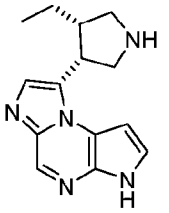


(XIX)

wherein Ts is tosyl; and

c) reacting the compound of formula (XIX) with a carbamate in the presence of a catalyst and a ligand to form the compound of formula (IVa), wherein the carbamate is selected from the group consisting of methyl carbamate and ethyl carbamate.

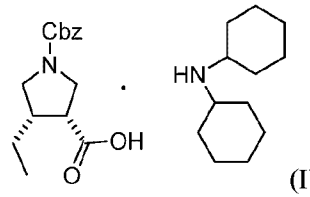
[0020] In another aspect, the present disclosure relates to a compound of formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof.

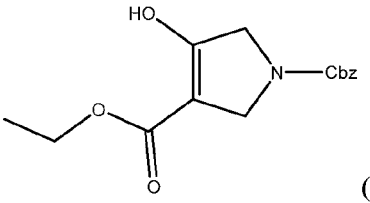
[0021] In another aspect, the present disclosure relates to a process for preparing a compound of formula (Ib)



(Ib),

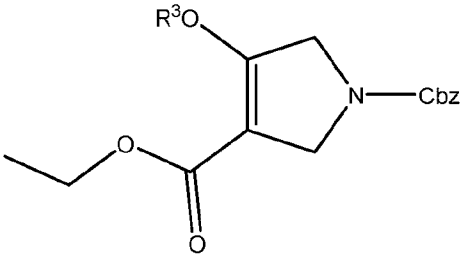
wherein Cbz is carboxybenzyl, the process comprising:

(i) reacting carboxybenzyl-glycine ethyl ester with ethyl acrylate to form a compound of formula (VIII):



(VIII)

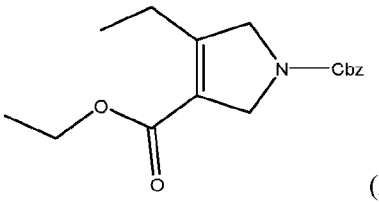
(ii) protecting the compound of formula (VIII) to form a compound of formula (IX):



(IX)

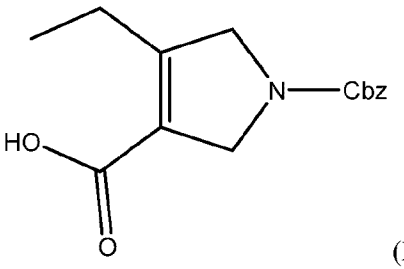
wherein R^3 is selected from the group consisting of CF_3SO_2-; CH_3SO_2-; and tosyl;

(iii) contacting the compound of formula (IX) with one of ethyl boronic acid, ethyl magnesium bromide, or ethyl zinc chloride in the presence of a catalyst to form a compound of formula (X):



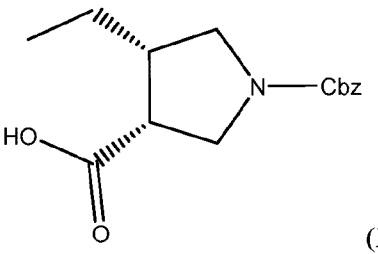
(X)

(iv) hydrolyzing the compound of formula (X) to produce the compound of formula (XI):



(XI)

(v) converting the compound of formula (XI) to the compound of formula (XII):



(XII)

(vi) contacting the compound of formula (XII) with dicyclohexylamine to form the compound of formula (Ib).

[0022] In another aspect, the present disclosure relates to the dicyclohexylamine salt of (3R,4S)-1-((benzyloxy)carbonyl)-4-ethylpyrrolidine-3-carboxylate.

[0023] In one aspect, the present disclosure relates to pharmaceutically acceptable solid state forms of Compound 1.

[0024] In another aspect, the present disclosure relates to Amorphous Freebase of Compound 1.

[0025] In another aspect, the present disclosure relates to crystalline Compound 1.

[0026] In another aspect, the present disclosure relates to crystalline hydrates of Compound 1.

[0027] In another aspect, the present disclosure relates to crystalline tartrates of Compound 1.

[0028] In another aspect, the present disclosure relates to the Freebase Hydrate Form C of Compound 1.

[0029] In another aspect, the present disclosure relates to the Freebase Hydrate Form B of Compound 1.

[0030] In another aspect, the present disclosure relates to crystalline anhydrates of Compound 1.

[0031] In another aspect, the present disclosure relates to the Freebase Anhydrate Form D of Compound 1.

[0032] In another aspect, the present disclosure relates to pharmaceutical compositions comprising one or more solid state forms of Compound 1, and a pharmaceutically acceptable carrier.

[0033] In another aspect, the present disclosure is directed to a pharmaceutical composition comprising one or more solid state forms of Compound 1, from about 10 w/w% to about 35 w/w% of an organic acid selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and combinations thereof, and a pharmaceutically acceptable carrier. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the solid state form is Freebase Hydrate Form C.

[0034] In another aspect, the present disclosure relates to pharmaceutical compositions comprising one or more solid state forms of Compound 1, and, optionally, one or more additional therapeutic agents.

[0035] In another aspect, the present disclosure relates to methods of treating a JAK-associated condition (such as rheumatoid arthritis) in a human subject suffering from or susceptible to such a condition comprising administering to the subject a therapeutically effective amount of a solid state form of Compound 1. In another aspect, the disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a solid state form of Compound 1 as described in the present disclosure, for use in treatment of a JAK-associated condition (such as rheumatoid arthritis) in a subject, particularly in a human subject suffering from or susceptible to the condition.

[0036] In another aspect, the present disclosure relates to methods of treating rheumatoid arthritis, wherein the term "rheumatoid arthritis" includes juveline rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis disease, Sjogren's syndrome, psoriatic arthritis.

[0037] In another aspect, the present disclosure relates to methods of treating inflammatory bowel disease, wherein the term "inflammatory bowel disease" includes Crohn's disease, pediatric Crohn's disease and ulcerative colitis.

[0038] In another aspect, the present disclosure relates to a method of treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis and systemic lupus erythematosus in a human subject suffering from or susceptible to such a condition, the method comprising administering to the subject a therapeutically effective amount a solid state

form of Compound 1. In another aspect, the disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a solid state form of Compound 1 as described in the present disclosure, for use in treatment of a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus in a subject, particularly in a human subject suffering from or susceptible to the condition.

[0039] In another aspect, the present disclosure relates to methods of treating a JAK-associated condition (such as rheumatoid arthritis) in a human subject suffering from or susceptible to such a condition comprising administering to the subject a solid state form of Compound 1, in combination with one or more additional therapeutic agents (*e.g.*, a therapeutic agent for treating rheumatoid arthritis that is not a JAK inhibitor). In another aspect, the disclosure relates to a pharmaceutical composition comprising a solid state form of Compound 1, as described in the present disclosure, in combination with one or more additional therapeutic agents (*e.g.*, a therapeutic agent for treating rheumatoid arthritis that is not a JAK inhibitor), for use in treatment of a JAK-associated condition (such as rheumatoid arthritis) in a subject, particularly in a human subject suffering from or susceptible to the condition.

[0040] In another aspect, the present disclosure relates to a method of treating moderate to severely active rheumatoid arthritis, the method comprising administering a therapeutically effective amount of Compound 1 in one or more forms as disclosed herein to a subject suffering from or susceptible to the condition. In a particular aspect, such a method may comprise administering 7.5 mg once daily or 15 mg once daily, or 30 mg once daily, or 45 mg once daily of the Compound 1, in one or more forms as disclosed herein, to the subject. In this or another particular aspect, the subject may be administered the Compound 1 in Freebase Form C. In this or yet another particular aspect, the subject may have an inadequate response to methotrexate. In this or yet another particular aspect, the subject may have an inadequate response to biologics medicines approved for rheumatoid arthritis. In this or yet another particular aspect, the subject may have not previously been administered biologics medicines approved for rheumatoid arthritis.

[0041] In another aspect, the present disclosure relates to a method of treating an adult subject having moderate to severly active rheumatoid arthritis, the method comprising administering to the subject: a) about 7.5 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an

amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent. In one embodiment, the present disclosure is directed to a pharmaceutical composition for use in treating an adult subject having moderate to severely active rheumatoid arthritis, the use comprising adiminstering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises a) about 7.5 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg of Compound 1 freebase, or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or a crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent.

[0042] In another embodiment, the present disclosure relates to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, the method comprising administering to the subject: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically

acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; such that the structural damage in the adult subject is inhibited or lessened. In one embodiment, the disclosure relates to a pharmaceutical composition for use in treating structural damage associated with rheumatoid arthritis in an adult subject, the use comprising administering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; such that the structural damage in the adult subject is inhibited or lessened.

[0043] In another aspect, the disclosure is directed to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, the method comprising administering to the subject: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day

of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one embodiment, the disclosure is directed to a pharmaceutical composition for use in treating moderate to severely active rheumatoid arthritis in an adult subject, the use comprising administering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg per day of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg per day of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg per day of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg per day of Compound 1 freebase equivalent; wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating.

[0044] In another aspect, the disclosure is directed to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically

acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent. In one embodiment, the disclosure is directed to a pharmaceutical composition for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the use comprising administering the pharmaceutical composition to the subject, wherein the pharmaceutical composition comprises: a) about 7.5 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent; or b) about 15 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent; or c) about 30 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent; or d) about 45 mg per day of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a crystalline hydrate or crystalline anhydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent.

[0045] In another aspect, the present disclosure relates to kits comprising one or more pharmaceutical compositions comprising a solid state form of Compound 1. The kit optionally can comprise another pharmaceutical composition comprising one or more additional therapeutic agents and/or instructions, for example, instructions for using the kit.

[0046] In another aspect, the present disclosure relates to methods for the preparation of a solid state form of Compound 1.

[0047] In another aspect, the present disclosure relates to solid state forms of Compound 1 prepared in accordance with such methods.

[0048] In another aspect, the present disclosure relates to a method of treating an adult subject having moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg of Compound 1 freebase, or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C. In this or yet another particular aspect, the subject may have an inadequate response or tolerance to one or more

disease-modifying antirheumatic drugs (DMARDS), such as methotrexate. In this or yet another particular aspect, the subject may have not previously been administered DMARDS. In this or yet another particular aspect, the subject may further be administered one or more DMARD.

[0049] In another aspect, the present disclosure relates to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase equivalent, such that the structural damage in the adult subject is inhibited or lessened. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0050] In another aspect, the present disclosure relates to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of Compound 1 freebase equivalent, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0051] In another aspect, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0052] In another aspect, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 15 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 15 mg of Compound 1 freebase equivalent. In this or another particular

aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0053] In another aspect, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 30 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 30 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0054] In another aspect, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 45 mg per day of Compound 1 freebase or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject about 45 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0055] In another aspect, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to deliver about 7.5 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0056] In another aspect, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to deliver about 15 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0057] In another aspect, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to deliver about 30 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate

may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0058] In another aspect, the present disclosure relates to a pharmaceutical composition comprising a crystalline hydrate of Compound 1 and a pharmaceutically acceptable carrier, wherein the composition comprises the crystalline hydrate in an amount sufficient to deliver about 45 mg of Compound 1 freebase equivalent. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0059] In another aspect, the present disclosure relates to a method of treating an adult subject having moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg of a crystalline hydrate of Compound 1. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0060] In another aspect, the present disclosure relates to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of a crystalline hydrate of Compound 1, such that the structural damage in the adult subject is inhibited or lessened. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0061] In another aspect, the present disclosure relates to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of a crystalline hydrate of Compound 1, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0062] In another aspect, the present disclosure relates to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject with moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg per day of a crystalline hydrate of Compound 1. In this or another particular aspect, the hydrate may be a hemihydrate. In this or another aspect, the hemihydrate may be Freebase Hydrate Form C.

[0063] In another aspect, the present disclosure is directed to an extended release formulation for oral administration comprising Compound 1 or a pharmaceutically acceptable salt thereof, a hydrophilic polymer, and a pH modifier, wherein the hydrophilic polymer, in contact with water, forms a gel layer that provides an environment suitable for Compound 1 and the pH modifier to dissolve.

[0064] In another aspect, the present disclosure is directed to a process for preparing a pharmaceutical composition, the process comprising: (a) combining Compound 1 or a pharmaceutically acceptable salt thereof, or a solid state form of Compound 1, and at least a portion of one additional composition component to form a dry granulation mixture; (b) contacting the dry granulation mixture with a granulation fluid to form a wet granulation mixture; (c) drying the wet granulation mixture to form a granulated material; (d) milling the granulated material to form a milled granulated material; (e) combining the milled granulation material with any remaining composition components; and (f) compressing the composition to form the pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

[0065] Figure 1A schematically illustrates one method of preparing the Amorphous Freebase.

[0066] Figure 1B schematically illustrates one method of preparing the Freebase Hydrate Form C .

[0067] Figure 1C schematically illustrates one method of preparing the Tartrate Hydrate.

[0068] Figures 2A and 2B are powder X-ray diffraction patterns corresponding to the Amorphous Freebase (via precipitation) and the Amorphous Freebase (via dehydration), respectively.

[0069] Figure 3A is a powder X-ray diffraction pattern corresponding to the Freebase Solvate Form A (Isopropyl Acetate/Water Solvate).

[0070] Figure 3B is a powder X-ray diffraction pattern corresponding to the Freebase Hydrate Form B.

[0071] Figure 3C is a powder X-ray diffraction pattern corresponding to the Freebase Hydrate Form C.

[0072] Figure 3D is a powder X-ray diffraction pattern corresponding to the Tartrate Hydrate. The experimental PXRD pattern is shown at the bottom of Figure 3D and the calculated PXRD pattern is shown at the top of Figure 3D.

[0073] Figure 3E is a powder X-ray diffraction pattern corresponding to the Hydrochloride Solvate Form AA.

[0074] Figure 3F is powder X-ray diffraction pattern corresponding to the Hydrochloride Solvate Form BB.

[0075] Figure 3G is a powder X-ray diffraction pattern corresponding to the Hydrochloride Solvate Form CC.

[0076] Figure 3H is a powder X-ray diffraction pattern corresponding to L-Maleate Form AAA.

[0077] Figure 3I is a powder X-ray diffraction pattern corresponding to L-Maleate Form BBB.

[0078] Figure 3J is a powder X-ray diffraction pattern corresponding to Freebase Anhydrate Form D.

[0079] Figures 4A and 4B are thermogravimetric analysis thermograms corresponding to the Amorphous Freebase (via precipitation) and the Amorphous Freebase (via dehydration), respectively.

[0080] Figure 4C is a thermogravimetric analysis thermogram corresponding to the Freebase Solvate Form A.

[0081] Figure 4D is a thermogravimetric analysis thermogram corresponding to the Freebase Hydrate Form B.

[0082] Figure 4E is a thermogravimetric analysis thermogram corresponding to the Freebase Hydrate Form C.

[0083] Figure 4F is a thermogravimetric analysis thermogram corresponding to the Tartrate Hydrate.

[0084] Figure 4G is a thermogravimetric analysis thermogram corresponding to the Hydrochloride Solvate Form AA.

[0085] Figure 4H is a thermogravimetric analysis thermogram corresponding to L-Maleate Form BBB.

[0086] Figure 4I is a thermogravimetric analysis thermogram corresponding to Freebase Anhydrate Form D.

[0087] Figure 5A is a differential scanning calorimetry thermogram corresponding to the Amorphous Freebase (via dehydration).

[0088] Figure 5B is a differential scanning calorimetry thermogram corresponding to the Freebase Hydrate Form B.

[0089] Figure 5C is a differential scanning calorimetry thermogram corresponding to the Freebase Hydrate Form C.

[0090] Figure 5D is a differential scanning calorimetry thermogram corresponding to the Tartrate Hydrate.

[0091] Figure 5E is a differential scanning calorimetry thermogram corresponding to the Freebase Anhydrate Form D.

[0092] Figure 6A is a moisture sorption isotherm corresponding to the Amorphous Freebase (via dehydration).

[0093] Figure 6B is a moisture sorption isotherm corresponding to the Freebase Hydrate Form C.

[0094] Figure 6C is a moisture sorption isotherm corresponding to the Tartrate Hydrate.

[0095] Figure 6D is a moisture sorption isotherm corresponding to the Freebase Anhydrate Form D.

[0096] Figure 7 is a comparison of the dissolution profile of the extended release tablets from Example 26 (Freebase Hydrate Form C) and Example 27 (Amorphous Freebase) at pH 6.8.

[0097] Figure 8 is a comparison of the dissolution profile of the extended release tablets from Example 24 (ER1), Example 25 (ER2), and Example 26 (ER3) in a dual pH system and at pH 6.8.

[0098] Figure 9 is a comparison of the dissolution profile of the extended release tablet from Example 32 (ER4) and Example 33 (ER4, no mannitol) at pH 1.2, pH 6.8, or a dual pH system.

[0099] Figure 10 is a comparison of the dissolution profile of the extended release tablet from Example 34 (ER5) at pH 1.2, pH 6.8, and a dual pH system.

[00100] Figure 11 is a comparison of the dissolution profile of the extended release tablet from Example 35 (ER6) at pH 1.2, pH 6.8, and a dual pH system.

[00101] Figure 12 is a comparison of the dissolution profile of the extended release tablet from Example 28 (ER7) and Example 32 (ER4) in a dual pH system.

[00102] Figure 13 is a comparison of the dissolution profile of the extended release tablet from Example 31 (ER8) and Example 32 (ER4) in a dual pH system.

[00103] Figure 14 is comparison of the dissolution profile of the extended release tablets from Example 24 (ER1), Example 26 (ER3), and Example 32 (ER4) in a dual pH system.

[00104] Figures 15A-15H are comparisons of the dissolution profile at pH 1.2 and 6.8 for the extended release tablets from Example 43, which contain either HPMC (Figs. 15A-15D) or Carbopol® (Figs. 15E-15H) as release control polymers, and tartaric acid (Figs. 15A and 15E), citric acid (Figs. 15B and 15F), succinic acid (Figs. 15C and 15G), or fumaric acid (Figs. 15D and 15H) as a pH modifier.

[00105] Figures 16A and 16B show the Compound 1 mean plasma concentration versus time following administration of a 12 mg immediate release capsule (Regimen A) or a 15 mg once-daily extended release tablet (Regimen B) under fasting conditions using a linear (Figure 16A) or semi-log (Figure 16B) scale.

[00106] Figures 17A and 17B show the Compound 1 mean plasma concentration versus time following administration of a 24 mg dose (2 x 12 mg) of immediate release capsule (Regimen C) or a 30 mg once-daily extended release tablet (Regimen D) under fasting conditions using a linear (Figure 17A) or semi-log (Figure 17B) scale.

[00107] Figures 18A and 18B show the Compound 1 mean plasma concentration versus time following administration of a 30 mg once-daily extended release tablet under fasting conditions (Regimen D) or a 30 mg once-daily extended release tablet after consumption of a high-fat meal (Regimen E) using a linear (Figure 18A) or semi-log (Figure 18B) scale.

[00108] Figure 19 shows the Compound 1 mean plasma concentration versus time following administration of a 15 mg once-daily extended release tablet (Regimen F) or a 30 mg once-daily extended release tablet (Regimen G) for seven days under non-fasting conditions.

[00109] Figure 20 shows the Compound 1 mean plasma concentration versus time following administration of 6 mg twice daily immediate release capsules (Regimen K) or a 15 mg once-daily extended release tablet (Regimen L) for seven days under fasting conditions.

[00110] Figure 21 shows the Compound 1 pre-morning dose trough concentration (C_{trough}) following administration of 6 mg twice daily immediate release capsules or a 15 mg once-daily extended release tablet over seven days under fasting conditions.

[00111] Figure 22 shows the Compound 1 mean plasma concentration versus time following administration of 12 mg twice daily immediate release capsules (Regimen M) or a 30 mg once-daily extended release tablet (Regimen N) for seven days under fasting conditions.

[00112] Figure 23 shows the Compound 1 pre-morning dose trough concentration (C_{trough}) following administration of 12 mg twice daily immediate release capsules or a 30 mg once-daily extended release tablet over seven days under fasting conditions.

[00113] Figures 24A and 24B show the Compound 1 mean plasma concentration versus time following administration under fasting conditions of various 30 mg once-daily extended release tablets having varying concentrations of tartaric acid, using a linear (Figure 24A) or log-linear (Figure 24B) scale.

[00114] Figures 25A and 25B show the Compound 1 mean plasma concentration versus time following administration under fasting conditions or after a high-fat meal (non-fasting) of a 30 mg once-daily extended release tablet (ER10) using a linear (Figure 25A) or log-linear (Figure 25B) scale.

[00115] Figures 26A and 26B show the individual change in Compound 1 C_{max} (Figure 26A) and AUC_{inf} (Figure 26B) following administration under fasting conditions or after a high-fat meal (non-fasting) of a 30 mg once-daily extended release tablet (ER10).

[00116] Figures 27A and 27B show the Compound 1 mean plasma concentration versus time following administration under fasting conditions or after a high-fat meal (non-fasting) of a 30 mg once-daily extended release tablet (ER11) using a linear (Figure 27A) or log-linear (Figure 27B) scale.

[00117] Figures 28A and 28B show the individual change in Compound 1 C_{max} (Figure 28A) and AUC_{inf} (Figure 28B) following administration under fasting conditions or after a high-fat meal (non-fasting) of a 30 mg once-daily extended release tablet (ER11).

[00118] Figures 29A and 29B show the Compound 1 mean plasma concentration versus time following administration under fasting conditions or after a high-fat meal (non-fasting) of a 30 mg once-daily extended release tablet (ER12) using a linear (Figure 29A) or log-linear (Figure 29B) scale.

[00119] Figures 30A and 30B show the individual change in Compound 1 C_{max} (Figure 30A) and AUC_{inf} (Figure 30B) following administration under fasting conditions or after a high-fat meal (non-fasting) of a 30 mg once-daily extended release tablet (ER12).

[00120] Figure 31 shows a plot of the pH of the gel formed on tablets comprising varying amounts of tartaric acid,.

[00121] Figures 32A and 32B show the Compound 1 mean plasma concentrations versus time profiles following administration of single oral doses of Compound 1 immediate release capsules to healthy subjects using a linear (Figure 32A) or log-linear (Figure 32B) scales.

[00122] Figure 33 shows the Compound 1 mean plasma concentration versus time profiles following administration of multiple twice-daily oral doses of Compound 1 immediate release capsules to healthy subjects.

[00123] Figure 34A-34D shows the dose-normalized Compound 1 mean C_{max} and AUC after administration of single doses in healthy subjects (Figure 34A – single dose, C_{max}; Figure 34C – single dose, AUC_{∞}) and multiple-doses in healthy subjects and subjects with rheumatoid arthritis (Figure 34B – multiple-doses, C_{max}; Figure 34D – multiple-doses, AUC_{0-12}).

[00124] Figures 35A and 35B show the lack of effect of concomitant methotrexate administration on Compound 1 dose-normalized AUC (Figure 35A) and lack of effect of concomitant Compound 1 administration on methotrexate dose-normalized AUC (Figure 35B).

[00125] Figure 36A shows the ACR20, ACR50, and ACR70 response rate at week 12 following administration of placebo or various doses of Compound 1 to subjects with active rheumatoid arthritis and prior inadequate response or intolerance to an anti–TNF biologic agent (*P<0.05; **P<0.01; ***P<0.001 relative to placebo; modified intent-to-treat population (NRI)). Figure 36B shows the ACR20 response rate at week 12 in the same population, broken down by number of prior anti-TNF biologic agents.

[00126] Figures 37A-37D show the ACR20 (Figure 37A), ACR50 (Figure 37B), and ACR70 (Figure 37C) responses or DAS28(CRP) mean change from baseline (Figure 37D) over time following administration of placebo or various doses of Compound 1 to subjects with active rheumatoid arthritis and prior inadequate response or intolerance to an anti–TNF biologic agent (*P<0.05; **P<0.01; ***P<0.001 relative to placebo; modified intent-to-treat population (NRI)). Figure 37E shows the subjects achieving a DAS28(CRP) score of ≤3.2 or <2.6 at week 12 in the same population. Figure 37F shows the subjects achieving low disease activity (LDA)

or clinical remission (CR) based on clinical disease activity index (CDAI) criteria (LDA is CDAI ≤10; CR is CDAI ≤2.8) at week 12 in the same population.

[00127] Figure 38A shows the mean hemoglobin levels over time for all subjects following administration of placebo or various doses of Compound 1 to subjects with active rheumatoid arthritis and prior inadequate response or intolerance to an anti–TNF biologic agent (safety population with observed data (no imputation of missing values)). Figure 38B shows the mean hemoglobin change from baseline over time in subjects with high-sensitivity C-reactive protein (hsCRP) greater than the upper limit of normal (ULN) (normal ranges for hemoglobin: 11.5–15.5 g/dL in females and 13.2–17.0 g/dL in males; ULN for hsCRP = 5 mg/L).

[00128] Figure 39 shows the subject disposition for the study described in Example 55.

[00129] Figures 40A and 40B show the subject disposition for the study described in Example 56.

[00130] Figure 41 shows the ACR20, ACR50, and ACR70 responses at week 12 following administration of placebo or various doses of Compound 1 to subjects with active rheumatoid arthritis and inadequate response to methotrexate (*P<0.05; **P<0.01; ***P<0.001 relative to placebo; modified intent-to-treat population with NRI of missing values).

[00131] Figures 42A-42D show the ACR20 (Figure 42A, NRI analysis), ACR50 (Figure 42B, NRI analysis), and ACR70 (Figure 42C, NRI analysis) responses or DAS28(CRP) mean change from baseline (Figure 42D, observed cases) over time following administration of placebo or various doses of Compound 1 to subjects with active rheumatoid arthritis and inadequate response to methotrexate (*P<0.05; **P<0.01; ***P<0.001 relative to placebo; modified intent-to-treat population).

[00132] Figures 43A and 43B show subjects achieving a DAS28(CRP) score of ≤3.2 or <2.6 (Figure 44A) or CDAI of ≤10 or ≤2.8) at week 12 following administration of placebo or various doses of Compound 1 to subjects with active rheumatoid arthritis and inadequate response to methotrexate (*P<0.05; **P<0.01; ***P<0.001 relative to placebo; modified intent-to-treat population (NRI)). For Figures 43A and 43B, the bottom number indicates the percentage of subjects who achieved both cutoff values, the middle number indicates the percentage of subjects who achieved the less stringent cutoff but not the more stringent cutoff value, and the top number indicates the percentage of patients who achieved either cutoff value.

[00133] Figures 44A-44C show the mean change in hemoglobin from baseline over time by treatment group in all subjects (Figure 44A), subjects with hsCRP ⩽ 5 mg/mL at baseline

(Figure 44B), and subjects with hsCRP >5 mg/mL at baseline (Figure 44C) following administration of placebo or various doses of Compound 1 to subjects with active rheumatoid arthritis and inadequate response to methotrexate (safety population with observed data (no imputation of missing values)).

DETAILED DESCRIPTION OF THE INVENTION

[00134] This written description uses examples to disclose the invention and also to enable any person skilled in the art to practice the invention, including making and using any of the disclosed solid state forms or compositions, and performing any of the disclosed methods or processes.

I. Definitions

[00135] Section headings as used in this section and the entire disclosure are not intended to be limiting.

[00136] Where a numeric range is recited, each intervening number within the range is explicitly contemplated with the same degree of precision. For example, for the range 6 to 9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0 to 7.0, the numbers 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9 and 7.0 are explicitly contemplated. In the same manner, all recited ratios also include all sub-ratios falling within the broader ratio.

[00137] The singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

[00138] The term "about" generally refers to a range of numbers that one of skill in the art would consider equivalent to the recited value (*i.e.*, having the same function or result). In many instances, the term "about" may include numbers that are rounded to the nearest significant figure.

[00139] The term "alkyl" refers to straight chained or branched hydrocarbons which are completely saturated. For purposes of exemplification, which should not be construed as limiting the scope of this invention, examples of alkyls include methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, and isomers thereof.

[00140] The term "alkenyl" refers to a hydrocarbon moiety containing two to eight carbons, including straight chained or branched hydrocarbons which contain one or more double bonds. Non-limiting examples of alkenyls are ethenyl, propenyl, and butenyl.

[00141] The term "amorphous" as applied to a compound refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ("glass transition")..

[00142] The term "anhydrate" as applied to a compound refers to a solid state wherein the compound contains no structural water within the crystal lattice.

[00143] The term "aryl" refers to a mono-, bi-, or tricyclic aromatic hydrocarbon radical. Examples include phenyl, naphthyl, biphenyl, and 1,2,3,4-tetrahydronaphthyl.

[00144] Unless the context requires otherwise, the terms "comprise," "comprises," and "comprising" are used on the basis and clear understanding that they are to be interpreted inclusively, rather than exclusively, and that Applicant intends each of those words to be so interpreted in construing this patent, including the claims below.

[00145] The term "crystalline" as applied to a compound refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ("melting point").

[00146] The term "crystalline purity" means the crystalline purity of a compound with regard to a particular crystalline form of the compound as determined by the powder X-ray diffraction analytical methods described in this application.

[00147] The term "crystallization" as used throughout this application can refer to crystallization and/or recrystallization depending upon the applicable circumstances relating to the preparation of the compound.

[00148] The term "pharmaceutically acceptable" (such as in the recitation of a "pharmaceutically acceptable salt" or a "pharmaceutically acceptable diluent") refers to a material that is compatible with administration to a human subject, *e.g.*, the material does not

cause an undesirable biological effect. Examples of pharmaceutically acceptable salts are described in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002). Examples of pharmaceutically acceptable excipients are described in the "Handbook of Pharmaceutical Excipients," Rowe et al., Ed. (Pharmaceutical Press, 7th Ed., 2012).

[00149] The term "subject" refers to a human subject.

[00150] The terms "treating" and "treatment" refer to ameliorating, suppressing, eradicating, reducing the severity of, decreasing the frequency of incidence of, preventing, reducing the risk of, slowing the progression of damage caused by or delaying the onset of the condition or improving the quality of life of a patient suffering from the condition.

[00151] The term "Xantphos" refers to 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

[00152] The abbreviation "2-Me THF" refers to 2-methyl tetrahydrofuran.

[00153] The abbreviation "ACN" refers to acetonitrile.

[00154] The abbreviation "AcOH" refers to acetic acid.

[00155] As used herein, the term "$AUC_{24,ss}$" refers to the steady-state area under the plasma concentration time curve from time zero to twenty-four hours after administration of the referent drug. The term "$AUC_{12,ss}$" refers to the steady-state area under the plasma concentration time curve from time zero to twelve hours after administration of the referent drug.

[00156] As used herein, the term "AUC_{inf}" refers to the area under the plasma concentration time curve from time zero to infinity following a single dose, calculated using the trapezoidal rule. $AUC_{inf} = AUC_t + C_{last}/k$, where C_{last} is the last measured concentration and k is the calculated terminal elimination rate constant.

[00157] As used herein, the term "AUC_t" refers to the area under the plasma concentration time curve from the time of administration of the referent drug to the time of the last measured concentration calculated using the trapezoidal rule. "AUC_{24}" refers to the area under the plasma concentration time curve from time zero to twenty-four hours after administration of the referent drug following a single dose.

[00158] The abbreviation "Bn" refers to benzyl.

[00159] As used herein, the term "C_{12}" is the plasma concentration of the referent drug observed 12 hours after administration of a single dose, or the indicated number of doses, of the referent drug. The term "$C_{12,ss}$" refers to the C_{12} as measured at a steady-state.

[00160] As used herein, the term "C_{24}" is the plasma concentration of the referent drug observed 24 hours after administration of a single dose, or the indicated number of doses, of the referent drug. The term "$C_{24,ss}$" refers to the C_{24} as measured at a steady-state.

[00161] The abbreviation "Cbz" refers to carboxybenzyl.

[00162] The abbreviation "CDI" refers to carbonyldiimidazole.

[00163] The abbreviation "%CV" refers to the coefficient of variation, expressed as a percent. % CV is calculated according to the following equation: %CV = (SD/x) * 100, wherein x is the mean value and SD is the standard deviation.

[00164] As used herein, the term "C_{max}" refers to the plasma concentration of the referent drug at T_{max}, expressed herein as ng/mL, produced by the oral ingestion of a single dose, or indicated number of doses, of the dosage form or pharmaceutical composition, such as the dosage forms and compositions of the present disclosure. Unless specifically indicated, C_{max} refers to the overall maximum observed concentration.

[00165] As used herein, the term "$C_{max,ss}$" refers to the steady-state C_{max} of the referent drug during a dosage interval.

[00166] As used herein, the term "$C_{min,ss}$" refers to the minimum steady-state plasma concentration of the referent drug during a dosage interval.

[00167] As used herein, the term "C_{trough}" refers to the trough plasma concentration of the referent drug, as measured at the end of a dosing interval at steady state.

[00168] The abbreviation "DBU" refers to 1,8-diazabicyclo[5.4.0]undec-7-ene.

[00169] The abbreviation "DCHA" refers to dicyclohexylamine.

[00170] The abbreviation "DCM" refers to dichloromethane.

[00171] The abbreviation "DIPEA" refers to diisopropylethylamine.

[00172] The abbreviation "DMA" refers to dimethylacetamide, or N,N-dimethylacetamide.

[00173] The abbreviation "DMAP" refers to 4-dimethylaminopyridine.

[00174] The abbreviation "DSC" means differential scanning calorimetry.

[00175] As used herein, the term "entry into a use environment" means contact of a formulation of the disclosure with the gastric fluids of the subject to whom it is administered, or with a fluid intended to simulate gastric fluid.

[00176] The abbreviation "$EtB(OH)_2$" refers to ethyl boronic acid.

[00177] The abbreviation "EtOAc" refers to ethyl acetate.

[00178] The abbreviation "$Fe(acac)_3$" refers to iron(III) acetylacetonate.

[00179] The abbreviation "HDPE" refers to high-density polyethylene.

[00180] The abbreviation "HOAc" refers to acetic acid.

[00181] The abbreviation "HPMC" refers to hydroxypropyl methylcellulose.

[00182] The abbreviation "IPAc" refers to isopropyl acetate.

[00183] The abbreviation "KOtBu" refers to potassium tert-butoxide.

[00184] The abbreviation LiOtBu" refers to lithium tert-butoxide.

[00185] The abbreviation "Me_3SOCl" refers to trimethylsulfoxonium chloride.

[00186] The abbreviations "MeOH" and "EtOH" refer to methanol and ethanol, respectively.

[00187] The abbreviation "MS" means mass spectrometry.

[00188] The abbreviation "MTBE" refers to methyl tert-butyl ether.

[00189] The abbreviation "MTX" refers to methotrexate.

[00190] The abbreviations "NatOBu" or "NaOtBu" refer to sodium tert-butoxide.

[00191] The abbreviation "$Ni(acac)_2$" refers to nickel (II) acetylacetonate.

[00192] The abbreviation "NMM" refers to N-methyl morpholine.

[00193] The abbreviation "Pd/C" refers to palladium on carbon.

[00194] The abbreviation "$PdCl_2(dppf)$" refers to [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II).

[00195] The abbreviation "$PdCl_2(Ph_3P)_2$" refers to bis(triphenylphosphine)palladium(II) dichloride.

[00196] The abbreviation "$Pd(OAc)_2$" refers to palladium (II) acetate.

[00197] The abbreviation "$Pd(OH_2)/C$" refers to palladium hydroxide on carbon.

[00198] The abbreviation "PFPAA" refers to pentafluoropropionic anhydride.

[00199] The abbreviation "pTsOH" refers to p-toluenesulfonic acid.

[00200] The abbreviation "PVA" refers to polyvinyl acetate.

[00201] The abbreviation "PXRD" means powder X-ray diffraction.

[00202] The abbreviation "(S)-Segphos $Ru(OAc)_2$" or "$Ru(OAc)_2$-Segphos" refers to diacetato[(S)-(-)5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II).

[00203] As used herein, the term "$t_{1/2}$" refers to the terminal half-life of the referent drug after oral ingestion of a single dose, or indicated number of doses, of the referent drug. The term "$t_{1/2,ss}$" refers to the terminal half-life as measured at a steady-state.

[00204] The abbreviation "TEA" refers to triethylamine."

[00205] The abbreviation "TFAA" refers to trifluoroacetic anhydride.

[00206] The abbreviation "TF_2O" refers to trifluoromethanesulfonic anhydride.

[00207] The abbreviation "TGA" means thermogravimetric analysis.

[00208] The abbreviation "TGA-MS" means thermogravimetric analysis-mass spectrometer.

[00209] The abbreviation "THF" refers to tetrahydrofuran.

[00210] As used herein, the term "T_{max}" refers to the time to peak plasma concentration of the referent drug after oral ingestion of a single dose, or indicated number of doses, of the referent drug.

[00211] As used herein, the term "$T_{max,ss}$" refers to the time to peak plasma concentration of the referent drug after oral ingestion of the referent drug at steady-state.

[00212] The abbreviation "TMS" refers to trimethylsilyl.

[00213] The term "triflate" refers to trifluoromethanesulfonate.

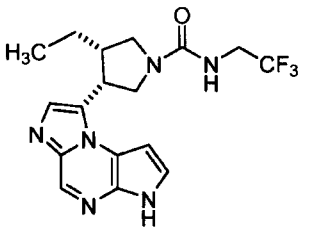
[00214] The abbreviation "v/v" refers to volume/volume.

[00215] The abbreviation "w/w" refers to weight/weight.

[00216] For clarity and convenience purposes only, the convention is utilized herein of designating the time of drug administration or initiation of dissolution testing as zero (0) hours (t=0 hours) and times following administration in appropriate time units, for example, t=30 minutes or t=2 hours, etc.

II. Processes for Preparing (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (Compound 1) and Intermediates

[00217] The present disclosure relates to improved processes for preparing (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (referred to herein as "Compound 1" or as "Compound 1 freebase"), to pharmaceutically acceptable salts of Compound 1, and to intermediates used in the preparation of Compound 1. Compound 1 has the structure shown below:



Methods for making and using this compound are described, for example, in International Application WO 2011/068881A1.

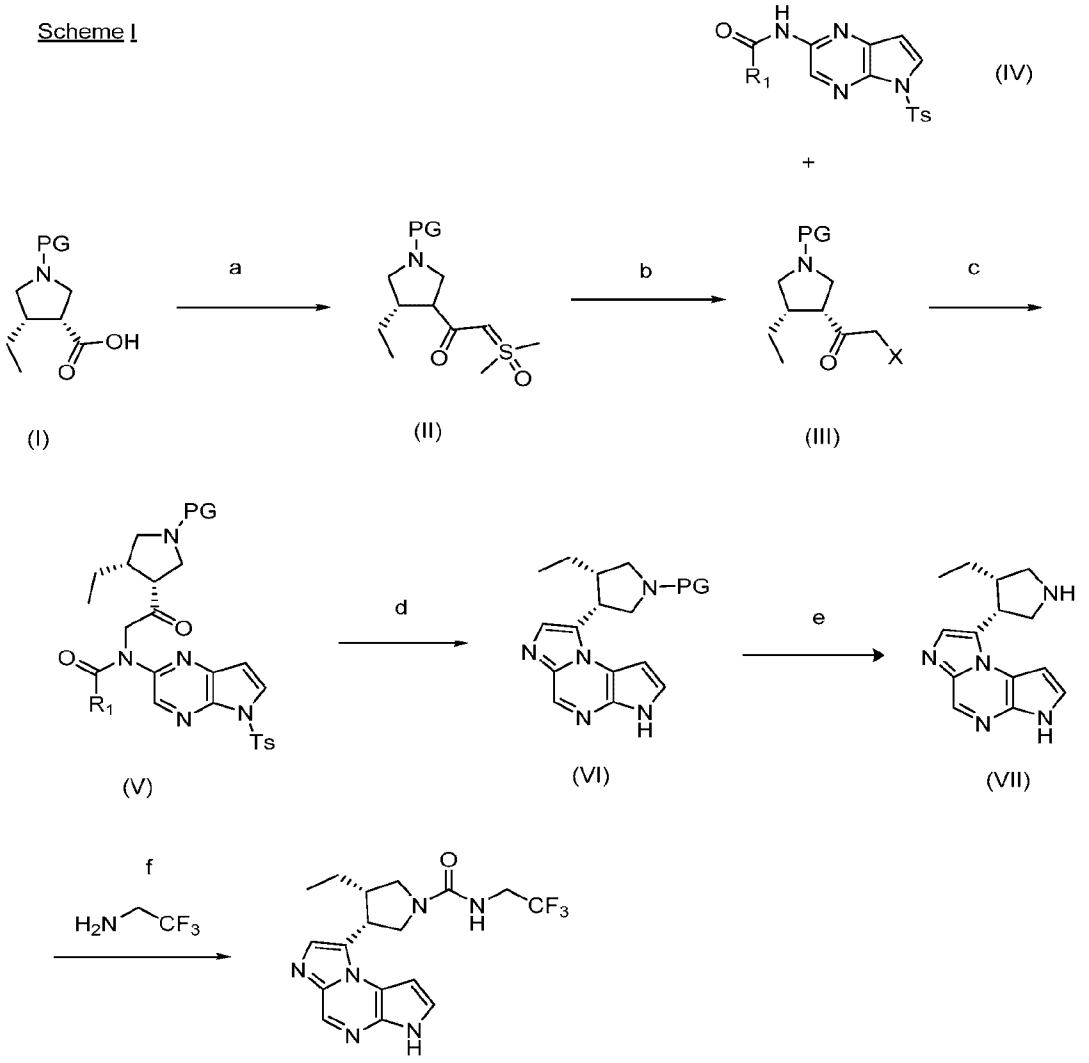
[00218] Previously disclosed processes for preparing Compound 1, and pharmaceutically acceptable salts thereof suffer from several drawbacks. In particular, these processes involve the use of particularly hazardous reagents, such as trimethylsilyldiazomethane or diazomethane, and/or do not produce a crystalline product. The processes of the present disclosure overcome these drawbacks by avoiding the use of these hazardous reagents, and producing crystalline intermediates, which aid in purification.

[00219] Compounds of the present disclosure may be prepared using synthetic transformations such as those illustrated in Schemes I-XVI. Starting materials are commercially available, may be prepared by the procedures described herein, by literature procedures, or by procedures that would be well known to one skilled in the art of organic chemistry (see, for example, Larock, R.C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd edition", 1999, Wiley-VCH or Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience).

A. Preparation of Compound 1

[00220] In one aspect, the present disclosure is directed to a process for preparing Compound 1, or a pharmaceutically acceptable salt thereof. A process for preparing Compound 1 is illustrated in Scheme I. Reaction of protected (3R,4S)-4-ethylpyrrolidine-3-carboxylic acid (I) or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride gives sulfur ylide (II). Contacting sulfur ylide (II) with LiX and a sulfonic acid yields the corresponding halomethyl ketone (III). Reaction of (III) with (IV) in the presence of a base yields (V). Cyclization of (V) in the presence of a perfluoro acid anhydride and an organic base produces (VI). Removal of the protecting group and contacting the deprotected compound with an acid yields a pharmaceutically acceptable salt of (VII). Reacting the pharmaceutically acceptable salt of (VII) with 2,2,2-trifluoroethylamine produces Compound 1.

Scheme I



wherein:

PG is a protecting group;

X is Br or Cl;

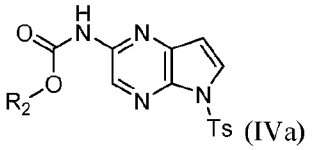
R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$;

R_2 is alkyl; and

Ts is tosyl.

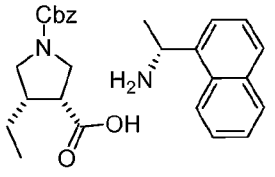
[00221] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl. In another embodiment, the protecting group is carboxybenzyl.

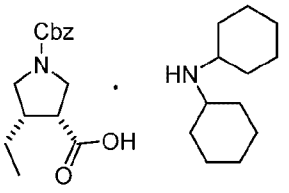
[00222] In another embodiment, R_1 is $-OR_2$, and R_2 is methyl or ethyl. In such embodiments, the compound of formula (IV) is a compound of formula (IVa):


(IVa)

wherein R_2 is methyl or ethyl. It has surprisingly been discovered that when R_2 is ethyl or methyl, the compound of formula (V) and subsequent downstream compounds can be isolated as crystalline solids, which aids in purification of these intermediates. In contrast, previously known processes, which use compounds where R_2 is t-butyl, result in formation of compounds of formula (V) which are isolated as amorphous solids.

[00223] In certain embodiments, a pharmaceutically acceptable salt of a compound of the compound of formula (I) is used in the reaction of step (a). In one embodiment, the pharmaceutically acceptable salt of the compound of formula (I) is selected from the group consisting of the naphthalenethane amine salt (Ia) and the dicyclohexylamine salt (Ib)

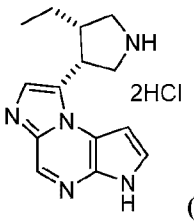

(Ia)



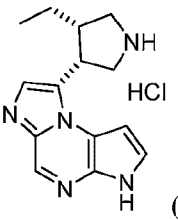
(Ib)

wherein Cbz is carboxybenzyl.

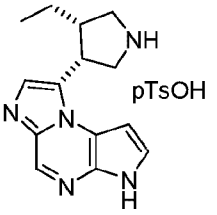
[00224] In one embodiment, the pharmaceutically acceptable salt of compound (VII) is selected from the group consisting of (VIIa), (VIIb), and (VIIc)



(VIIa),



(VIIb),

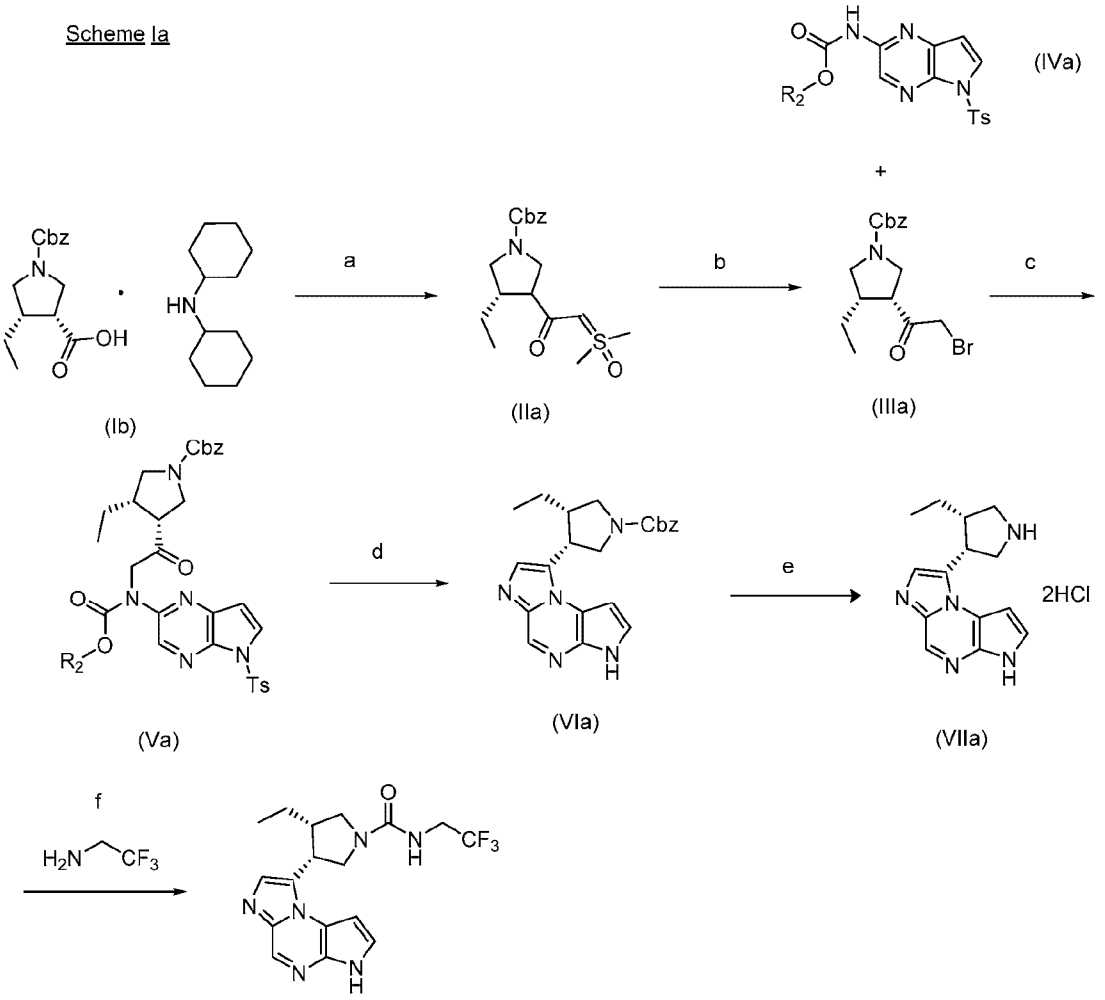


(VIIc).

[00225] Another process for preparing Compound 1 is illustrated in Scheme Ia. Reaction of (3R,4S)-1-((benzyloxy)carbonyl)-4-ethylpyrrolidine-3-carboxylate dicyclohexylamine salt (Ib) with trimethylsulfoxonium chloride in the presence of carbonyldiimidazole and a strong base gives sulfur ylide (IIa). Contacting sulfur ylide (IIa) with lithium bromide and a sulfonic acid yields the corresponding bromomethyl ketone (IIIa). Reaction of (IIIa) with alkyl 5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-ylcarbamate (IVa) in the presence of lithium *tert*-butoxide yields (Va). Cyclization of (Va) in the presence of a perfluoro acid anhydride and an organic base produces (VIa). Removal of the carboxybenzyl protecting group and contacting the deprotected compound with hydrochloric acid yields the pharmaceutically acceptable salt (VIIa). Reacting

the pharmaceutically acceptable salt (VIIa) with 2,2,2-trifluoroethylamine produces Compound 1.

Scheme Ia



wherein:

Cbz is carboxybenzyl;

Ts is tosyl; and

R_2 is methyl or ethyl.

[00226] The reaction in step (a) of Schemes I and Ia is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations

thereof. The step (a) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide.

[00227] More particularly, in certain embodiments, a solution of a compound of formula (I), (Ia), or (Ib) in solvent is slowly added (e.g., over 30 minutes) to a slurry of CDI in solvent, and the resulting mixture is stirred at room temperature for 30 minutes to 12 hours, and typically for about 1 hour. The resulting solution is slowly added (e.g., over 15 minutes) to a suspension of the trimethylsulfoxonium chloride, strong base, and solvent, while maintaining the internal temperature below -1°C. In another embodiment, the reaction is quenched and the resulting compound of formula (II) or (IIa) is isolated prior to step (b).

[00228] In some embodiments, the reaction of step (a) may further involve contact of (Ia) or (Ib) with an acid prior to reaction with the trimethylsulfoxonium chloride, in order to extract the amine to obtain a compound of formula (I). Suitable acids include any mineral acid or organic acid, such as phosphoric acid, hydrochloric acid (HCl), acetic acid (HOAc), citric acid, and the like. The compound of formula (I) may subsequently be taken up in a suitable solvent, and reacted with trimethylsulfoxonium chloride, as described herein. In one embodiment, a pharmaceutically acceptable salt of a compound of formula (I) is used in step (a), wherein the pharmaceutically acceptable salt is (Ia) or (Ib), and the reaction of step (a) is conducted according to the procedure set forth in Step A of Example 3.

[00229] In step (b) of Schemes I and Ia, a compound of formula (II) or (IIa) is contacted with LiX and a sulfonic acid to form a compound of formula (III) or (IIIa), respectively. In one embodiment, the sulfonic acid is selected from the group consisting of methanesulfonic acid and p-toluenesulfonic acid. In one embodiment, the sulfonic acid is p-toluenesulfonic acid. LiX may be selected from lithium bromide and lithium chloride. In one embodiment, LiX is lithium bromide. In one embodiment, the reaction is conducted in lithium bromide and p-toluensulfonic acid. The reaction of step (b) may be conducted in any suitable solvent including, but not limited to tetrahydrofuran, ethyl acetate, heptanes, ethanol, water, and combinations thereof.

[00230] More particularly, in certain embodiments, the sulfonic acid is added to a solution of the compound of formula (II) or (IIa) and LiX in a solvent. The resulting mixture is warmed to about 35°C to about 65°C and stirred overnight. In one embodiment, the mixture is warmed to about 40°C and stirred overnight. The mixture is cooled to room temperature and washed. The compound of formula (III) or (IIIa) may be isolated, or optionally used in the next step without purification.

[00231] In step (c) of Schemes I and Ia a compound of formula (III) or (IIIa) are reacted with a compound of formula (IV) or (IVa) (prepared as described herein). The step (c) reaction is conducted in the presence of a base, such as lithium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. In one embodiment, the base is lithium *tert*-butoxide. The reaction of step (c) may be conducted in any suitable solvent including, but not limited to dimethylacetamide, tetrahydrofuran, dichloromethane, ethyl acetate, heptanes, and combinations thereof.

[00232] More particularly, in certain embodiments, the base is added to a cooled suspension of the compound of formula (III) or (IIIa) in a solvent. The resulting solution is stirred for about 30 minutes to about 12 hours, or about 30 minutes, and cooled to about -20°C to about 0°, or about -10°C. In one embodiment, the solution is stirred for about 30 minutes and cooled to about -20°C to about 0°. A solution of a compound of formula (IV) or (IVa) in a solvent is slowly added (e.g., over 30 minutes), and the resulting mixture is stirred for about 30 minutes to about 6 hours, or about 30 minutes, at a temperature of about -20°C to about 0°C, or about -10°C. In one embodiment, following addition of the solution of the compound of formula (IV) or (IVa) in a solvent, the resulting mixture is stirred for about 30 minutes at a temperature of about -10°C. In one embodiment, the reaction is quenched, and, in some embodiments, the resulting product (V) or (Va) is isolated prior to step (d).

[00233] In step (d) of Schemes I and Ia, a compound of formula (V) or (Va) is contacted with a perfluoro acid anhydride and an organic base to form a compound of formula (VI) or (VIa), respectively. Non-limiting examples of suitable organic bases include pyridine, triethylamine, and combinations thereof. Examples of suitable perfluoro acid anhydrides include trifluoroacetic anhydride, pentafluoropropionic anhydride, heptafluorobutyric anhydride, and combinations thereof. In certain embodiments, the organic base is pyridine and the perfluoro acid anhydride is trifluoroacetic anhydride. In other embodiments, the organic base is triethylamine, and the perfluoro acid anhydride is pentafluoropropionic anhydride. Suitable solvents for use in step (d) include, but are not limited to acetonitrile, toluene, and combinations thereof.

[00234] More particularly, in certain embodiments, the organic base and the perfluoro acid anhydride are charged into a solution of a compound of formula (V) or (Va) in solvent. The resulting mixture is warmed to about 55°C to about 75°C, or about 55°C, and stirred for about 4 hours to about 18 hours, or about 6 hours. In one embodiment, the mixture of perfluoro acid anhydride and the compound of formula (V) or (Va) is warmed to about 55°C and stirred

for about 4 hours to about 18 hours. In one embodiment, the mixture is stirred for about 6 hours. Upon completion of the reaction, in some embodiments, the reaction mixture may be cooled, and concentrated prior to contacting with a hydroxide solution to quench excess reagents, and remove the tosyl protecting group. Suitable hydroxide solutions include a sodium hydroxide (NaOH) solution, a potassium hydroxide (KOH) solution, and the like. The resulting mixture may be stirred at room temperature to about 85°C, including at about 55°C, for about 30 minutes to about 8 hours. In one embodiment, the mixture is stirred for about 1 hour. Upon completion, the solvent may optionally be removed and switched to methanol, ethanol, isopropanol, or other suitable solvents prior to step (e).

[00235] In step (e) of Schemes I and Ia, a compound of formula (VI) or (VIa) is deprotected, and a pharmaceutically acceptable salt of compound (VII), such as (VIIa), (VIIb), or (VIIc) is formed. The protecting group on the compound of formula (VI) or (VIa) may be removed using any suitable means known in the art. In one embodiment, deprotection occurs by contacting the compound of formula (VI) or (VIa) with palladium on carbon (e.g., Pd/C or $Pd(OH_2)/C$) under hydrogen pressure. In other embodiments, deprotection occurs by contacting the compound of formula (VI) or (VIa) with an acid. Non-limiting examples of suitable acids include hydrochloric acid (HCl), hydrobromic acid (HBr), hydrobromic acid in acetic acid (e.g., HBr/HOAc), and the like. In other embodiments, deprotection occurs by subjecting the compound of formula (VI) or (VIa) to heating, e.g., at a temperature of from room temperature to about 85°C, including about 50°C. Upon deprotection, the compound of formula (VII) is contacted with the appropriate acid (e.g., hydrochloric acid or p-toluenesulfonic acid) to form the pharmaceutically acceptable salt.

[00236] Step (e) may occur in any suitable solvent including, but not limited to ethanol, isopropyl acetate, ethyl acetate, and combinations thereof.

[00237] More particularly, in some embodiments, palladium on carbon and the compound of formula (VI) or (VIa) in solvent are mixed under hydrogen pressure at about 1 psig to about 100 psig. In another embodiment, the hydrogen pressure is about 20 psig. The mixture is agitated for about 2 hours to about 24 hours, including about 16 hours, at about 20°C to about 85°C, including about 50 °C. In one embodiment, the mixture is agitated for about 16 hours at about 20°C to about 80°C. In one embodiment, the mixture is agitated for about 16 hours at about 50°C. Upon completion of the reaction, the reaction mixture is cooled and filtered, followed by addition of the appropriate acid. The resulting salt is optionally isolated prior to step (f).

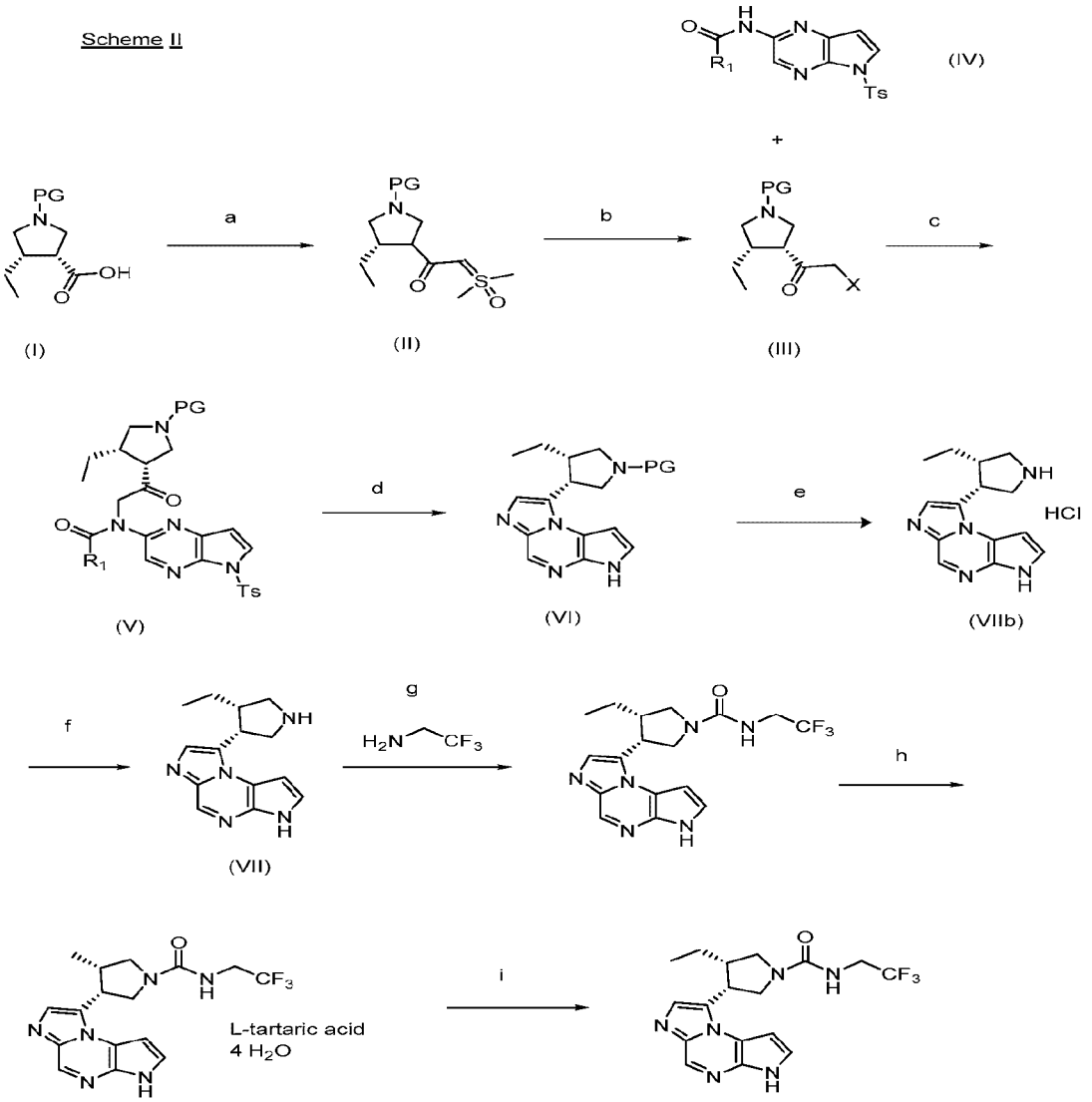
[00238] In step (f), the salt produced in step (e) is reacted with 2,2,2-trifluoroethylamine to produce Compound 1. The step (f) reaction is conducted in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and optionally buffers, such as dipotassium phosphate, potassium hydroxide, and combinations thereof. In one embodiment, the step (f) reaction is conducted in the presence of CDI, dipotassium phosphate, and potassium hydroxide. The step (f) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, ethyl acetate, heptanes, ethanol, water, and combinations thereof.

[00239] More particularly, in certain embodiments, 2,2,2-trifluoroethyl amine is added slowly (e.g., over 20 minutes) to a slurry of CDI in solvent, while maintaining an internal temperature of less than 30°C. The resulting solution is stirred for about 10 minutes to about 12 hours, and in one embodiment for about 1 hour, to form an imidazolide solution. The pH of a biphasic mixture of the pharmaceutically acceptable salt from step (e) in buffer and solvent is adjusted to about 7 to about 11, and in one embodiment to about 9, by addition of a base. The imidazolide solution is added, and the resulting mixture is mixed at about 25°C while maintaining a pH of about 9 by portionwise addition of base for about 30 minutes to about 18 hours. In one embodiment, the mixture formed after addition of the imidazolide solution is mixed at about 25°C while maintaining a pH of about 9 by portionwise addition of base for about 1 hour. In one embodiment, upon completion, the reaction is quenched and the resulting product isolated.

[00240] In one embodiment, Compound 1 is prepared according to the process set forth in Scheme Ia. In certain embodiments, the process may further comprise preparation of (Ib) according to the process set forth in Scheme V herein.

[00241] An alternate process for preparing Compound 1 is illustrated in Scheme II. Reaction of protected (3R,4S)-4-ethylpyrrolidine-3-carboxylic acid (I) or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride gives sulfur ylide (II). Contacting sulfur ylide (II) with LiX and a sulfonic acid yields the corresponding halomethyl ketone (III). Reaction of (III) with (IV) in the presence of a base yields (V). Cyclization of (V) in the presence of a perfluoro acid anhydride and an organic base produces (VI). Removal of the protecting group and contacting the deprotected compound (VII) (not shown) with hydrochloric acid yields pharmaceutically acceptable salt (VIIb). The pharmaceutically acceptable salt (VIIb) is converted to the freebase (VII), which is reacted with 2,2,2-trifluoroethylamine to produce Compound 1. Compound 1 is contacted with L-tartaric acid to form the corresponding tartrate salt, followed by formation of the Compound 1 freebase.

Scheme II



wherein PG, Ts, X, and R_1 are as defined above.

[00242] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl. In one embodiment, the protecting group is carboxybenzyl.

[00243] In one embodiment, R_1 is $-OR_2$, and R_2 is ethyl or methyl.

[00244] In certain embodiments, a pharmaceutically acceptable salt of the compound of formula (I) is used in the reaction of step (a). In one embodiment, the pharmaceutically acceptable salt of the compound of formula (I) is selected from the group consisting of the naphthalenethane amine salt (Ia) and the dicyclohexylamine salt (Ib).

[00245] Steps (a)-(e) of Scheme II are conducted as described above for Scheme I, wherein following deprotection of the compound of formula (VI), deprotected compound (VII) is contacted with hydrochloric acid to form pharmaceutically acceptable salt (VIIb).

[00246] In step (f) of Scheme II, salt (VIIb) is contacted with a base to form the corresponding freebase (VII). Suitable bases include, but are not limited to hydroxides, such as sodium hydroxide, potassium hydroxide, and the like, and combinations thereof. In one embodiment, the base is sodium hydroxide. The reaction of step (f) may be conducted in any suitable water-containing solvent including, but not limited to, water alone or in combination with THF, 2-methyl tetrahydrofuran, ethanol, methanol, and the like.

[00247] In step (g) compound (VII) is reacted with 2,2,2-trifluoroethylamine to produce Compound 1. The step (g) reaction is conducted in the presence of a coupling agent, such as CDI. Step (g) in Scheme II is conducted using similar reagents and under similar conditions as those set forth above for step (f) of Scheme I.

[00248] In step (h) of Scheme II, Compound 1 is contacted with L-tartaric acid to form the corresponding tartrate salt (step (h)). Formation of the tartrate salt advantageously aids in removal of impurities prior to isolation of the freebase. In one embodiment, the tartrate salt may be formed using the procedure described in Example 8, Method B, only without drying the tartrate salt prior to step (i). The tartrate salt is subsequently converted back to the freebase form (step (i)) to produce Compound 1. In particular, in step (i) the tartrate salt may be contacted with a base, such as an inorganic base, to produce the corresponding freebase. Suitable bases include, but are not limited to, sodium bicarbonate, sodium carbonate, sodium hydroxide, potassium carbonate, potassium bicarbonate, potassium hydroxide, and the like, or combinations thereof. In one embodiment, the tartrate salt is contacted with sodium bicarbonate and sodium carbonate to produce the corresponding freebase.

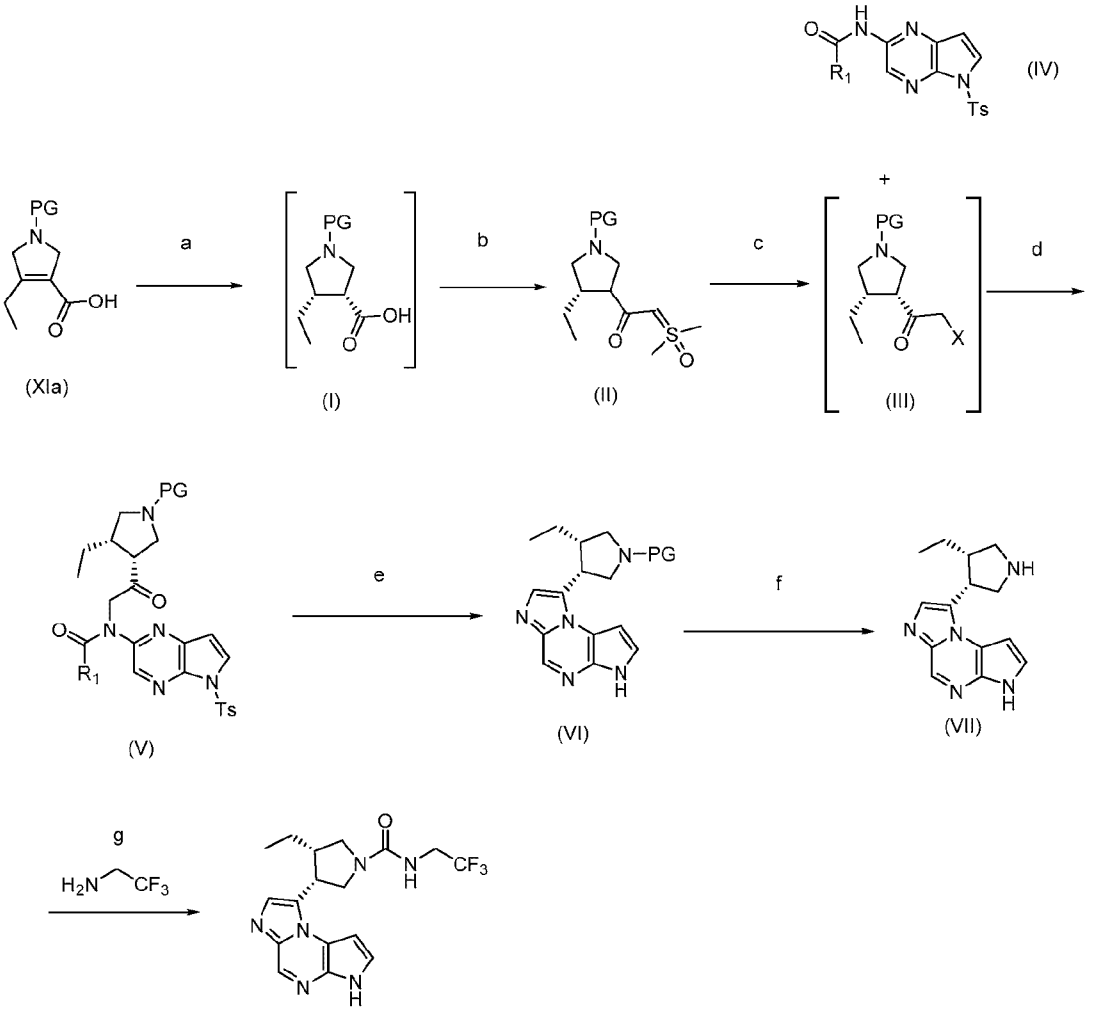
[00249] Suitable solvents for use in step (h) include, but are not limited to, isopropyl acetate, methyl tert-butyl ether, water, isopropyl alcohol, and combinations thereof. Suitable solvents for use in step (i) include, but are not limited to, ethyl acetate, ethanol, water, and combinations thereof.

[00250] In some embodiments, the products of steps (d), (e), (g), and (h) of Scheme II are not isolated prior to the subsequent step.

[00251] An alternate process for preparing Compound 1 is illustrated in Scheme III. Compound (XIa) is hydrogenated to produce (I). Reaction of protected (3R,4S)-4-

ethylpyrrolidine-3-carboxylic acid (I) with trimethylsulfoxonium chloride gives sulfur yilde (II). Contacting sulfur yilde (II) with an anhydrous source of HBr or HCl yields the corresponding halomethyl ketone (III). Reaction of (III) with (IV) in the presence of a base yields (V). Cyclization of (V) in the presence of a perfluoro acid anhydride and an organic base produces (VI). Removal of the protecting group and contacting the deprotected compound with an acid yields a pharmaceutically acceptable salt of (VII). Reacting the pharmaceutically acceptable salt of (VII) with 2,2,2-trifluoroethylamine produces Compound 1.

Scheme III



wherein:

PG is a protecting group;

X is Br or Cl;

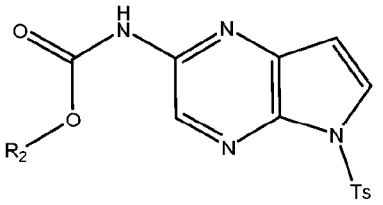
R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$;

R_2 is alkyl; and

Ts is tosyl.

[00252] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl. In another embodiment, the protecting group is carboxybenzyl.

[00253] In another embodiment, R_1 is $-OR_2$, and R_2 is methyl or ethyl. In such embodiments, the compound of formula (IV) is a compound of formula (IVa):

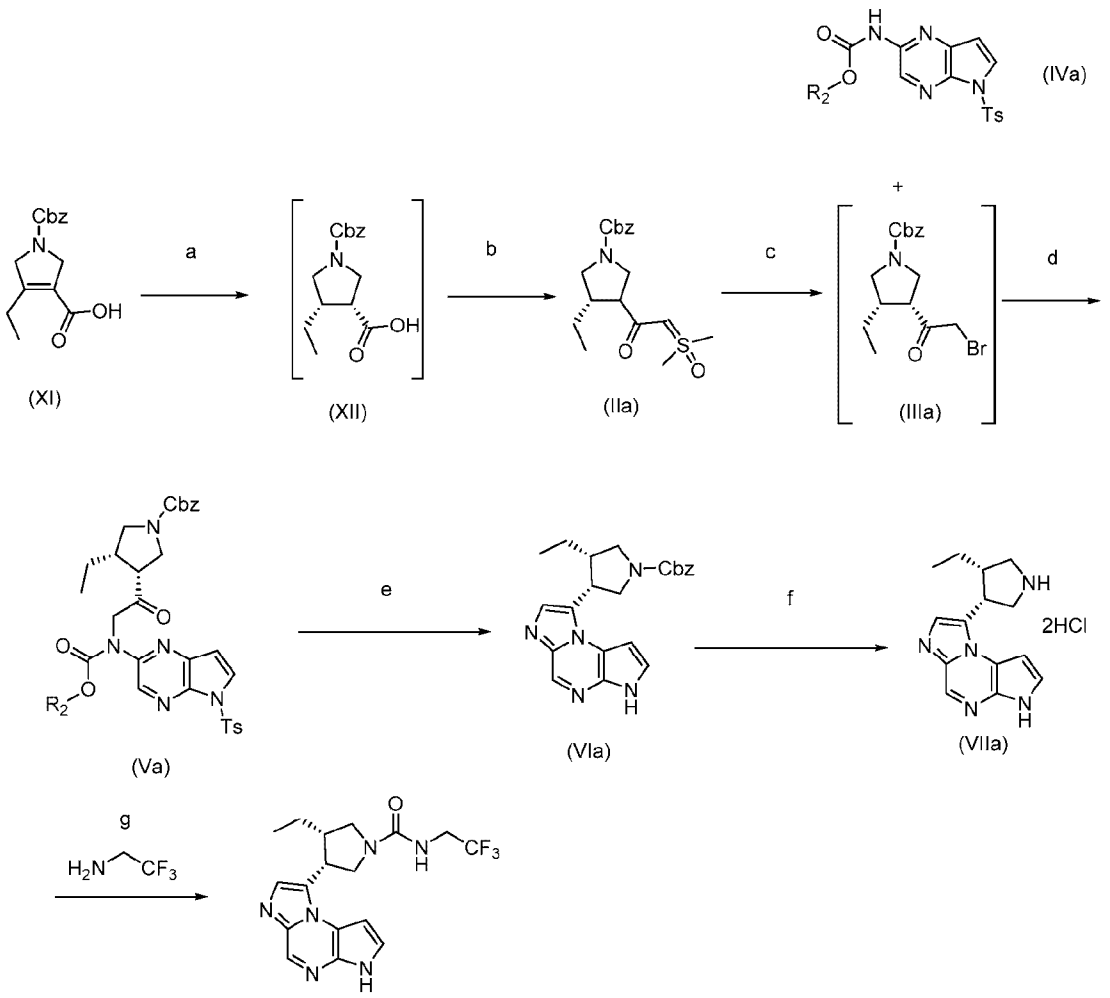


(IVa)

wherein R_2 is methyl or ethyl. It has surprisingly been discovered that when R_2 is ethyl or methyl, the compound of formula (V) and subsequent downstream compounds can be isolated as crystalline solids, which aids in purification of these intermediates. In contrast, previously known processes, which use compounds where R_2 is t-butyl, result in formation of compounds of formula (V) which are isolated as amorphous solids.

[00254] Another process for preparing Compound 1 is illustrated in Scheme IIIa. 1-((benzyloxy)carbonyl)-4-ethyl-2,5-dihydro-1H-pyrrole-3-carboxylic acid (XI) is hydrogenated to produce (XII). Reaction of (3R,4S)-1-((benzyloxy)carbonyl)-4-ethylpyrrolidine-3-carboxylate (XII) with trimethylsulfoxonium chloride gives sulfur yilde (IIa). Contacting sulfur yilde (IIa) with an anhydrous source of HBr yields the corresponding bromomethyl ketone (IIIa). Reaction of (IIIa) with alkyl 5-tosyl-5H-pyrrolo[2,3-b]pyrazine-2-ylcarbamate (IVa) in the presence of lithium *tert*-butoxide yields (Va). Cyclization of (Va) in the presence of a perfluoro acid anhydride and an organic base produces (VIa). Removal of the carboxybenzyl protecting group and contacting the deprotected compound with hydrochloric acid yields the pharmaceutically acceptable salt (VIIa). Reacting the pharmaceutically acceptable salt (VIIa) with 2,2,2-trifluoroethylamine produces Compound 1.

Scheme IIIa



wherein:

Cbz is carboxyben zyl;

Ts is tosyl; and

R_2 is methyl or ethyl.

[00255] In step (a) of Schemes III and IIIa, (XIa) or (XI) (which may be prepared as described in Scheme V) is converted to (I) or (XII), respectively. In particular, in step (a), compound (XI) or (XIa) may be contacted with a catalyst, such as a ruthenium catalyst. Any catalyst comprising a chiral phosphine may be used. One particular example of a suitable catalyst is diacetato[(S)-(-)5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II)

(i.e., (S)-Segphos $Ru(OAc)_2$). Suitable solvents for use in step (a) include, but are not limited to, methanol, triethylamine, and combinations thereof.

[00256] In particular, in certain embodiments, a solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 30°C to about 100°C for from about 1 hour to about 18 hours. In one embodiment, the solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 580 psi. In one embodiment, the solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 200 psi gauge (psig). In one embodiment, the solution of (XI) or (XIa) and the catalyst in solvent is hydrogenated at about 80°C for from about 1 hour to about 8 hours, or for about 2 hours, or for about 4 hours. Upon completion, the reaction mixture is cooled to room temperature, filtered, and concentrated. In one particular embodiment, step (a) of Schemes III and IIIa is performed as described in Step A of Example 4.

[00257] The reaction in step (b) of Schemes III and IIIa, is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. The step (b) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide.

[00258] More particularly, in certain embodiments, a suspension of trimethylsulfoxonium chloride, strong base, and solvent is heated (e.g., to about 35°C to about 65°C, or to about 45°C) for about 30 minutes to about 8 hours, or for about 1 hour, followed by cooling. In one embodiment, the suspension is cooled to a temperature of about -1°C or less, or to about -5°C or less. In some embodiments, the concentrated filtrate from step (a) is diluted with a suitable solvent (e.g., tetrahydrofuran), and to this solution is slowly added (e.g., over 30 minutes to 1 hour, or over 30 minutes) CDI. The resulting mixture is stirred at room temperature for 30 minutes to 12 hours, and typically for about 1 hour. The resulting solution is slowly added (e.g., over 15 minutes to 1 hour, or over 1 hour) to the suspension of the trimethylsulfoxonium chloride, strong base, and solvent, while maintaining the internal temperature below -1°C. In embodiments, the reaction may be stirred for about 30 minutes to about 8 hours, or for about 1 hour at a temperature of below about -1°C, or at about -5°C. In another embodiment, the reaction is quenched and the resulting compound of formula (II) or (IIa) is isolated prior to step (c). In one particular embodiment, step (b) of Schemes III or IIIa is performed as described in Step A of Example 4.

[00259] Steps (a) and (b) of Schemes III and IIIa advantageously allow for preparation of a protected (3R,4S)-4-ethylpyrrolidine-3-carboxylic acid without formation and isolation of the naphthalenethane amine salt (Ia) or the dicyclohexylamine salt (Ib), or isolation of (I) or (XI).

[00260] In step (c) of Schemes III and IIIa, a compound of formula (II) or (IIa) is contacted with an anhydrous source of HBr or HCl to form a compound of formula (III) or (IIIa), respectively. In particular, the anhydrous source of HBR or HCl comprises no more than 0.2% water (by volume), or no more than about 0.15% water (by volume). The reaction of step (c) may be conducted in any suitable solvent including, tetrahydrofuran.

[00261] More particularly, in certain embodiments, (II) or (IIa) is combined with the HBr or HCl in a suitable solvent. In one embodiment, the solvents are tetrahydrofuran and acetic acid. In one embodiment, the solvent comprises no more than 0.2 % water (by volume). In one embodiment, (II) or (IIa) is combined with a solvent (e.g., THF) and a solution of HBr in HOAc. The resulting mixture is warmed to about 35°C to about 65°C, or about 40°C and agitated. In one embodiment, the mixture is agitated for about 4 to about 12 hours, or for about 5 hours. In one embodiment, the mixture is warmed to about 40°C and agitated (e.g., stirred) for about 5 hours. In one embodiment, the mixture is cooled to room temperature (e.g., around 20°C) and distilled, followed by washing. In one particular embodiment, the product (compound (III) or (IIIa)) is concentrated to dryness, and resuspended in a solvent (e.g., N,N-dimethylacetamide) to form a solution of (III) or (IIIa) for use in step (d). In one embodiment, step (c) of Schemes III or IIIa is performed as described in Step B of Example 4.

[00262] Step (c) advantageously produces the halomethyl ketone (III) or (IIIa) in higher purity than Scheme I or Ia.

[00263] In step (d) of Schemes III and IIIa, a compound of formula (III) or (IIIa) is reacted with a compound of formula (IV) or (IVa) (prepared as described herein). The step (d) reaction is conducted in the presence of a base, such as lithium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. In one embodiment, the base is lithium *tert*-butoxide. The reaction of step (d) may be conducted in any suitable solvent including, but not limited to dimethylacetamide, tetrahydrofuran, dichloromethane, ethyl acetate, heptanes, and combinations thereof.

[00264] More particularly, in certain embodiments, the base is slowly added (e.g., over about 30 minutes) to a cooled suspension of the compound of formula (IV) or (IVa) in a solvent. In one embodiment, the suspension of the compound of formula (IV) or (IVa) is cooled to about

0°C. The resulting solution is stirred for about 30 minutes to about 12 hours, or about 30 minutes, and cooled to about -20°C to about 0°C, or about -10°C. In one embodiment, the solution is stirred for about 30 minutes and cooled to about -20°C to about 0°C, or about -10°C. The halomethyl ketone solution prepared in step (c) is then slowly added (e.g., over about 1 hour), and the resulting mixture is agitated (e.g., stirred) for about 30 minutes to about 6 hours, or about 30 minutes, at a temperature of about -20°C to about 0°C, or about -10°C. In one embodiment, following addition of the step (c) solution, the resulting mixture is stirred for about 30 minutes at a temperature of about -10°C. In one embodiment, the reaction is quenched, and, in some embodiments, the resulting product (V) or (Va) is isolated prior to step (e). In one embodiment, step (d) of Schemes III and IIIa is performed as described in Step C of Example 4.

[00265] Steps (e)-(g) of Schemes III and IIIa may be conducted as described above for steps (d)-(f) of Scheme I, respectively.

[00266] In one embodiment, Compound 1 is prepared according to the process set forth in Scheme IIIa.

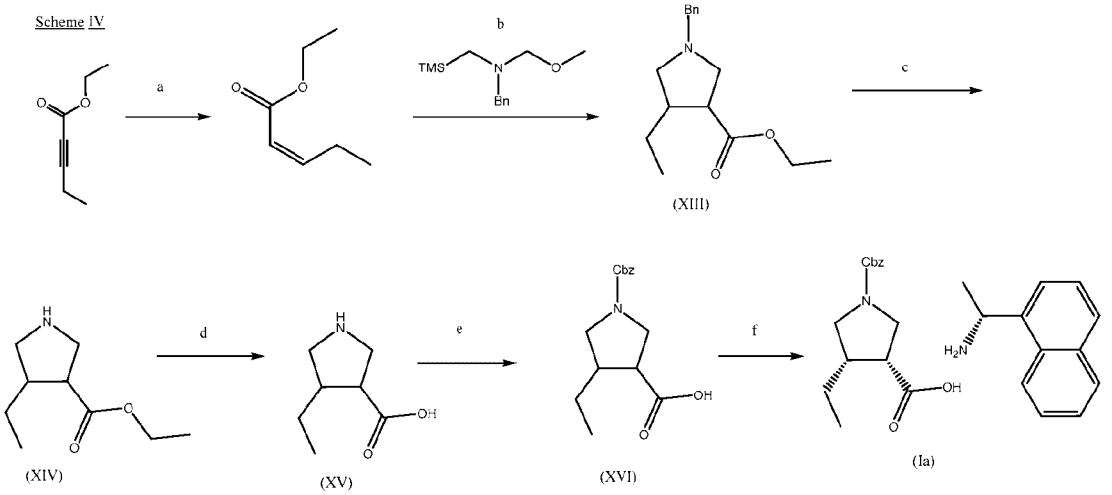
B. Preparation of compounds of formula (I), (Ia), (Ib), and (XIa)

[00267] The processes for preparing Compound 1 disclosed herein may use a compound of formula (I), or a pharmaceutically acceptable salt thereof, and/or a compound of formula (XI) or (XIa). In one embodiment, the processes use either the naphthalenethane amine salt of formula (Ia), or the dicyclohexylamine salt of formula (Ib). Compounds of formula (I) and (Ia) and their preparation are described in, for example, US 2013/0072470.. (Ia) can also be prepared as described in Scheme IV, set forth below. (Ib) can be prepared as described in Scheme V, set forth below. Compounds of formula (I) wherein PG is Cbz (i.e., compounds of formula (XII)) can be prepared using the procedure set forth in Scheme IV or V. Compounds of formula (XI) can be prepared using the procedure set forth in Scheme V. Other protecting groups may be substituted for Cbz using techniques known to those skilled in the art.

Formula (Ia)

[00268] The preparation of (Ia) has been previously described (*see, e.g.*, US 2013/0072470, Example 12.). One suitable process for preparing the naphthalenethane amine salt of the compound of formula (I) is illustrated in Scheme IV. Ethyl pent-2-ynoate is hydrogenated with a Lindlar catalyst to form (Z)-ethyl pent-2-enoate. The (Z)-ethyl pent-2-enoate is reacted with N-(methoxymethyl)-N-(trimethylsilyl

methyl)benzylamine to form (XIII). (XIII) is deprotected to form (XIV), followed by hydrolysis of (XIV) to form (XV). (XV) is reacted with N-(benzyloxycarbonyloxy) succinimide to form (XVI). The protected (XVI) is contacted with (R)-1-(naphthalene-1-yl)ethanamine to form (Ia).



wherein:

TMS is trimethylsilyl;

Cbz is carboxybenzyl; and

Bn is benzyl.

[00269] In step (a) of Scheme IV, ethyl pent-2-ynoate is hydrogenated with a Lindlar catalyst to form (Z)-ethyl pent-2-enoate. In particular, in certain embodiments, the ethyl pent-2-ynoate is added to a slurry of the Lindlar catalyst in solvent (e.g., THF) and organic base (e.g., pyridine). The reaction mixture is sparged with hydrogen (e.g., for about 15 hours). In one embodiment, upon reaction completion, the reaction mixture is filtered, and the (Z)-ethyl pent-2-enoate washed prior to step (b).

[00270] In step (b) of Scheme IV, the (Z)-ethyl pent-2-enoate is reacted with N-(methoxymethyl)-N-(trimethylsilyl methyl)benzylamine to form (XIII). In particular, trifluoroacetic acid (TFA) is added to a solution of the (Z)-ethyl pent-2-enoate and N-(methoxymethyl)-N-(trimethylsilyl methyl)benzylamine in solvent (e.g., dichloromethane (DCM)). After about 2 days, the reaction mixture is concentrated to provide (XIII).

[00271] In steps (c) and (d) of Scheme IV, (XIII) is deprotected to form (XIV), followed by hydrolysis of (XIV) to form (XV). (XIII) may be deprotected using any suitable means

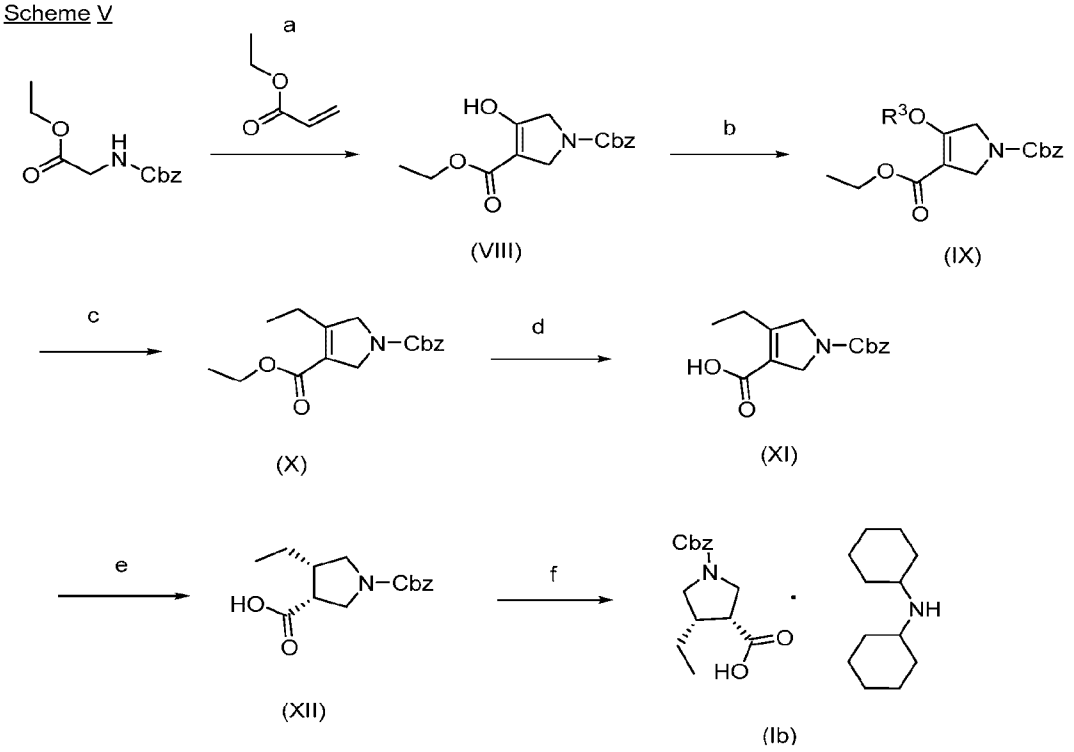
known in the art, including those set forth above for step (e) of Scheme I. In one embodiment, (XIII) is deprotected by contacting (XIII) with a catalyst (e.g., a palladium catalyst such as Pd/C or $Pd(OH_2)/C$) under hydrogen pressure. In one embodiment, the resulting mixture is filtered to provide (XIV). In step (d), (XIV) is contacted with an acid (e.g., HCl). In one embodiment, the reaction mixture is heated (e.g., to about 100 °C), typically for about 24 hours. The reaction mixture is cooled and concentrated. In step (e), the reaction mixture from step (d) containing (XV) is reacted with N-(benzyloxycarbonyloxy) succinimide (e.g., for about 15 hours) to form (XVI).

[00272] In step (f) of Scheme IV, (XVI) is contacted with (R)-1-(naphthalene-1-yl)ethanamine to form (Ia).

Formula (Ib)

[00273] In some embodiments, the present disclosure is directed to compound (Ib) and a process for preparing compound (Ib). A process for preparing the dicyclohexylamine salt of the compound of formula (I) is illustrated in Scheme V. Carboxybenzyl-glycine ethyl ester is reacted with ethyl acrylate to form (VIII). Protection of (VIII) yields (IX). Contacting (IX) with one of ethyl boronic acid, ethyl magnesium bromide, or ethyl zinc chloride in the presence of a catalyst results in (X). (X) is hydrolyzed to produce (XI), which is hydrogenated to produce (XII). (XII) is contacted with dicyclohexylamine to form (Ib).

Scheme V



wherein

Cbz is carboxybenzyl; and

R^3 is selected from the group consisting of CF_3SO_2-, CH_3SO_2-, and tosyl.

[00274] In step (a) of Scheme V, carboxybenzyl-glycine ethyl ester is reacted with ethyl acrylate to form (VIII). The step (a) reaction is conducted in the presence of a strong base. Suitable bases include, but are not limited to, sodium tert-butoxide, potassium tert-butoxide, and lithium tert-butoxide. In one embodiment, the strong base is sodium tert-butoxide. In one embodiment, the step (a) reaction is conducted in an organic solvent, such as tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, 2-methyl tetrahydrofuran, and the like, and combinations thereof.

[00275] In particular, in certain embodiments, the base is slowly added (e.g., over 1 hour) to a mixture of the carboxybenzyl-glycine ethyl ester and ethyl acrylate in solvent at about -5°C to about 20°C. In one embodiment, the base is slowly added (e.g., over 1 hour) to a mixture of the carboxybenzyl-glycine ethyl ester and ethyl acrylate in solvent at about 0°C. The resulting mixture is warmed to room temperature, and stirred overnight. In one embodiment, upon

completion, the reaction is quenched and the product crystallized. The product may optionally be isolated prior to step (b).

[00276] In step (b) of Scheme V, the compound of formula (VIII) is protected to form (IX). In one embodiment, the compound of formula (VIII) is reacted with a reagent selected from the group consisting of trifluoromethanesulfonic anhydride, methanesulfonyl chloride, and p-toluenesulfonyl chloride to form (IX). In one embodiment, the step (b) reaction is conducted in the presence of an organic base. Suitable organic bases include, but are not limited to, diisopropylethylamine (DIPEA), 4-dimethylamino pyridine (DMAP), triethylamine (TEA), pyridine, N-methylmorpholine (NMM), and combinations thereof. The step (b) reaction may be conducted in any suitable solvent including, but not limited to, triethylamine, N-methylmorpholine, pyridine, diisopropyl ether, and combinations thereof.

[00277] In particular, in certain embodiments, the trifluoromethanesulfonic anhydride, methanesulfonyl chloride, or p-toluenesulfonyl chloride is added to a mixture of (VIII) in solvent at about -5°C to about 20°C. In one embodiment, the trifluoromethanesulfonic anhydride, methanesulfonyl chloride, or p-toluenesulfonyl chloride is added to a mixture of (VIII) in solvent at a temperature of about 0°C. The organic base is subsequently slowly added (e.g., over about 30 minutes), and the mixture warmed to room temperature and stirred for about 30 minutes to about 18 hours. In one embodiment, the mixture is stirred for about 1 hour. Upon completion, the reaction is preferably quenched and the product washed. In some embodiments, a solution of (IX) in solvent is prepared and used directly in step (c).

[00278] In step (c) of Scheme V, (IX) is contacted with one of ethyl boronic acid, ethyl magnesium bromide, or ethyl zinc chloride in the presence of a catalyst to produce (X). Any suitable catalyst known in the art may be used. In certain embodiments, the catalyst is a palladium catalyst, such as $PdCl_2$(dppf). In some embodiments, the catalyst is a nickel catalyst, such as $Ni(acac)_2$. In some embodiments, the catalyst is an iron catalyst, and in particular a Fe(III) catalyst, such as $FeCl_3$ and $Fe(acac)_3$. Step (c) may be conducted in a buffer. Suitable buffers include, but are not limited to, potassium carbonate, sodium carbonate, potassium phosphate tribasic, and combinations thereof. Suitable solvents for use in step (c) include, but are not limited to, toluene, water, dioxane, tetrahydrofuran, and combinations thereof.

[00279] In particular, in certain embodiments, the ethyl boronic acid and buffer is added to the solution of (IX) in solvent prepared in step (b). A suitable catalyst may then be added, and the resulting mixture warmed to about 75°C to about 110°C, or about 85°C, and stirred for about 4 hours to about 18 hours, or about 6 hours. In one embodiment, the mixture is warmed to

about 85°C, and stirred for about 6 hours. Upon completion, the reaction mixture is cooled to room temperature, and the product filtered. In one embodiment, the product is isolated prior to step (d).

[00280] In step (d), (X) is hydrolyzed to produce (XI). (X) may be hydrolyzed using any suitable means known in the art. In one embodiment, (X) is contacted with an alkali metal hydroxide. The alkali metal hydroxide may be selected from the group consisting of sodium hydroxide and lithium hydroxide. In one embodiment, the alkali metal hydroxide is sodium hydroxide. Any suitable solvent may be used in the step (d) reaction including, but not limited to, tetrahydrofuran, water, dioxane, and combinations thereof.

[00281] In particular, in certain embodiments, the alkali metal hydroxide is added to a solution of (X) in solvent. The resulting mixture is warmed to about 20°C to about 65°C, and stirred for about 2 hours to about 18 hours. In one embodiment, the mixture is warmed to about 50°C, and stirred for about 2 hours to about 18 hours. In one embodiment, the mixture is stirred for about 7 hours. Upon completion, the mixture is cooled to room temperature, the pH adjusted to about 9, and the solvent removed. In one embodiment, the product is washed and isolated prior to step (e).

[00282] In steps (e) and (f) of Scheme V, (XI) is converted to (XII), and (XII) is contacted with dicyclohexylamine to form (Ib). In particular, in step (e) compound (XI) may be contacted with a catalyst, such as a ruthenium catalyst. Any catalyst comprising a chiral phosphine may be used. One particular example of a suitable catalyst is diacetato[(S)-(-)5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II) (i.e., (S)-Segphos $Ru(OAc)_2$). Suitable solvents for use in step (e) include, but are not limited to, methanol, triethylamine, and combinations thereof.

[00283] In particular, in certain embodiments, a solution of (XI) and the catalyst in solvent is hydrogenated at about 30°C to about 100°C for from about 1 hour to about 18 hours. In one embodiment, the solution of (XI) and the catalyst in solvent is hydrogenated at about 580 psi. In one embodiment, the solution of (XI) and the catalyst in solvent is hydrogenated at about 80°C for from about 1 hour to about 8 hours, or for about 2 hours. Upon completion, the reaction mixture is cooled to room temperature, filtered, and concentrated. In one embodiment, the product is washed, and transferred to a suitable solvent, such as acetonitrile, prior to step (f). In step (f), additional solvent (e.g., acetonitrile) and dicyclohexylamine are added, and the mixture is heated to about 50°C to about 80°C. In one embodiment, the mixture is heated to about 80°C. The resulting solution is cooled to room temperature and stirred for about 1 hour to

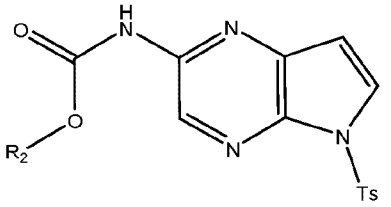
about 18 hours. In one embodiment, the mixture is cooled to room temperature and stirred for about 1 hour. The resulting product (Ib) may be isolated prior to use in preparation of Compound 1.

C. Intermediate Compounds

[00284] In some embodiments, the present disclosure is directed to intermediate compounds useful in the preparation of Compound 1, as well as to processes for preparing the intermediate compounds.

Formula (IVa)

[00285] In one embodiment, the present disclosure is directed to a compound of formula (IVa).

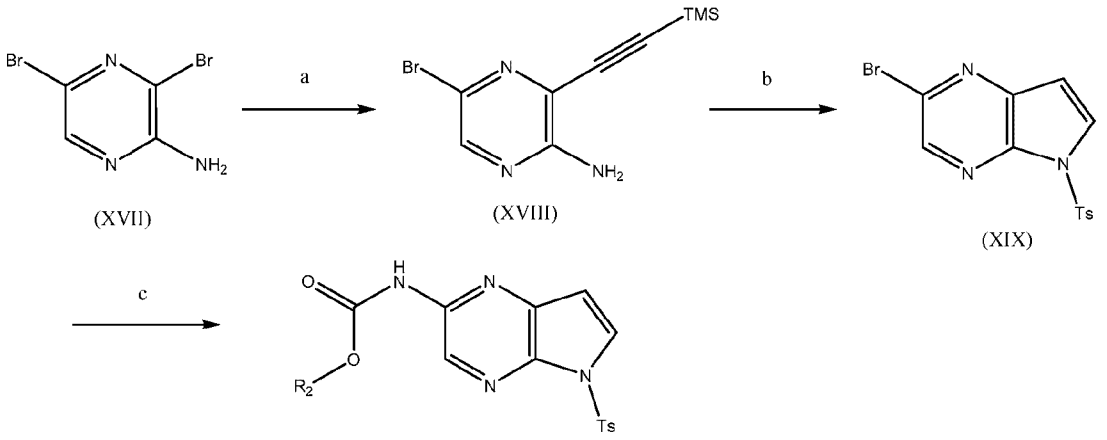

(IVa)

wherein R_2 and Ts are as defined above.

[00286] As discussed herein and as depicted in Schemes I, II, and III, compounds of formula (IVa) may be reacted with a compound of formula (III) or (IIIa) to produce a compound of formula (V) or (Va). Advantageously, the methyl or ethyl carbamate moiety present on the compound of formula (IVa) results in a crystalline product when the compound of formula (IVa) is reacted with a compound of formula (III) or (IIIa) in Schemes I, II, or III.

[00287] In another aspect, the present disclosure is directed to a process for preparing a compound of formula (IVa). One suitable process for preparing a compound of formula (IVa) is illustrated in Scheme VI. In particular, (XVII) is reacted with trimethylsilylacetylene in the presence of a catalyst to form (XVIII). (XVIII) is contacted with p-toluenesulfonyl chloride in the presence of a base to form (XIX). (XIX) is reacted with an ethyl or methyl carbamate in the presence of a catalyst and a ligand to form a compound of formula (IVa).

Scheme VI



(XVII) (XVIII) (XIX)

(IVa)

wherein:

R_2 is methyl or ethyl;

Ts is tosyl; and

TMS is trimethylsilyl.

[00288] In step (a) of Scheme VI, compound (XVII), which is commercially available, is reacted with trimethylsilylacetylene in the presence of a catalyst to form (XVIII). Any suitable catalyst known in the art may be used. In some embodiments, the catalyst is a palladium catalyst, such as bis(triphenylphosphine)palladium (II) dichloride ($PdCl_2(Ph_3P)_2$). Step (a) is typically conducted in the presence of copper (I) iodide (CuI). Any suitable solvent may be used in step (a), including, but not limited to, triethylamine.

[00289] In particular, in certain embodiments, the catalyst is added to a solution of (XVII) and CuI in solvent. The reaction mixture is cooled (e.g., to about -5 to 0°C), and a solution of the trimethylsilylacetylene in solvent is slowly added (e.g., over about 15 minutes). The reaction mixture is stirred at about -5 to 0°C (e.g., for about 1.5 hours), and allowed to warm to room temperature overnight. In one embodiment, the reaction mixture is filtered and washed, and the product isolated prior to step (b).

[00290] In step (b) of Scheme VI, (XVIII) is contacted with p-toluenesulfonyl chloride in the presence of a base to form (XIX). Suitable bases for use in step (b) include, but are not

limited to, potassium tert-butoxide, sodium hydride, and the like, and combinations thereof. Suitable solvents for use in step (b) include, but are not limited to, dimethylformamide.

[00291] In particular, in certain embodiments, the base is added to a solution of (XVIII) in solvent (e.g., at about 0°C). The p-toluenesulfonyl chloride is subsequently added, and the mixture is allowed to warm to room temperature. After reaction (e.g., for about 16 hours), the reaction mixture is poured into ice cold water, and the precipitate is collected. In one embodiment, the product is isolated and purified prior to step (c).

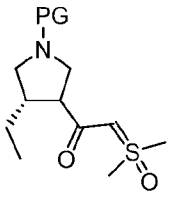
[00292] In step (c) of Scheme VI, (XIX) is reacted with an ethyl or methyl carbamate in the presence of a catalyst and a ligand to form a compound of formula (IVa). The reaction may be conducted in the presence of buffers, such as potassium carbonate, tetramethylammonium hydroxide, and the like. Any suitable catalyst known in the art may be used in step (c). In one embodiment, the catalyst is a palladium catalyst, such as palladium (II) acetate. Suitable ligands for use in step (c) include bidentate ligands, such as Xantphos. In one embodiment, the catalyst is palladium (II) acetate and the ligand is Xantphos. Suitable solvents for use in step (c) include, but are not limited to, dioxane, toluene, and tetrahydrofuran.

[00293] In particular, in certain embodiments, a degassed mixture of the catalyst, ligand, (XIX), carbamate, and the buffer in solvent is heated to about 75°C to about 110°C, or about 95°C, and stirred overnight. After completion, the reaction mixture is cooled to about 30°C to about 60°C. In one embodiment, the reaction mixture is cooled to about 50 °C. Optionally, additional solvent may be added, and the resulting solution filtered. In another embodiment, the product is washed and isolated prior to use in preparation of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00294] Compound (XVII) used in Scheme VI is commercially available. The preparation of compounds (XVIII) and (XIX) are also described in Example 1 of WO 2011/068881.

Formula (II)

[00295] In one aspect, the present disclosure is directed to a compound of formula (II):

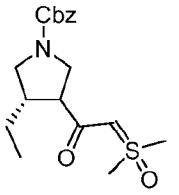


(II)

wherein PG is a protecting group.

[00296] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl.

[00297] In one preferred embodiment, the protecting group is carboxybenzyl, and the compound of formula (II) is compound (IIa):

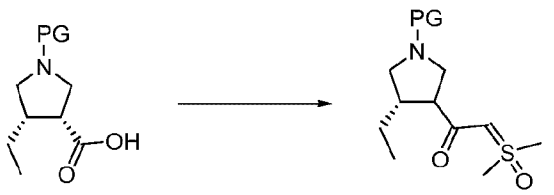


(IIa)

wherein Cbz is carboxybenzyl.

[00298] In another aspect, the present disclosure is directed to a process for preparing a compound of formula (II) or (IIa). One process for preparing a compound of formula (II) or (IIa) is illustrated in Scheme VII. In Scheme VII, a compound of formula (I) or a pharmaceutically acceptable salt thereof is reacted with trimethylsulfoxonium chloride to form a compound of formula (II). In one particular embodiment, the pharmaceutically acceptable salt is a compound of formula (Ib).

Scheme VII



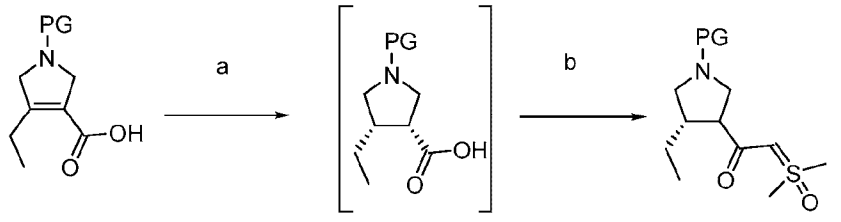
(I) (II)

wherein PG is a protecting group as defined herein.

[00299] The reaction of Scheme VII is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. The Scheme VII reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide. In one embodiment, the reaction of Scheme VII is conducted under the conditions described above for step (a) of Scheme I.

[00300] Another process for preparing a compound of formula (II) or (IIa) is illustrated in Scheme VIII. In step (a) of Scheme VIII, a compound of formula (XIa) is hydrogenated to a compound of formula (I), and in step (b) of Scheme VIII, the compound of formula (I) is reacted with trimethylsulfoxonium chloride to form a compound of formula (II).

Scheme VIII



(XIa) (I) (II)

wherein PG is a protecting group as defined herein.

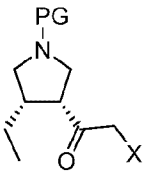
[00301] In step (a) of Scheme VIII, the compound of formula (XIa) may be contacted with a catalyst, such as a ruthenium catalyst. Any catalyst comprising a chiral phosphine may be used. One particular example of a suitable catalyst is diacetato[(S)-(-)5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II) (i.e., (S)-Segphos $Ru(OAc)_2$).

Suitable solvents for use in step (a) include, but are not limited to, methanol, triethylamine, and combinations thereof. In one embodiment, the reaction of step (a) of Scheme VIII is conducted under the conditions described above for step (a) of Scheme III.

[00302] The reaction in step (b) of Scheme VIII is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. The step (b) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide. In one embodiment, the reaction of step (b) of Scheme VIII is conducted under the conditions described above for step (b) of Scheme III.

Formula (III)

[00303] In another embodiment, the present disclosure is directed to a process for preparing a compound of formula (III):

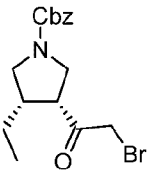


(III)

wherein PG is a protecting group, and X is Br or Cl.

[00304] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl.

[00305] In one preferred embodiment, the protecting group is carboxybenzyl and X is Br, and the compound of formula (III) is compound (IIIa)

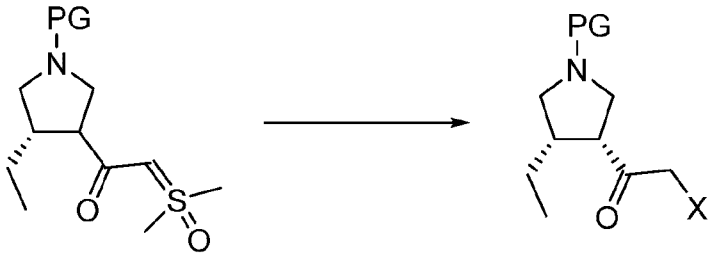


(IIIa)

wherein Cbz is carboxybenzyl.

[00306] One process for preparing a compound of formula (III) or (IIIa) is illustrated in Scheme IX.

Scheme IX



(II) (III)

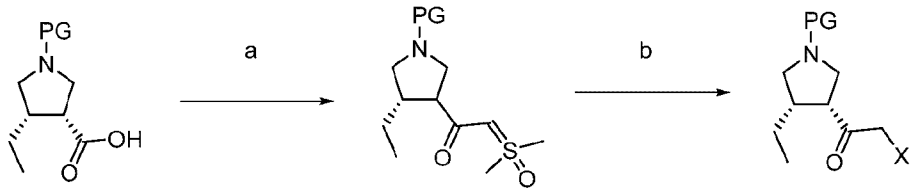
wherein PG and X are as defined herein.

[00307] Referring to Scheme IX, in one embodiment, a compound of formula (II) is contacted with LiX and a sulfonic acid to form a compound of formula (III). In this embodiment, the sulfonic acid is selected from the group consisting of methanesulfonic acid and p-toluenesulfonic acid. In one embodiment, the sulfonic acid is p-toluenesulfonic acid. LiX may be selected from lithium bromide and lithium chloride. In one embodiment, LiX is lithium bromide. In one embodiment, the reaction is conducted in lithium bromide and p-toluensulfonic acid. The reaction may be conducted in any suitable solvent including, but not limited to tetrahydrofuran, ethyl acetate, heptanes, ethanol, water, and combinations thereof. In one embodiment, the reaction of Scheme XI is conducted under the conditions described above for step (b) of Scheme I.

[00308] Referring to Scheme IX, in an alternate embodiment, the compound of formula (II) is contacted with an anhydrous source of HBr or HCl to form the compound of formula (III). The reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, ethyl acetate, acetic acid, N,N-dimethylacetamide, heptanes, and combinations thereof. In one embodiment, the reaction of Scheme IX is conducted under the conditions described above for step (c) of Scheme III.

[00309] In some embodiments, the process for preparing a compound of formula (III) or (IIIa) may further comprise preparing a compound of formula (II). One such process is illustrated in Scheme X.

Scheme X



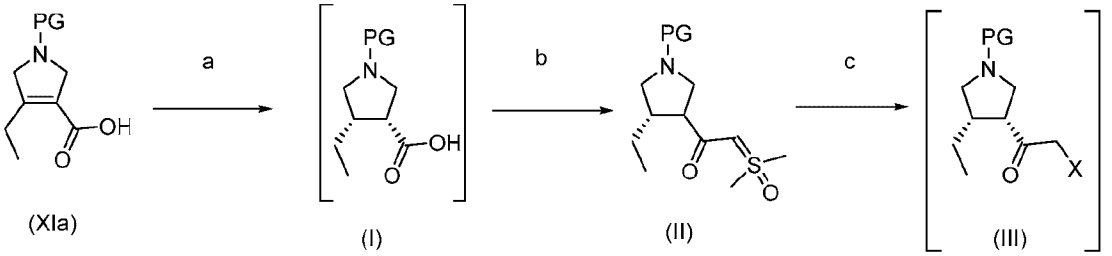
(I) (II) (III)

wherein PG and X are as defined above.

[00310] In Scheme X, a compound of formula (I) or a pharmaceutically acceptable salt thereof is reacted with trimethylsulfoxonium chloride in the presence of carbonyldiimidazole and a strong base (e.g., potassium tert-butoxide, sodium tert-butoxide, and combinations thereof) to form a compound of formula (II). The compound of formula (II) is then contacted with LiX and a sulfonic acid to form a compound of formula (III), as described above in Scheme IX. In one embodiment, step (a) of Scheme X is conducted under the conditions described above for step (a) of Scheme I. In one embodiment, the protecting group is carboxybenzyl, and the compound of formula (II) is compound (IIa). In another embodiment, in step (a) of Scheme X, a pharmaceutically acceptable salt of a compound of formula (I) is reacted with trimethylsulfoxonium chloride to form a compound of formula (II). In one embodiment, the salt is (Ia) or (Ib).

[00311] In some embodiments, the process for preparing a compound of formula (III) or (IIIa) may further comprise preparing a compound of Formula (I) and (II). One such process is illustrated in Scheme XI.

Scheme XI



(XIa) (I) (II) (III)

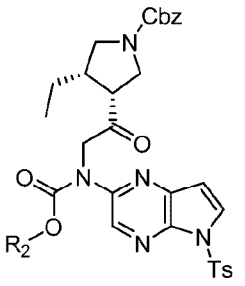
wherein PG and X are as defined above.

[00312] In step (a) of Scheme XI, a compound of formula (XIa) is hydrogenated to a compound of formula (I), and in step (b), the compound of formula (I) is reacted with trimethylsulfoxonium chloride in the presence of CDI and a strong base (e.g., KOtBu, NatOBu,

and combinations thereof) to form a compound of formula (II). The compound of formula (II) is then contacted with an anhydrous source of HBr or HCl to form the compound of formula (III), as described above for Scheme IX. In one embodiment, the protecting group is carboxybenzyl, and the compound of formula (XIa), (I), and (II) is compound (XI), (XII), and (IIa), respectively. In one embodiment, step (a), step (b), and step (c) of Scheme XI are conducted under the conditions described above for step (a), step (b), and step (c) of Scheme III, respectively.

Formulae (V) and (Va)

[00313] In another embodiment, the present disclosure is directed to a compound of formula (Va):

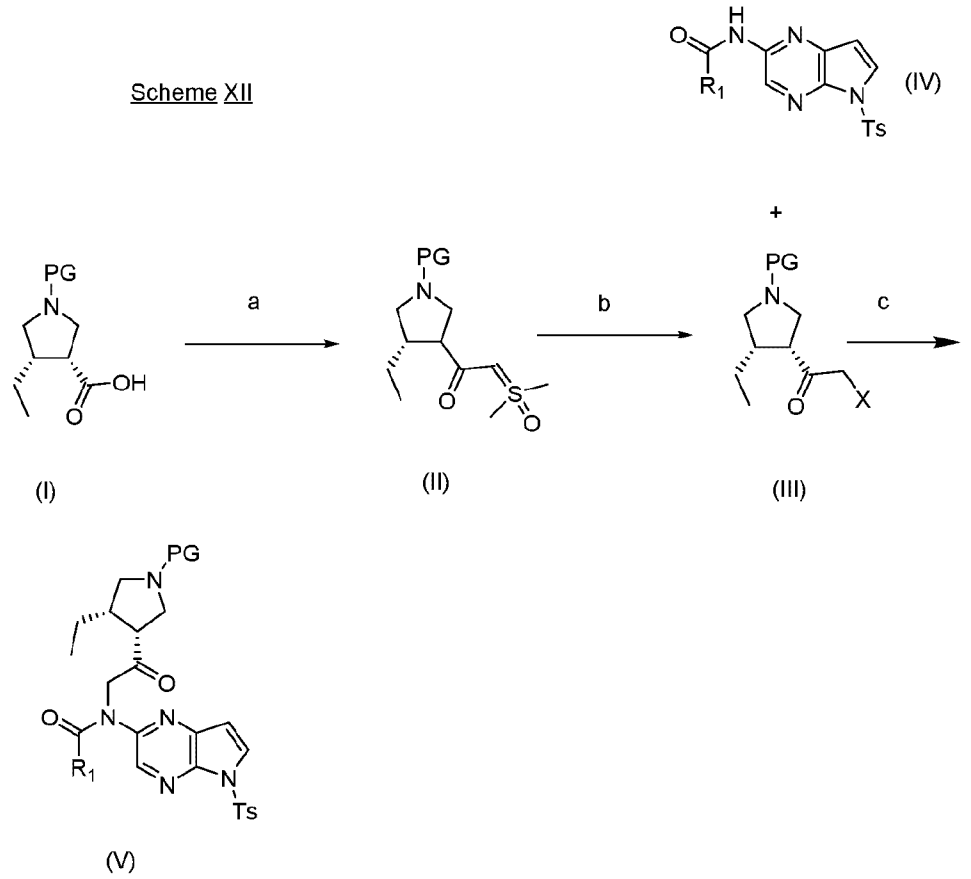


(Va)

wherein R_2, Cbz, and Ts are as defined above.

[00314] In another aspect, the present disclosure is directed to a process for preparing a compound of formula (V) or (Va). One process for preparing a compound of formula (V) or (Va) is illustrated in Scheme XII. In Scheme XII, a compound of formula (I) or a pharmaceutically acceptable salt thereof is reacted with trimethylsulfoxonium chloride to form a compound of formula (II). Contacting the compound of formula (II) with LiX and a sulfonic acid yields the corresponding halomethyl ketone (III). Reaction of a compound of formula (III) with a compound of formula (IV) in the presence of a base yields a compound of formula (V).

Scheme XII



wherein PG, Ts, R_1, and X are as defined above.

[00315] The protecting group may be any suitable protecting group known in the art. In some embodiments, the protecting group is selected from the group consisting of carboxybenzyl, *p*-methoxybenzyl carbonyl, benzyl, *p*-methoxybenzyl, and 3,4-dimethoxyenzyl.

[00316] In one embodiment, the protecting group is carboxybenzyl, and the compound is a compound of formula (Va). In one embodiment, the protecting group is carboxybenzyl, and X is Br.

[00317] In one embodiment, R_1 is $-OR_2$, and R_2 is methyl or ethyl. In such embodiments, the compound of formula (IV) is a compound of formula (IVa).

[00318] In certain embodiments, a pharmaceutically acceptable salt of a compound of formula (I) is used in the reaction of step (a) of Scheme XII. In one embodiment, the pharmaceutically acceptable salt of the compound of formula (I) is selected from the group consisting of the naphthalenethane amine salt (Ia) and the dicyclohexylamine salt (Ib).

[00319] The reaction in step (a) of Scheme XII is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. The step (a) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide.

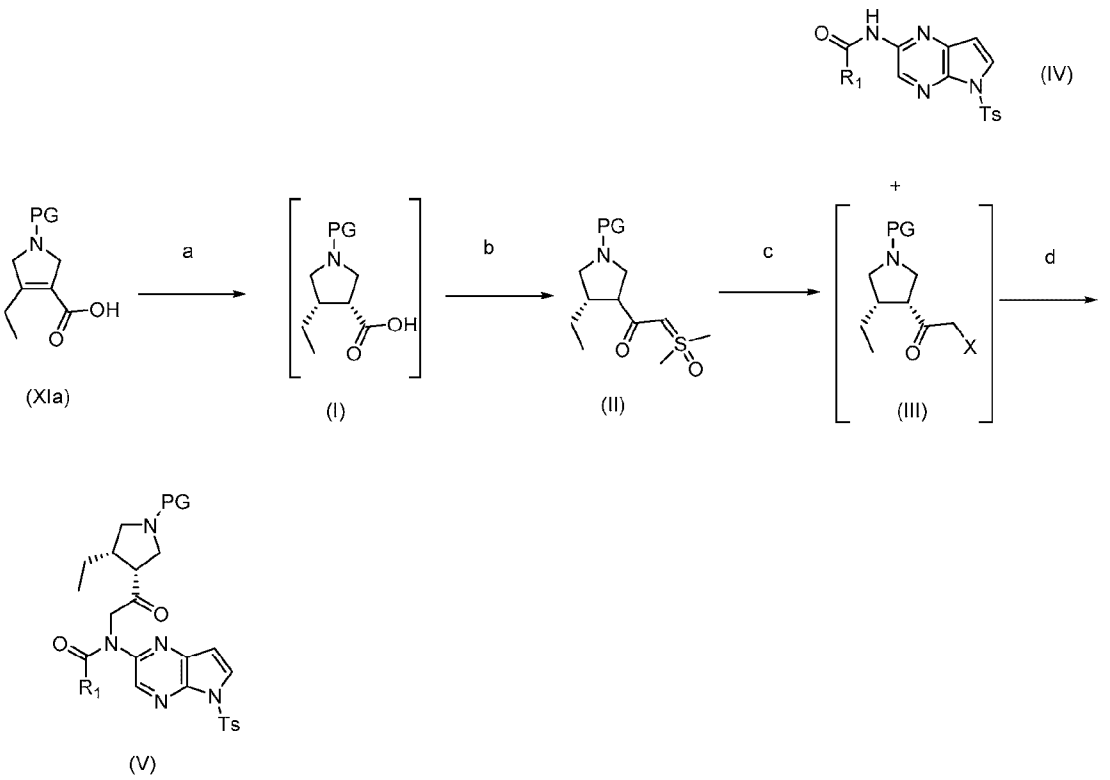
[00320] In step (b) of Scheme XII, a compound of formula (II) or (IIa) is contacted with LiX and a sulfonic acid to form a compound of formula (III) or (IIIa), respectively. In one embodiment, the sulfonic acid is selected from the group consisting of methanesulfonic acid and p-toluenesulfonic acid. In one embodiment, the sulfonic acid is p-toluenesulfonic acid. LiX may be selected from lithium bromide and lithium chloride. In one embodiment, LiX is lithium bromide. In one embodiment, the reaction is conducted in lithium bromide and p-toluensulfonic acid. The reaction of step (b) may be conducted in any suitable solvent including, but not limited to tetrahydrofuran, ethyl acetate, heptanes, ethanol, water, and combinations thereof.

[00321] In step (c) of Scheme XII, a compound of formula (III) or (IIIa) is reacted with a compound of formula (IV) or (IVa) (prepared as described herein). The step (c) reaction is conducted in the presence of a base, such as lithium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. In one embodiment, the base is lithium *tert*-butoxide. The reaction of step (c) may be conducted in any suitable solvent including, but not limited to dimethylacetamide, tetrahydrofuran, dichloromethane, ethyl acetate, heptanes, and combinations thereof.

[00322] In one embodiment, steps (a), (b), and (c) of Scheme XII are conducted under the conditions set forth herein for the corresponding step of Scheme I.

[00323] In another aspect, the present disclosure is directed to an alternate process for preparing a compound of formula (V) or (Va). One process for preparing a compound of formula (V) or (Va) is illustrated in Scheme XIII. In Scheme XIII, a compound of formula (XIa) is hydrogenated to a compound of formula (I), and the compound of formula (I) is reacted with trimethylsulfoxonium chloride to form a compound of formula (II). Contacting the compound of formula (II) with an anhydrous source of HBr or HCl yields the corresponding halomethyl ketone (III). Reaction of a compound of formula (III) with a compound of formula (IV) in the presence of a base yields a compound of formula (V).

Scheme XIII



wherein PG, Ts, R_1, and X are as defined above.

[00324] The protecting group may be any suitable protecting group, such as described herein. In one embodiment, the protecting group is carboxybenzyl, and the compound of formula (XIa), (I), (II), (III), (IV), and (V) is compound (XI), (XII), (IIa), (IIIa), (IVa), and (Va), respectively. In one embodiment, the protecting group is carboxybenzyl, and X is Br. In one embodiment, R_1 is $-OR_2$ and R_2 is methyl or ethyl. In such embodiments, the compound of formula (IV) is a compound of formula (IVa).

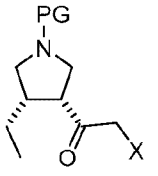
[00325] In step (a) of Scheme XIII, the compound of formula (XIa) may be contacted with a catalyst, such as a ruthenium catalyst. Any catalyst comprising a chiral phosphine may be used. One particular example of a suitable catalyst is diacetato[(S)-(-)5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II) (i.e., (S)-Segphos $Ru(OAc)_2$). Suitable solvents for use in step (a) include, but are not limited to, methanol, triethylamine, and combinations thereof. In one embodiment, the reaction of step (a) of Scheme XIII is conducted under the conditions described above for step (a) of Scheme III.

[00326] The reaction in step (b) of Scheme XIII is generally accomplished in the presence of a coupling agent, such as carbonyldiimidazole (CDI), and a strong base. The strong base may be, for example, potassium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. The step (b) reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, water, and methyl tert-butyl ether. In one embodiment, the reaction is conducted in the presence of carbonyldiimidazole and potassium *tert*-butoxide. In one embodiment, the reaction of step (b) of Scheme XIII is conducted under the conditions described above for step (b) of Scheme III.

[00327] In step (c) of Scheme XIII, the compound of formula (II) is contacted with an anhydrous source of HBr or HCl to form the compound of formula (III). The reaction may be conducted in any suitable solvent including, but not limited to, tetrahydrofuran, ethyl acetate, acetic acid, N,N-dimethylacetamide, heptanes, and combinations thereof. In one embodiment, the reaction of step (c) of Scheme XIII is conducted under the conditions described above for step (c) of Scheme III.

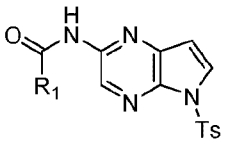
[00328] In step (d) of Scheme XIII, the compound of formula (III) is reacted with a compound of formula (IV) or (IVa) (prepared as described herein). The step (d) reaction is conducted in the presence of a base, such as lithium *tert*-butoxide, sodium *tert*-butoxide, or combinations thereof. In one embodiment, the base is lithium *tert*-butoxide. The reaction of step (d) may be conducted in any suitable solvent including, but not limited to dimethylacetamide, tetrahydrofuran, dichloromethane, ethyl acetate, heptanes, and combinations thereof. In one embodiment, the reaction of step (d) of Scheme XIII is conducted under the conditions described above for step (d) of Scheme III.

[00329] As discussed herein, it has surprisingly been discovered that when R_1 is $-OR_2$, and R_2 is ethyl or methyl, the compound of formula (V) and subsequent downstream compounds can be isolated as crystalline solids, which aids in purification of these intermediates. Thus, in another aspect, the present disclosure is directed to a process for preparing a crystalline compound of formula (V). The process comprises a) reacting a compound of formula (III):



(III)

with a compound of formula (IV):

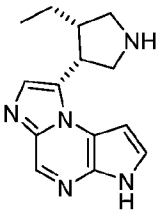


(IV)

to produce the compound of formula (V); wherein: PG is a protecting group; X is Br or Cl; R_1 is–OR_2; R_2 is methyl or ethyl; and Ts is tosyl. In one embodiment, the process is conducted under the conditions set forth above for step c) in Scheme XII or step (d) in Scheme XIII.

Formula (VII)

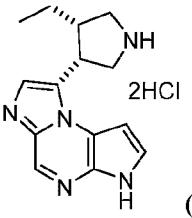
[00330] In another embodiment, the present disclosure is directed to compound (VII):



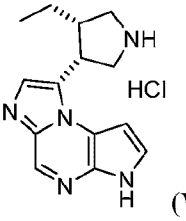
(VII)

[00331] or a pharmaceutically acceptable salt thereof.

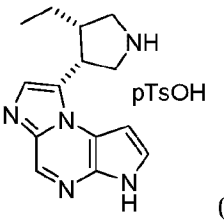
[00332] In one embodiment, the pharmaceutically acceptable salt of (VII) is selected from the group consisting of (VIIa), (VIIb), and (VIIc):



(VIIa),



(VIIb),



(VIIc).

[00333] In some embodiments, any of the processes for preparing (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide that are disclosed herein may further comprise forming one of the solid state forms described herein in Section III.

III. Solid State Forms

[00334] The present disclosure also relates to solid state forms of Compound 1. As with all pharmaceutical compounds and compositions, the chemical and physical properties of Compound 1 are important in its commercial development. These properties include, but are not limited to: (1) packing properties such as molar volume, bulk density and hygroscopicity, (2) thermodynamic properties such as melting temperature, vapor pressure and solubility, (3) kinetic properties such as dissolution rate and stability (including stability at ambient conditions, especially to moisture and under storage conditions), (4) surface properties such as surface area, wettability, interfacial tension and shape, (5) mechanical properties such as hardness, tensile strength, compactibility, handling, flow and blend; and (6) filtration properties. These properties can affect, for example, the processing and storage of the compound and pharmaceutical compositions comprising the compound.

[00335] Solid state forms of Compound 1 that improve upon one or more of these properties relative to other solid state forms of the compound are desirable. Isolating pharmaceutically acceptable solid state forms of the compound that can be manufactured and formulated on a commercial-scale has been a challenge.

[00336] The Amorphous Freebase form of Compound 1 generally has greater solubility, and increased bioavailability relative to most of the corresponding crystalline forms of the compound. The Amorphous Freebase also has acceptable chemical stability. However, it is hygroscopic, and environmental controls potentially are required to ensure appropriate control of potency and water content during storage, dispensing, and handling of the Amorphous Freebase. In addition, the Amorphous Freebase exhibits an oiling-out limit close to the solubility curve during manufacturing.

[00337] Crystalline Hydrochloride Solvate Form AA, crystalline Hydrochloride Solvate Form BB, and crystalline Hydrochloride Solvate Form CC generally convert to an amorphous hydrochloride upon ambient drying. The resulting amorphous hydrochloride is hygroscopic. Yields obtained for each of the crystalline hydrochlorides generally have been low. Hydrochloride Solvate Form AA, Hydrochloride Solvate Form BB, and Hydrochloride Solvate form CC may not be suitable for large scale manufacturing.

[00338] The crystalline L-Maleate forms generally may be less chemically stable than the Amorphous Freebase, the Freebase Hydrate Form C, and the Tartrate Hydrate, and may not exhibit pharmaceutically acceptable stability for use as an active ingredient in a pharmaceutical dosage form.

[00339] The Tartrate Hydrate form has acceptable chemical stability, high solubility, generally good impurity rejection during isolation and is not hygroscopic. However, the Tartrate Hydrate presented challenges because of lack of physical stability which also impacted manufacturing. The Tartrate Hydrate dehydrated into Amorphous at low relative humidity and high temperature, e.g., <10% RH at 25°C. Shearing and compression potentially cause conversion to the amorphous tartrate, and therefore it is not suitable for compressing into tablet form. Additionally, the filter cake solidified during drying, resulting in the need for additional controls during drying.

[00340] Freebase Hydrate Form B has been manufactured on a large scale without the need for labor-intensive and expensive techniques such as spray-drying. It also provided for appropriate control of the bulk properties of the Amorphous Freebase. However, the Amorphous Freebase exhibited poor impurity rejection when isolated via Freebase Hydrate Form B, and required a dry environment for storage and control of relative humidity during manufacturing and packaging.

[00341] The Freebase Hydrate Form B was not physically stable. It desolvated (or dehydrated) and converted to the Amorphous Freebase upon drying. Although the Freebase Hydrate Form B generally did not exhibit pharmaceutically acceptable physical stability for use as an active ingredient in a pharmaceutical dosage form, it may be a useful intermediate in the preparation of other solid state forms such as the Amorphous Freebase.

[00342] After years of experimentation, Freebase Hydrate Form C was serendipitously discovered when attempting to scale up the Amorphous Freebase. It offers many surprising and

superior properties over the Amorphous Freebase, the Tartrate Hydrate and other forms of Compound 1.

[00343] Freebase Hydrate Form C generally exhibits excellent chemical stability, physical stability, and solid state properties, including low hygroscopicity and prismatic morphology. Freebase Hydrate Form C has improved bulk properties such as powder flow, bulk density, which are beneficial in the formulation process. In addition, Freebase Hydrate Form C offers at least the following unexpected advantages over the other forms: 1) efficient purification is obtained since there is no need to use the tartrate crystal; 2) the seeding step is straightforward since Freebase Hydrate Form C can be stored at normal conditions; 3) the drying step can be carried out at normal conditions with standard equipment since no dehydration occurs up to around 110°C; 4) Freebase Hydrate Form C can be crystallized in different particle sizes. Large-scale manufacture of the Freebase Hydrate Form C is relatively straightforward with minimal scaling, good yield, good impurity rejection, fast filtration, conventional drying, and minimal milling issues. In addition, Freebase Hydrate Form C can be grown into different particle sizes.

[00344] Freebase Anhydrate Form D can be manufactured only when the water content of the crystallization solvent is low, and will convert to Freebase Hydrate Form C in solutions at high water content. The manufacture of Freebase Anhydrate Form D thus requires strict control of water content. Freebase Anhydrate Form D is slow to crystallize, and difficult to manufacture in higher yield. This anhydrate is reversibly hygroscopic (up to 1.8% water at 90% RH at 25°C), and is metastable relative to Freebase Hydrate Form C at typical environmental conditions (e.g., above 2.4% RH at 23°C) used during storage for downstream processing. Freebase Hydrate Form C will convert to Freebase Anhydrate Form D in a solution of ethyl acetate with low water content.

[00345] The sections below discuss solid state forms that have been identified and selected properties of those solid state forms.

A. Amorphous Freebase

[00346] In one embodiment, the solid state form is amorphous Compound 1 (the "Amorphous Freebase"). In one aspect, the Amorphous Freebase comprises less than about 13% by weight water. In another aspect, the Amorphous Freebase comprises less than about 12% by weight water. In another aspect, the Amorphous Freebase comprises less than about 10% by weight water. In another aspect, the Amorphous Freebase comprises less than about 9%

by weight water. In another aspect, the Amorphous Freebase comprises less than about 8% by weight water. In another aspect, the Amorphous Freebase comprises less than about 7% by weight water. In another aspect, the Amorphous Freebase comprises less than about 6% by weight water. In another aspect, the Amorphous Freebase comprises less than about 5% by weight water. In another aspect, the Amorphous Freebase comprises less than about 4% by weight water. In another aspect, the Amorphous Freebase comprises less than about 3% by weight water. In another aspect, the Amorphous Freebase comprises less than about 2% by weight water. In another aspect, the Amorphous Freebase comprises less than about 1 % by weight water. In another aspect, the Amorphous Freebase has a glass transition temperature onset at about 119°C. In another aspect, the Amorphous Freebase has a glass transition temperature midpoint at about 122°C. In another aspect, the Amorphous Freebase has a glass transition temperature onset at about 119°C and a glass transition temperature midpoint at about 122°C. The Amorphous Freebase is further described in the Examples of the application.

[00347] The Amorphous Freebase generally has greater solubility, and increased bioavailability, relative to the corresponding crystalline forms of the compound. The Amorphous Freebase also has acceptable chemical stability. For example, when chemical stability was evaluated in closed vials at 30°C/65% relative humidity and 40°C/75% relative humidity over 12 weeks, and at 50°C/75% relative humidity over 6 weeks, no degradation of the Amorphous Freebase was observed in the closed vials under any of those conditions. In addition, the Amorphous Freebase exhibits acceptable stability to light and peroxide. The Amorphous Freebase, however, is hygroscopic and can comprise as much as 12% by weight water at 25°C/90% relative humidity. Environmental controls potentially are required to ensure appropriate control of potency and water content during storage, dispensing, and handling of the Amorphous Freebase.

[00348] The Amorphous Freebase can be prepared, for example, using anti-solvent crystallization to prepare the Freebase Solvate Form A or Freebase Hydrate Form B (described below) followed by dehydration or desolvation to yield the Amorphous Freebase. This crystallization/dehydration/desolvation method allows for the large-scale manufacture of the Amorphous Freebase without the need for labor-intensive and expensive techniques such as spray-drying. It also provides for appropriate control of the bulk properties of the Amorphous Freebase (*i.e.*, particle size, flow properties *etc.*). When the Amorphous Freebase is prepared by desolvation of the Freebase Solvate Form A or dehydration of the Freebase Hydrate Form B, the Amorphous Freebase generally retains the morphology of the Freebase Solvate Form A or

Freebase Hydrate Form B (*i.e.*, blades with hexagonal crystal faces when prepared by dehydration of Freebase Hydrate Form B, or irregular when desolvated from Freebase Solvate Form A).

[00349] The process volumes required for crystallization during the large-scale manufacture of the Freebase Solvate Form A or Freebase Hydrate Form B generally are within conventional processing volumes, but impurity rejection potentially may be lower than desired. Drying and dehydration/desolvation of the Freebase Hydrate Form B/Freebase Solvate Form A to the Amorphous Freebase generally can be carried out with standard equipment under conventional conditions and the isolated Amorphous Freebase typically can be co-milled without adversely impacting the amorphous state.

B. Crystalline Freebase Solvates and Hydrates

[00350] In another embodiment, the solid state form is a crystalline freebase of Compound 1. In one aspect, the crystalline freebase is a solvate. In another aspect, the crystalline freebase is an isopropyl acetate/water solvate (the "Freebase Solvate Form A"). In another aspect, the crystalline freebase is a hydrate (the "Freebase Hydrate Form B"). The Freebase Solvate Form A and the Freebase Hydrate Form B are further described in the Examples of the application.

[00351] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00352] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 13.7 ± 0.2, 20.8 ± 0.2 and 25.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00353] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00354] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, and 25.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00355] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00356] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00357] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00358] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00359] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00360] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00361] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00362] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00363] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00364] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00365] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2, 13.7 ± 0.2, 20.8 ± 0.2, and 25.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00366] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-A ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00367] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-B ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00368] In one embodiment, the crystalline freebase solvate or hydrate has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-B ± 0.2 degrees two theta that have a relative intensity of at least 10.0%, when measured at about 25°C with monochromatic Kα1 radiation.

[00369] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[00370] In one embodiment, the crystalline freebase has an X-ray powder diffraction pattern substantially as shown in Figure 3B.

[00371] In one embodiment, the crystalline freebase has a thermogravimetric analysis profile showing a weight loss of about 5% to about 6% between about 100°C and about 160°C when heated at a rate of 10°C/minute.

[00372] In one embodiment, the crystalline freebase has a thermogravimetric analysis profile substantially as shown in Figure 4D.

[00373] In one embodiment, the crystalline freebase has a differential scanning calorimetry profile comprising a first endotherm between about 25°C to about 100°C when heated at a rate of 10°C/minute.

[00374] In one embodiment, the crystalline freebase has a differential scanning calorimetry profile comprising a first endotherm between about 59.90°C to about 98.79°C when heated at a rate of 10°C/minute.

[00375] In one embodiment, the crystalline freebase has a differential scanning calorimetry profile comprising a second endotherm between about 100°C to about 160°C when heated at a rate of 10°C/minute.

[00376] In one embodiment, the crystalline freebase has a differential scanning calorimetry profile comprising a second endotherm between about 109.31°C to about 132.94°C when heated at a rate of 10°C/minute.

[00377] In one embodiment, the crystalline freebase has a differential scanning calorimetry profile comprising a first endotherm between about 25°C to about 100°C, and a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute.

[00378] In one embodiment, the crystalline freebase has a differential scanning calorimetry profile substantially as shown in Figure 5B.

[00379] In one embodiment, the crystalline freebase has a thermogravimetric analysis profile showing a weight loss of about 5% to about 6% between about 100°C and about 160°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising a first endotherm between about 25°C to about 100°C and/or a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute. In one aspect, the differential scanning calorimetry profile comprises a first endotherm between about 25°C to about 100°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a second endotherm between about 100°C to about 160°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a

first endotherm between about 25°C to about 100°C, and a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute.

[00380] In one embodiment, the crystalline freebase has a thermogravimetric analysis profile showing a weight loss of about 5% to about 6% between about 100°C and about 160°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising a first endotherm between about 59.90°C to about 98.79°C and/or a second endotherm between about 109.31°C to about 132.94°C, when heated at a rate of 10°C/minute. In one aspect, the differential scanning calorimetry profile comprises a first endotherm between about 59.90°C to about 98.79°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a second endotherm between about 109.31°C to about 132.94°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a first endotherm between about 59.90°C to about 98.79°C, and a second endotherm between about 109.31°C to about 132.94°C, when heated at a rate of 10°C/minute.

[00381] In one embodiment, the crystalline freebase has an X-ray diffraction pattern as previously described above, and further has at least one of the following: (a) a thermogravimetric analysis profile showing a weight loss of about 5% to about 6% between about 100°C and about 160°C when heated at a rate of 10°C/minute; and (b) a differential scanning calorimetry profile comprising a first endotherm between about 25°C to about 100°C, and/or a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute. In one aspect, the differential scanning calorimetry profile comprises a first endotherm between about 25°C to about 100°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a second endotherm between about 100°C to about 160°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a first endotherm between about 25°C to about 100°C, and a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute.

[00382] In one embodiment, the crystalline freebase has an X-ray diffraction pattern as previously described above, and further has a thermogravimetric analysis profile showing a weight loss of about 5% to about 6% between about 100°C and about 160°C when heated at a rate of 10°C/minute.

[00383] In one embodiment, the crystalline freebase has an X-ray diffraction pattern as previously described above, and further has a differential scanning calorimetry profile comprising a first endotherm between about 25°C to about 100°C, and/or a second endotherm

between about 100°C to about 160°C, when heated at a rate of 10°C/minute. In one aspect, the differential scanning calorimetry profile comprises a first endotherm between about 25°C to about 100°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a second endotherm between about 100°C to about 160°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a first endotherm between about 25°C to about 100°C, and a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute.

[00384] In one embodiment, the crystalline freebase has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 5% to about 6% between about 100°C and about 160°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising a first endotherm between about 25°C to about 100°C, and/or a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute. In one aspect, the differential scanning calorimetry profile comprises a first endotherm between about 25°C to about 100°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a second endotherm between about 100°C to about 160°C when heated at a rate of 10°C/minute. In another aspect, the differential scanning calorimetry profile comprises a first endotherm between about 25°C to about 100°C, and a second endotherm between about 100°C to about 160°C, when heated at a rate of 10°C/minute.

[00385] The Freebase Solvate Form A and Freebase Hydrate Form B are not physically stable. As discussed above, they desolvate (or dehydrate) and convert to the Amorphous Freebase upon drying. Although the Freebase Solvate Form A and Freebase Hydrate Form B generally do not exhibit pharmaceutically acceptable physical stability for use as an active ingredient in a pharmaceutical dosage form, they are useful intermediates in the preparation of other solid state forms such as the Amorphous Freebase.

C. Crystalline Freebase Hydrate Form C (Hemihydrate)

[00386] In another embodiment, the solid state form is a crystalline hydrate, wherein the crystalline hydrate is a hemihydrate. In another embodiment, the solid state form is crystalline hemihydrate of Compound 1 having a powder X-ray diffraction pattern corresponding to Freebase Hydrate Form C. The Freebase Hydrate Form C is further described in the Examples of the application.

[00387] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00388] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 7.7 ± 0.2, 7.9 ± 0.2, 9.6 ± 0.2, 10.3 ± 0.2, 13.9 ± 0.2, 15.5 ± 0.2, 15.9 ± 0.2, 17.0 ± 0.2, 17.2 ± 0.2, 17.8 ± 0.2, 18.1 ± 0.2, 18.3 ± 0.2, 19.3 ± 0.2, 19.7 ± 0.2, 20.5 ± 0.2, 20.9 ± 0.2, 21.9 ± 0.2, 22.2 ± 0.2, 23.5 ± 0.2, 24.4 ± 0.2, 24.9 ± 0.2, 28.2 ± 0.2, and 29.5 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00389] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00390] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 17.0 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00391] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 20.9 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00392] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern that is characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, 15.5 ± 0.2, 17.0 ± 0.2, 20.9 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00393] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00394] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00395] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00396] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00397] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00398] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00399] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00400] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00401] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00402] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks at 15.5 ± 0.2, 13.4 ± 0.2, 15.1 ± 0.2, 19.3 ± 0.2, 20.5 ±

0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00403] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-C ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00404] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-C ± 0.2 degrees two theta that have a relative intensity of at least 10.0%, when measured at about 25°C with monochromatic Kα1 radiation.

[00405] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[00406] In one embodiment, the Freebase Hydrate Form C has an X-ray powder diffraction pattern substantially as shown in Figure 3C when measured at about 25°C with monochromatic Kα1 radiation.

[00407] In one embodiment, the Freebase Hydrate Form C has a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute.

[00408] In one embodiment, the Freebase Hydrate Form C has a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 114.52°C and 168.15°C when heated at a rate of 10°C/minute.

[00409] In one embodiment, the Freebase Hydrate Form C has a thermogravimetric analysis profile substantially as shown in Figure 4E.

[00410] In one embodiment, the Freebase Hydrate Form C has a differential scanning calorimetry profile comprising an endotherm between about 120°C and about 170°C when heated at a rate of 10°C/minute.

[00411] In one embodiment, the Freebase Hydrate Form C has a differential scanning calorimetry profile comprising an endotherm between about 134.70°C and about 167.53°C when heated at a rate of 10°C/minute.

[00412] In one embodiment, the Freebase Hydrate Form C has a differential scanning calorimetry profile substantially as shown in Figure 5C.

[00413] In one embodiment, the Freebase Hydrate Form C has a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00414] In one embodiment, the Freebase Hydrate Form C has a moisture sorption isotherm profile substantially as shown in Figure 6B.

[00415] In one embodiment, the Freebase Hydrate Form C has a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute.

[00416] In one embodiment, the Freebase Hydrate Form C has a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00417] In one embodiment, the Freebase Hydrate Form C has a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00418] In one embodiment, the Freebase Hydrate Form C has a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 0% to

about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00419] In one embodiment, the Freebase Hydrate Form C has a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 134.70 and about 167.53°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00420] In one embodiment, the Freebase Hydrate Form C has an orthorhombic lattice type.

[00421] In one embodiment, the Freebase Hydrate Form C has a P212121 space group.

[00422] In one embodiment, the Freebase Hydrate Form C has unit cell a, b and c values of about 12.7Å, about 13.1Å, and about 22.6Å, respectively.

[00423] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above, and at least one of the following: (a) a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; (b) a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute; and/or (c) a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00424] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above, and a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute.

[00425] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above, and a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute.

[00426] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above, and a moisture sorption isotherm profile showing a

weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00427] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute.

[00428] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00429] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above; a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00430] In one embodiment, the Freebase Hydrate Form C has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 120 and about 170°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 0% to about 0.2% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00431] The Freebase Hydrate Form C generally exhibits good chemical stability, physical stability, and solid state properties (including low hygroscopicity). Large-scale manufacture of the Freebase Hydrate Form C is relatively straightforward with minimal scaling, good yield, good impurity rejection, fast filtration, conventional drying, and minimal milling

issues (even after subjecting the isolated material to high energy pinmilling). In addition, different particle sizes can be achieved through appropriate control of the crystallization process.

D. Crystalline Freebase Anhydrate Form D

[00432] In another embodiment, the solid state form is a crystalline anhydrate freebase of Compound 1 having a powder X-ray diffraction pattern corresponding to Freebase Anhydrate Form D. The Freebase Anhydrate Form D is further described in the Examples of the application.

[00433] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00434] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 4.0 ± 0.2, 18.4 ± 0.2, 19.0 ± 0.2, 23.0 ± 0.2, and 24.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00435] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ±0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00436] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 18.4 ± 0.2 and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00437] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2 and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00438] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2 and 20.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00439] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 20.3 ± 0.2, and 23.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00440] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 20.3 ± 0.2, and 24.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00441] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 14.5 ± 0.2, and 19.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00442] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 14.5 ± 0.2, and 19.0 ± 0.2 degrees two theta, and that is further characterized by a peak at one or more of 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 18.4 ± 0.2, 20.3 ± 0.2, 23.0 ± 0.2, and 24.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00443] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00444] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00445] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00446] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00447] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00448] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00449] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00450] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00451] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00452] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00453] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00454] In one embodiment the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks at 4.0 ± 0.2, 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, 19.0 ± 0.2, and 20.3 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 20.8 ± 0.2 degrees two theta, and without a significant peak at one or more of 6.8 ± 0.2, 15.7 ± 0.2, and 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2, 15.5 ± 0.2, and 21.7 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00455] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-J ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00456] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern characterized by peaks substantially at the positions listed in Table 16-J ± 0.2 degrees two theta that have a relative intensity of at least 10.0%, when measured at about 25°C with monochromatic Kα1 radiation.

[00457] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[00458] In one embodiment, the Freebase Anhydrate Form D has an X-ray powder diffraction pattern substantially as shown in Figure 3J when measured at about 25°C with monochromatic Kα1 radiation.

[00459] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute.

[00460] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 41.36°C and 190.48°C when heated at a rate of 10°C/minute.

[00461] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.45% to about 0.55% between about 43°C and 100°C when heated at a rate of 10°C/minute.

[00462] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.5 % between about 43°C and 100°C when heated at a rate of 10°C/minute.

[00463] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile substantially as shown in Figure 4I.

[00464] In one embodiment, the Freebase Anhydrate Form D has a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute.

[00465] In one embodiment, the Freebase Anhydrate Form D has a differential scanning calorimetry profile comprising an endotherm between about 199.55°C and about 217.41°C when heated at a rate of 10°C/minute.

[00466] In one embodiment, the Freebase Anhydrate Form D has a differential scanning calorimetry profile comprising an endotherm with an onset melting point of about 199.55°C and a melting enthalpy of about 85.4 J/g.

[00467] In one embodiment, the Freebase Anhydrate Form D has a differential scanning calorimetry profile substantially as shown in Figure 5E.

[00468] In one embodiment, the Freebase Anhydrate Form D has a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00469] In one embodiment, the Freebase Anhydrate Form D has a moisture sorption isotherm profile substantially as shown in Figure 6D.

[00470] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute.

[00471] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00472] In one embodiment, the Freebase Anhydrate Form D has a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00473] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00474] In one embodiment, the Freebase Anhydrate Form D has a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 199.55°C and about 217.41°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00475] In one embodiment, the Freebase Anhydrate Form D has an orthorhombic lattice type.

[00476] In one embodiment, the Freebase Anhydrate Form D has a $P2_12_12$ space group.

[00477] In one embodiment, the Freebase Anhydrate Form D has unit cell a, b and c values of about 43.8Å, about 8.6Å, and about 9.2Å, respectively.

[00478] In one embodiment, the Freebase Anhydrate Form D has an X-ray diffraction pattern as previously described above, and at least one of the following: (a) a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and

188°C when heated at a rate of 10°C/minute; (b) a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute; and/or (c) a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00479] In one embodiment, the Freebase Anhydrate Form D has an X-ray diffraction pattern as previously described above, and a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute.

[00480] In one embodiment, the Freebase Anhyhdrate Form D has an X-ray diffraction pattern as previously described above, and a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute.

[00481] In one embodiment, the Freebase Anhydrate Form D has an X-ray diffraction pattern as previously described above, and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00482] In one embodiment, the Freebase Anhydrate Form D has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute.

[00483] In one embodiment, the Freebase Anhydrate Form D has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00484] In one embodiment, the Freebase Anhydrate Form D has an X-ray diffraction pattern as previously described above; a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when

relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00485] In one embodiment, the Freebase Anhydrate Form D has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1.6% to about 2.0% when relative humidity is increased from about 0% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00486] Freebase Anhydrate Form D is reversibly hygroscopic (up to 1.8% water at 90% RH at 25°C), and is metastable relative to Freebase Hydrate Form C at typical environmental conditions (e.g., above 2.4% RH at 23°C) used during storage for downstream processing. The manufacture of Freebase Anhydrate Form D requires strict control of water, as the Freebase Anhydrate Form D can be manufactured only when the water content of the crystallization solvent is low (e.g., less than 0.15% at 23°C, corresponding to a water activity of 2.4%), and will convert to Freebase Hydrate Form C in solutions at high water content. Freebase Anhydrate Form D is slow to crystallize, and difficult to manufacture in higher yield.

E. Crystalline Tartrate

[00487] In another embodiment, the solid state form is a tartrate of Compound 1. In one aspect, the tartrate is amorphous. In another aspect, the tartrate is crystalline. In another aspect, the crystalline tartrate is a solvate. In another aspect, the crystalline tartrate is a hydrate. In another aspect, the tartrate is a crystalline L-tartrate. In another aspect, the crystalline L-tartrate is a hydrate. In another aspect, the crystalline tartrate is a tetrahydrate (the "Tartrate Hydrate"). The Tartrate Hydrate (a tetrahydrate) is further described in the Examples of the application.

[00488] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00489] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2, and 25.9 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00490] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00491] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00492] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2 and 9.3 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00493] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00494] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00495] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00496] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, when measured at about 25°C with monochromatic Kα1 radiation.

[00497] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta.

[00498] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, 14.1 ± 0.2, 15.7 ± 0.2, 21.9 ± 0.2 degrees two theta, and without a significant peak at one or more of 13.4 ± 0.2 and 15.1 ± 0.2 degrees two theta, and without a significant peak at one or more of 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta.

[00499] In further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.1 degrees two theta rather than ± 0.2 degrees two theta. In still further aspects of each of the above embodiments, the significant peak values have a variation of ± 0.05 degrees two theta rather than ± 0.2 degrees two theta.

[00500] In one embodiment, the Tartrate Hydrate has an X-ray powder diffraction pattern substantially as shown in Figure 3D, when measured at about 25°C with monochromatic Kα1 radiation.

[00501] In one embodiment, the Tartrate Hydrate has a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when heated at a rate of 10°C/minute.

[00502] In one embodiment, the Tartrate Hydrate has a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 32.98°C and 159.76°C when heated at a rate of 10°C/minute.

[00503] In one embodiment, the Tartrate Hydrate has a thermogravimetric analysis profile substantially as shown in Figure 4F.

[00504] In one embodiment, the Tartrate Hydrate has a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute.

[00505] In one embodiment, the Tartrate Hydrate has a differential scanning calorimetry profile comprising an endotherm between about 75.74°C and about 110.26°C when heated at a rate of 10°C/minute.

[00506] In one embodiment, the Tartrate Hydrate has a differential scanning calorimetry profile substantially as shown in Figure 5D.

[00507] In one embodiment, the Tartrate Hydrate has a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when

heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute.

[00508] In one embodiment, the Tartrate Hydrate has a moisture sorption isotherm profile showing a weight gain of about 1% to about 2% when relative humidity is increased from about 10% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00509] In one embodiment, the Tartrate Hydrate has a moisture sorption isotherm profile substantially as shown in Figure 6C.

[00510] In one embodiment, the Tartrate Hydrate has a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1% to about 2% when relative humidity is increased from about 10% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00511] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above, and at least one of the following: (a) a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when heated at a rate of 10°C/minute; (b) a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute; and/or (c) a moisture sorption isotherm profile showing a weight gain of about 1% to about 2% when relative humidity is increased from about 10% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00512] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above, and a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when heated at a rate of 10°C/minute.

[00513] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above, and a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute.

[00514] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above, and a moisture sorption isotherm profile showing a weight gain of

about 1% to about 2% when relative humidity is increased from about 10% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00515] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute.

[00516] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1% to about 2% when relative humidity is increased from about 10% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00517] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above; a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1% to about 2% when relative humidity is increased from about 10% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00518] In one embodiment, the Tartrate Hydrate has an X-ray diffraction pattern as previously described above; a thermogravimetric analysis profile showing a weight loss of about 11.8% to about 12.2% between about 25°C and 160°C when heated at a rate of 10°C/minute; a differential scanning calorimetry profile comprising an endotherm between about 60°C and about 100°C when heated at a rate of 10°C/minute; and a moisture sorption isotherm profile showing a weight gain of about 1% to about 2% when relative humidity is increased from about 10% relative humidity to about 90% relative humidity at a temperature of 25°C.

[00519] The Tartrate Hydrate has acceptable chemical stability and exhibits acceptable stability to light and peroxide. For example, when chemical stability was evaluated in closed vials at 30°C/65% relative humidity and 40°C/75% relative humidity over 12 weeks, and at 50°C/75% relative humidity over 6 weeks, no degradation of the Tartrate Hydrate was observed in the closed vials under any of the conditions. The Tartrate Hydrate has good solubility (BCS Class I) and is not hygroscopic. The Tartrate Hydrate, however, potentially will convert to an

amorphous tartrate below 10% relative humidity, when heated, or when compressed or under shear.

[00520] The Tartrate Hydrate can be manufactured, for example, using anti-solvent crystallization. Impurity rejection during the large-scale manufacture of the Tartrate Hydrate generally is good, but scaling may be greater than desired and specific anti-solvent addition controls and process volume restrictions potentially may be required. In addition, appropriate control of the filtration, washing, and drying steps may be required to minimize consolidation of the wet cake and formation of hard lumps in the isolated material. For example, control of the relative humidity (*e.g.*, greater than 10% and less than 100% relative humidity), temperature (*e.g.*, crystallization at about 10°C works well), and mixing rate may be required during drying to minimize the formation of hard lumps in the isolated material. Insufficient control of the drying conditions potentially will produce a consolidated, harder material that may be difficult to break up during subsequent processing. As previously noted, shearing and compression potentially will cause conversion to the amorphous tartrate. The dried material typically is milled with mechanical impact mills (*e.g.*, Fitzmills and pin mills) because shear-based mills (*e.g.*, comills) can lead to loss of crystallinity. In addition, loss of crystallinity potentially can result from pressure or compression forces during formulation (such as would be required for tableting).

F. Crystalline Hydrochloride

[00521] In another embodiment, the solid state form is a crystalline hydrochloride of Compound 1. In one aspect, the crystalline hydrochloride corresponds to crystalline Hydrochloride Solvate Form AA. In another aspect, the crystalline hydrochloride corresponds to crystalline Hydrochloride Solvate Form BB. In another aspect, the crystalline hydrochloride corresponds to crystalline Hydrochloride Solvate Form CC. Hydrochloride Solvate Form AA, Hydrochloride Solvate Form BB, and Hydrochloride Solvate Form CC are further described in the Examples of the application.

[00522] Hydrochloride Solvate Form AA, Hydrochloride Solvate Form BB, and Hydrochloride Solvate Form CC appear to be solvates and generally convert to an amorphous hydrochloride upon ambient drying. The resulting amorphous hydrochloride is hygroscopic. Yields obtained for each of the crystalline hydrochlorides generally have been in the 10% to 15% range.

G. Crystalline L-Maleate

[00523] In another embodiment, the solid state form is a crystalline L-maleate of Compound 1. In one aspect, the crystalline L-maleate corresponds to crystalline L-Maleate Form AAA. In another aspect, the crystalline L-maleate corresponds to crystalline L-Maleate Form BBB. L-Maleate Form AAA and L-Maleate Form BBB are further described in the Examples of the application.

[00524] Because L-maleic acid will react with Compound 1, the L-Maleate Form AAA and L-Maleate Form BBB generally are less chemically stable than the Amorphous Freebase, the Freebase Hydrate Form C, and the Tartrate Hydrate and do not exhibit pharmaceutically acceptable stability for use as an active ingredient in a pharmaceutical dosage form.

H. Crystalline Purity

[00525] In additional embodiments of the solid state forms discussed above, the solid state form has a pharmaceutically acceptable crystalline purity (or a pharmaceutically acceptable amorphous purity in the case of the Amorphous Freebase). For example, in one aspect, Compound 1 comprises at least about 75% by weight of the desired solid state form. In another aspect, at least 80% by weight is the desired solid state form. In another aspect, at least 85% by weight is the desired solid state form. In another aspect, at least 90% by weight is the desired solid state form. In another aspect, at least 95% by weight is the desired solid state form. In another aspect, at least 96% by weight is the desired solid state form. In another aspect, at least 97% by weight is the desired solid state form. In another aspect, at least 98% by weight is the desired solid state form. In another aspect, at least 99% by weight is the desired solid state form. In another aspect, Compound 1 is present as the substantially crystalline pure (or amorphous pure in the case of the Amorphous Freebase) solid state form. In a preferred aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is Freebase Anhydrate Form D. In a more preferred aspect, the solid state form is the Freebase Hydrate Form B. In a particularly preferred aspect, the solid state form is the Freebase Hydrate Form C. In a preferred aspect, the solid state form is the Tartrate Hydrate.

IV. Methods of Treatment

[00526] The present disclosure also relates to methods of treating a JAK-associated condition in a subject, particularly a human subject suffering from or susceptible to the condition, comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or one or more solid state

forms of Compound 1 as described in the present disclosure. Another aspect of the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or one or more solid state forms of Compound 1 as described in the present disclosure for use in treatment of a JAK-associated condition in a subject, particularly in a human subject suffering from or susceptible to the condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or one or more solid state forms of Compound 1. In one aspect, the condition is a JAK-1-associated condition. In another aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00527] In one embodiment, the present disclosure relates to methods of treating a condition selected from the group consisting of immunomodulation, inflammation, and proliferative disorders (such as cancer) in a subject, wherein the method comprises administering to the subject, particularly a human subject suffering from or susceptible to the condition, a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a condition selected from the group consisting of immunomodulation, inflammation, and proliferative disorders (such as cancer) in a subject, particularly in a human subject suffering from or susceptible to the condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Anhydrate Form D. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate.

[00528] In one embodiment, the present disclosure relates to methods of treating a condition selected from the group consisting of rheumatoid arthritis, multiple sclerosis, experimental allergic encephalomyelitis, systemic lupus erythematosus, Crohn's disease, atopic dermatitis, vasculitis, cardiomyopathy, psoriasis, Reiter's syndrome, glomerulonephritis, ulcerative colitis, allergic asthma, insulin-dependent diabetes, peripheral neuropathy, uveitis, fibrosing alveolitis, type I diabetes, juvenile diabetes, juvenile arthritis, Castleman disease,

neutropenia, endometriosis, autoimmune thyroid disease, sperm and testicular autoimmunity, scleroderma, axonal and neuronal neuropathies, allergic rhinitis, Sjogren's syndrome, hemolytic anemia, Graves' disease, Hashimoto's thyroiditis, IgA nephropathy, amyloidosis, ankylosing spondylitis, Behcet's disease, sarcoidosis, vesiculobullous dermatosis, myositis, primary biliary cirrhosis, polymyalgia rheumatica, autoimmune immunodeficiency, Chagas disease, Kawasaki syndrome, psoriatic arthritis, celiac sprue, myasthenia gravis, autoimmune myocarditis, POEMS syndrome, and chronic fatigue syndrome in a subject, wherein the method comprises administering to the subject, particularly a human subject suffering from or susceptible to the condition, a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a condition selected from the group consisting of rheumatoid arthritis, multiple sclerosis, experimental allergic encephalomyelitis, systemic lupus erythematosus, Crohn's disease, atopic dermatitis, vasculitis, cardiomyopathy, psoriasis, Reiter's syndrome, glomerulonephritis, ulcerative colitis, allergic asthma, insulin-dependent diabetes, peripheral neuropathy, uveitis, fibrosing alveolitis, type I diabetes, juvenile diabetes, juvenile arthritis, Castleman disease, neutropenia, endometriosis, autoimmune thyroid disease, sperm and testicular autoimmunity, scleroderma, axonal and neuronal neuropathies, allergic rhinitis, Sjogren's syndrome, hemolytic anemia, Graves' disease, Hashimoto's thyroiditis, IgA nephropathy, amyloidosis, ankylosing spondylitis, Behcet's disease, sarcoidosis, vesiculobullous dermatosis, myositis, primary biliary cirrhosis, polymyalgia rheumatica, autoimmune immunodeficiency, Chagas disease, Kawasaki syndrome, psoriatic arthritis, celiac sprue, myasthenia gravis, autoimmune myocarditis, POEMS syndrome, and chronic fatigue syndrome in a subject, particularly in a human subject suffering from or susceptible to the condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00529] In one embodiment, the present disclosure relates to methods of treating a condition selected from the group consisting of rheumatoid arthritis (including moderate to severe rheumatoid arthritis), systemic lupus erythematosus, multiple sclerosis, Crohn's disease

(including moderate to severe Crohn's disease), psoriasis (including moderate to severe chronic plaque psoriasis), ulcerative colitis (including moderate to severe ulcerative colitis), ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis (including moderate to severe polyarticular juvenile idiopathic arthritis), diabetic nephropathy, dry eye syndrome, Sjogren's syndrome, alopecia areata, vitiligo, and atopic dermatitis in a subject, wherein the method comprises administering to the subject, particularly a human subject suffering from or susceptible to the condition, a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a condition selected from the group consisting of rheumatoid arthritis (including moderate to severe rheumatoid arthritis), systemic lupus erythematosus, multiple sclerosis, Crohn's disease (including moderate to severe Crohn's disease), psoriasis (including moderate to severe chronic plaque psoriasis), ulcerative colitis (including moderate to severe ulcerative colitis), ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis (including moderate to severe polyarticular juvenile idiopathic arthritis), diabetic nephropathy, dry eye syndrome, Sjogren's syndrome, alopecia areata, vitiligo, and atopic dermatitis in a subject, particularly in a human subject suffering from or susceptible to the condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00530] In one embodiment, the present disclosure relates to methods of treating a condition selected from the group consisting of an ocular condition, systemic inflammatory response syndrome, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, type III hypersensitivity reactions, type IV hypersensitivity, inflammation of the aorta, iridocyclitis/uveitis/optic neuritis, juvenile spinal muscular atrophy, diabetic retinopathy or microangiopathy, chronic inflammation, ulcerative colitis, inflammatory bowel disease, allergic diseases, dermatitis scleroderma, acute or chronic immune disease associated with organ transplantation, psoriatic arthropathy, ulcerative colitic arthropathy, autoimmune bullous disease, autoimmune haemolytic anaemia, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis

associated lung disease, Sjögren's syndrome / disease associated lung disease, ankylosing spondylitis and ankylosing spondylitis-associated lung disease, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycemia, psoriasis type 1, psoriasis type 2, plaque psoriasis, moderate to severe chronic plaque psoriasis, autoimmune neutropenia, sperm autoimmunity, multiple sclerosis (all subtypes), acute rheumatic fever, rheumatoid spondylitis, Sjögren's syndrome, and autoimmune thrombocytopaenia in a subject, wherein the method comprises administering to the subject, particularly a human subject suffering from or susceptible to the condition, a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a condition selected from the group consisting of an ocular condition, systemic inflammatory response syndrome, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, type III hypersensitivity reactions, type IV hypersensitivity, inflammation of the aorta, iridocyclitis/uveitis/optic neuritis, juvenile spinal muscular atrophy, diabetic retinopathy or microangiopathy, chronic inflammation, ulcerative colitis, inflammatory bowel disease, allergic diseases, dermatitis scleroderma, acute or chronic immune disease associated with organ transplantation, psoriatic arthropathy, ulcerative colitic arthropathy, autoimmune bullous disease, autoimmune haemolytic anaemia, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjögren's syndrome / disease associated lung disease, ankylosing spondylitis and ankylosing spondylitis-associated lung disease, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, psoriasis type 1, psoriasis type 2, plaque psoriasis, moderate to severe chronic plaque psoriasis, autoimmune neutropenia, sperm autoimmunity, multiple sclerosis (all subtypes), acute rheumatic fever, rheumatoid spondylitis, Sjögren's syndrome, and autoimmune thrombocytopaenia in a subject, particularly in a human subject suffering from or susceptible to the condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the

solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00531] In one embodiment, the present disclosure relates to methods of treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus in a subject, particularly in a human subject suffering from or susceptible to the condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a solid state form of Compound 1 . In one aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00532] In one embodiment, the present disclosure relates to methods of treating a condition selected from the group consisting of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, systemic lupus erythematosus, lupus nephritis, diabetic nephropathy, dry eye syndrome, Sjogren's syndrome, alopecia areata, vitiligo, and atopic dermatitis in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a condition selected from the group consisting of rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, systemic lupus erythematosus, lupus nephritis, diabetic nephropathy, dry eye syndrome, Sjogren's syndrome, alopecia areata, vitiligo, and atopic

dermatitis in a subject, particularly in a human subject suffering from or susceptible to the condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00533] In one embodiment, the present disclosure relates to methods of treating arthritis in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of arthritis in a subject, particularly in a human subject suffering from or susceptible to arthritis, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the arthritis is selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis. In another aspect, the arthritis is rheumatoid arthritis. In another aspect, the arthritis is juvenile idiopathic arthritis. In another aspect, the arthritis is psoriatic arthritis. In another aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB.

[00534] In one embodiment, the present disclosure relates to methods of treating a spondyloarthropathy in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of

Compound 1 for use in treatment of spondyloarthropathy, particularly in a human subject suffering from or susceptible to spondyloarthropathy, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the spondyloarthropathy is ankylosing spondylitis. In another aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB.

[00535] In one embodiment, the present disclosure relates to methods of treating a gastrointestinal condition in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a gastrointestinal condition, particularly in a human subject suffering from or susceptible to a gastrointestinal condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the gastrointestinal condition is selected from the group consisting of Crohn's disease and ulcerative colitis. In another aspect, the gastrointestinal condition is Crohn's disease. In another aspect, the gastrointestinal condition is ulcerative colitis. In another aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect,

the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB.

[00536] In one embodiment, the present disclosure relates to methods of treating a skin condition, wherein the method comprises administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of a skin condition, particularly in a human subject suffering from or susceptible to a skin condition, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one aspect, the skin condition is selected from the group consisting of psoriasis, plaque psoriasis, nail psoriasis, and hidradenitis suppurativa. In another aspect, the skin condition is psoriasis. In another aspect, the skin condition is plaque psoriasis. In another aspect, the skin condition is nail psoriasis. In another aspect, the skin condition is hidradenitis suppurativa. In another aspect, the skin condition is atopic dermatitis. In another aspect, the solid state form is the Amorphous Freebase. In another aspect, the solid state form is the Freebase Hydrate Form B. In another aspect, the solid state form is the Freebase Hydrate Form C. In another aspect, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB.

[00537] The therapeutically effective dose level for any particular subject will depend upon the specific situation and can depend upon a variety of factors including the type, age, weight, sex, diet, and condition of the subject being treated; the severity of the pathological condition; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the route of administration; the duration of the treatment; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular compound or salt used; whether a drug delivery system is utilized; drugs used in combination or coincidental with the specific compound employed; and like factors well-known in the medical arts. An ordinarily skilled

physician provided with the disclosure of the present application will be able to determine appropriate dosages and regimens for administration of the therapeutic agent to the subject, and to adjust such dosages and regimens as necessary during the course of treatment, in accordance with methods well-known in the therapeutic arts. It is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. Thus, the dosage regimen actually employed can vary widely, and therefore, can derive from the preferred dosage regimen set forth below.

[00538] The total daily dose of the solid state form (administered in single or divided doses) typically is from about 0.001 to about 100 mg/kg, or from about 0.001 to about 30 mg/kg, or from about 0.001 to about 15 mg/kg. In another embodiment, the total daily dose is from about 0.01 to about 10 mg/kg (*i.e.*, mg of the compound or salt per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

[00539] In one embodiment, the daily dose of the solid state form administered to the subject is from about 0.01 mg to about 3000 mg. In one aspect, the daily dose is from about 0.1 mg to about 1000 mg. In another aspect, the daily dose is from is from about 1 mg to about 500 mg. In another aspect, the daily dose is from about 1 mg to about 250 mg. In another aspect, the daily dose is from about 1 mg to about 100 mg. In another aspect, the daily dose is from about 1 mg to about 50 mg. In another aspect, the daily dose is from about 1 mg to about 45 mg. In another aspect, the daily dose is from about 1 mg to about 30 mg. In another aspect, the daily dose is from about 1 mg to about 25 mg. In another aspect, the daily dose is from about 1 mg to about 24 mg. In another aspect, the daily dose is from about 1 mg to about 15 mg. In another aspect, the daily dose is from about 1 mg to about 7.5 mg. In another aspect, the daily dose is from about 25 mg to about 50 mg. In another aspect, the daily dose is from about 1 mg to about 10 mg. In another aspect, the daily dose is from about 10 mg to about 20 mg. In another aspect, the daily dose is from about 20 mg to about 30 mg. In another aspect, the daily dose is from about 30 mg to about 40 mg. In another aspect, the daily dose is from about 7.5 mg to about 45 mg. In another aspect, the daily dose is from about 15 mg to about 30 mg. In another aspect, the daily dose is about 3 mg. In another aspect, the daily dose is about 6 mg. In another aspect, the daily dose is about 7.5 mg. In another aspect, the daily dose is about 12 mg. In another aspect, the daily dose is about 15 mg. In another aspect, the daily dose is about 18

mg. In another aspect, the daily dose is about 24 mg. In another aspect, the daily dose is about 30 mg. In another aspect, the daily dose is about 36 mg. In another aspect, the daily dose is about 45 mg.

[00540] In one embodiment, a dose of about 3 mg, about 6 mg, about 12 mg, or about 24 mg per unit dosage form (*e.g.*, per tablet or capsule) of a solid state form of Compound 1 is administered orally BID (twice daily) in equal amounts (*e.g.*, twice a day, about 3 mg each time) to a human subject.

[00541] In one embodiment, the disclosure relates to a method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 3 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 3 mg each time). In another aspect, the present disclosure relates a solid state form of Compound 1 for use in treating rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 3 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 3 mg each time).

[00542] In one embodiment, the disclosure relates to a method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 6 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 6 mg each time). In another aspect, the present disclosure relates a solid state form of Compound 1 for use in treating rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 6 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 6 mg each time).

[00543] In one embodiment, the disclosure relates to a method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 12 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 12 mg each time). In another aspect, the present disclosure relates a solid state form of Compound 1 for use in treating rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 12 mg, per unit dosage form

(e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 12 mg each time).

[00544] In one embodiment, the disclosure relates to a method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 24 mg each time). In another aspect, the present disclosure relates a solid state form of Compound 1 for use in treating rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally BID (twice daily) in equal amounts (e.g., twice a day, about 24 mg each time).

[00545] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 7.5 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof.

[00546] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 7.5 mg per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1. In one embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a solid state form of Compound 1 in an amount sufficient to deliver 7.5 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Amorphous Freebase. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00547] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 15 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof.

[00548] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 15 mg per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1. In one embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a solid state form of Compound 1 in an amount sufficient to deliver 15 mg per unit dosage form (e.g., per tablet or

capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Amorphous Freebase. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00549] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 24 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof. The 24 mg QD dose of Compound 1 freebase or a pharmaceutically acceptable salt thereof may be administered as either a single dosage form comprising about 24 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or two dosage forms comprising about 12 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof administered simultaneously.

[00550] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 24 mg of a solid state form of Compound 1. In one embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a solid state form of Compound 1 in an amount sufficient to deliver 24 mg of Compound 1 freebase equivalent to the subject. The 24 mg QD dose of the solid state form of Compound 1 may be administered as either a single dosage form comprising about 24 mg per unit dosage form (e.g., per tablet or capsule) of the solid state form of Compound 1, or two dosage forms comprising about 12 mg per unit dosage form (e.g., per tablet or capsule) of the solid state form of Compound 1 administered simultaneously. In one embodiment, the solid state form is the Amorphous Freebase. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00551] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 30 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof.

[00552] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 30 mg per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1. In one embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a solid state form of

Compound 1 in an amount sufficient to deliver 30 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Amorphous Freebase. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00553] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 36 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof.

[00554] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 36 mg per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1. In one embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a solid state form of Compound 1 in an amount sufficient to deliver 36 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Amorphous Freebase. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00555] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof.

[00556] In another embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a dose of about 45 mg per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1. In one embodiment, the methods or uses comprise administering orally QD (once daily) to a human subject a solid state form of Compound 1 in an amount sufficient to deliver 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Amorphous Freebase. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In another aspect, the solid state form is the Freebase Anhydrate Form D.

[00557] In certain embodiments, Compound 1 freebase or a pharmaceutically acceptable salt thereof and/or solid state forms thereof can be used to treat rheumatoid arthritis (RA), including reducing signs and symptoms of RA, inducing a major clinical response, inhibiting the progression of or treating structural damage associated with RA, and improving physical function in adult subjects, such as adult subjects with moderately to severely active RA. In one embodiment, Compound 1 freebase or a pharmaceutically acceptable salt thereof and/or solid state forms thereof are used to treat RA in adult subjects. In one embodiment, Compound 1 freebase or a pharmaceutically acceptable salt thereof and/or solid state forms thereof are used to reduce signs and symptoms of RA in adult subjects. In one embodiment, Compound 1 freebase or a pharmaceutically acceptable salt thereof and/or solid state forms thereof induce a major clinical response in adult subjects with RA. In one embodiment, Compound 1 freebase or a pharmaceutically acceptable salt thereof and/or solid state forms thereof are used to inhibit the progression of structural damage associated with RA in adult subjects. In one embodiment, Compound 1 freebase and/or solid state forms thereof are used to treat structural damage associated with RA in adult subjects. In one embodiment, Compound 1 freebase or a pharmaceutically acceptable salt thereof and/or solid state forms thereof are used to improve physical function in adult subjects. In one embodiment, the adult subjects have RA. In another embodiment, the adult subjects have moderately to severely active RA.

[00558] Compound 1 freebase or a pharmaceutically acceptable salt thereof or solid state forms thereof may be used alone, or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs), and/or in combination with anti-TNFα biological agents, such as TNF antagonists like chimeric, humanized or human TNF antibodies, adalimumab (such as HUMIRA™ brand adalimumab), infliximab such as CA2 (REMICADE™ brand infliximab), golimumab such as SIMPONI™ (golimumab), certolizumab pegol such as CIMZIA™, tocilizumab such as ACTEMRA™, CDP 571, and soluble p55 or p75 TNF receptors, derivatives, thereof, etanercept such as p75TNFR1gG (ENBREL™ brand etanercept) or p55TNFR1gG (lenercept).

[00559] Patients having active rheumatoid arthritis (RA) may be diagnosed according to 1987-revised American College of Rheumatology (ACR) classification criteria or the 2010 ACR/EULAR criteria. In certain embodiments, RA may be diagnosed based on patients having at least 6 swollen and 6 tender joints. In certain embodiments, patients treatable with Compound 1 or solid state forms thereof may include those who have failed therapy with at least one (e.g., at least one but no more than four) DMARDs and/or have inadequate response to methotrexate,

adalimumab, infliximab, etanercept, or other anti-TNFα biological agents, or non-anti-TNF biologics.

[00560] In certain embodiments, Compound 1 freebase or a pharmaceutically acceptable salt thereof or solid state forms thereof halt disease progression, and/or relieves at least a symptom of the disease, which may be detected or monitored by X-ray results, including radiographic progression of joint damage.

[00561] In certain embodiments, therapeutic efficacy can be measured by improvements in ACR20, ACR50, and/or ACR70, either in individual patients or a population of patients in need of treatment. In certain embodiments, statistically significant improvement (as compared placebo or untreated control) over a treatment period (e.g., 1 week, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 12 weeks, 2 months, 3 months, 6 months, 1 year, 2 years, 5 years, 10 years or more) in one or more of the ACR criteria is achieved. Statistical significance is manifested by a p value of less than 0.05, or less than 0.01.

[00562] Components of the ACR responses are well known in the art, and may include the median number of tender joints, the median number of swollen joints, physician global assessment such as one measured by visual analog scale (VAS), patient global assessment such as one measured by visual analog scale, pain such as one measured by visual analog scale, disability index of the Health Assessment Questionnaire (HAQ-DI score), and C-reactive protein (CRP) (mg/dL).

[00563] In certain embodiments, an ACR20 response is determined based on a 20% or greater improvement in tender joint count (TJC) and swollen joint count (SJC) and greater than or equal to 3 of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), HAQ-DI, or high sensitivity C-reactive protein (hsCRP). In some embodiments, an ACR50 response is determined based on a 50% or greater improvement in TJC and SJC and greater than or equal to 3 of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), HAQ-DI, or hsCRP. An ACR70 response is determined based on a 70% or greater improvement in TJC and SJC and greater than or equal to 3 of the 5 measures of Patient's Assessment of Pain (VAS), Patient's Global Assessment of Disease Activity (VAS), Physician's Global Assessment of Disease Activity (VAS), HAQ-DI, or hsCRP. In certain embodiments, the ACR20, ACR50, or ACR70 response occurs by week 12 of treatment.

[00564] In certain embodiments, a DAS28 (disease activity score based on the 28 joints examined) score is determined as a composite score derived from four of the following measures: examination of joints for swelling and tenderness, global scores of pain and overall status, blood markers of inflammation (e.g. ESR (erythrocyte sedimentation rate) and CRP (C reactive protein), referred to herein as DAS28(CRP)), questionnaires (e.g. the HAQ (health assessment questionnaire) which assess function) and X-rays and other imaging techniques such as ultrasound and MRI.

[00565] In certain embodiments, structural joint damage can be assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, for example, at week 12 compared to baseline, or at week 24 as compared to baseline.

[00566] In certain embodiments, improvement in signs and symptoms of the disease can be measured by patient physical function response, such as disability index of Health Assessment Questionnaire (HAQ-DI), and/or the health-outcomes as assessed by The Short Form Health Survey (SF 36). In one embodiment, improvement in signs and symptoms of the disease is measured by HAQ-DI, including the minimal clinically important difference (MCID) of -0.22. Improvement can also be measured by one or both of Physical Component Summary (PCS) and the Mental Component Summary (MCS). Improvements can further be measured by Work Instability Scale for RA (RA-WIS) (*see* Gilworth et al., Arthritis & Rheumatism (Arthritis Care & Research) 49(3): 349-354, 2003.).

[00567] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In one embodiment, the subject is an adult.

[00568] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human

subject suffering from or susceptible to rheumatoid arthritis, about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the method comprising administering to the subject a solid state form of Compound 1 orally QD (once daily) in an amount sufficient to deliver 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In another aspect, the present disclosure relates to a solid state form of Compound 1 for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the solid state form delivers about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB. In one embodiment, the subject is an adult.

[00569] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 15 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In one embodiment, the subject is an adult.

[00570] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 15 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the method comprising administering to the subject a solid state form of Compound 1 orally QD (once daily) in an amount sufficient to deliver 15 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In another aspect, the present disclosure relates to a solid state form of Compound 1 for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the solid state form delivers about 15 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB. In one embodiment, the subject is an adult.

[00571] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 24 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 24 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). The 24 mg dose of Compound 1 freebase or a pharmaceutically acceptable salt thereof may be administered as either a single dosage form comprising about 24

mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or two dosage forms comprising about 12 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof administered simultaneously. In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In one embodiment, the subject is an adult.

[00572] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 24 mg of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the method comprising administering to the subject a solid state form of Compound 1 orally QD (once daily) in an amount sufficient to deliver 24 mg of Compound 1 freebase equivalent to the subject. In another aspect, the present disclosure relates to a solid state form of Compound 1 for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 24 mg of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the solid state form delivers about 24 mg of Compound 1 freebase equivalent to the subject. The 24 mg dose of the solid state form of Compound 1 may be administered as either a single dosage form comprising about 24 mg per unit dosage form (e.g., per tablet or capsule) of the solid state form of Compound 1, or two dosage forms comprising about 12 mg per unit dosage form (e.g., per tablet or capsule) of the solid state form of Compound 1 administered simultaneously. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the solid state form is the Freebase Anhydrate Form D. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB. In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In one embodiment, the subject is an adult.

[00573] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 30 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt

thereof orally QD (once daily). In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In one embodiment, the subject is an adult.

[00574] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 30 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the method comprising administering to the subject a solid state form of Compound 1 orally QD (once daily) in an amount sufficient to deliver 30 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In another aspect, the present disclosure relates to a solid state form of Compound 1 for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the solid state form delivers about 30 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the solid state form is the Freebase Anhydrate Form D. In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB. In one embodiment, the subject is an adult.

[00575] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritins in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 36 mg, per unit dosage form

(e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 36 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In one embodiment, the subject is an adult.

[00576] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 36 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the method comprising administering to the subject a solid state form of Compound 1 orally QD (once daily) in an amount sufficient to deliver 36 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In another aspect, the present disclosure relates to a solid state form of Compound 1 for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 36 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the solid state form delivers about 36 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the solid state form is the Freebase Anhydrate Form D. In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB. In one embodiment, the subject is an adult.

[00577] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human

subject suffering from or susceptible to rheumatoid arthritis, about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In another aspect, the present disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof orally QD (once daily). In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In one embodiment, the subject is an adult.

[00578] In one embodiment, the disclosure relates to a method of treating rheumatoid arthritis in a subject, the method comprising administering to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, about 45 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the method comprising administering to the subject a solid state form of Compound 1 orally QD (once daily) in an amount sufficient to deliver 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In another aspect, the present disclosure relates to a solid state form of Compound 1 for use in treatment of rheumatoid arthritis in a subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis, the use comprising administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1 orally QD (once daily). In one embodiment, the solid state form delivers about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent to the subject. In one embodiment, the solid state form is the Freebase Hydrate Form B. In one embodiment, the solid state form is the Freebase Hydrate Form C. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the solid state form is the Freebase Anhdyrate Form D. In one embodiment, the subject has moderately to severely active rheumatoid arthritis. In another aspect, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In another aspect, the solid state form is the Hydrochloride Solvate Form BB. In another aspect, the solid state form is the Hydrochloride Solvate Form CC. In another aspect, the solid state form is the L-Maleate Form AAA. In another aspect, the solid state form is the L-Maleate Form BBB. In one embodiment, the subject is an adult.

[00579] In one embodiment, the disclosure relates to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the method comprising administering to the subject a therapeutically effective amount of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase equivalent. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered to the subject orally QD (once daily). In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 (e.g., a crystalline hydrate or crystalline anhydrate), as described in the present disclosure, for use in treatment of moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is a hemihydrate. In one embodiment, the hemihydrate is Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhydrate is Freebase Anhydrate Form D. In one embodiment, the solid state form is the Freebase Solvate Form A. In another aspect, the solid state form is the Hydrochloride Solvate form AA. In one embodiment, the solid state form is the Hydrochloride Solvate Form BB. In one embodiment, the solid state form is the Hydrochloride Solvate Form CC. In one embodiment, the solid state form is the L-Maleate Form AAA. In one embodiment, the solid state form is the L-Maleate Form BBB. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the formulation delivers about 7.5 mg or

about 15 mg or about 30 mg or about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) or a solid state form of Compound 1 orally QD (once daily).

[00580] In one embodiment, the subject having moderate to severely active rheumatoid arthritis has, prior to treatment, at least one of the following identifying characteristics: at least 6 swollen joints (based on 66 joint counts), at least 6 tender joints (based on 68 joint counts), high-sensitivity C-reactive protein (hsCRP) greater than the upper limit of normal (ULN), or positive test results for both rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP). In one embodiment, the subject having moderate to severely active rheumatoid arthritis has, prior to treatment, at least 6 swollen joints (based on 66 joint counts) and at least 6 tender joints (based on 68 joint counts). Methods for assessing tender and swollen joints are known, and described in, for example, Scott, et al., Clinical and Experimental Rheumatology, 2014, Vol. 32 (Supp. 85), S7-S12.

[00581] Thus, in another embodiment, the present disclosure is directed to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the method comprising administering to the subject a therapeutically effective amount of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 (e.g., a crystalline hydrate or a crystalline anhydrate) as described herein, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 (e.g., a crystalline hydrate or crystalline anhydrate), as described in the present disclosure, for use in treatment of moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human

subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the therapeutically effective amount of the solid state form of Compound 1 delivers to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) or a solid state form of Compound 1 orally QD (once daily). In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered to the subject orally QD (once daily). In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the symptoms result from the progression of structural damage assessed by radiograph.

[00582] In one embodiment, the present disclosure is directed to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one embodiment, the method comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or

susceptible to moderate to severely active rheumatoid arthritis, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating, the use comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the symptoms result from the progression of structural damage assessed by radiograph.

[00583] In one embodiment, the present disclosure is directed to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one embodiment, the method comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating, the use comprising administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically

acceptable salt thereof or a solid state form of Compound 1,. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the symptoms result from the progression of structural damage assessed by radiograph.

[00584] In one embodiment, the present disclosure is directed to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one embodiment, the method comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating, the use comprising administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate.

In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the symptoms result from the progression of structural damage assessed by radiograph.

[00585] In one embodiment, the present disclosure is directed to a method of treating moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the method comprising administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating. In one embodiment, the method comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treatment of moderate to severely active rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, wherein the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating, the use comprising administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically

acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the symptoms result from the progression of structural damage assessed by radiograph.

[00586] In one embodiment, the adult subject receiving the treatment achieves an ACR20 response after treatment. In one embodiment, the adult subject achieves an ACR20 response after treatment for at least twelve weeks (e.g., at week 12 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR50 response after treatment. In one embodiment, the adult subject achieves an ACR50 response after treatment for at least twelve weeks (e.g., at week 12 of treating), or after at least twenty-four weeks (e.g., at week 24). In another embodiment, the adult subject receiving the treatment achieves an ACR70 response after treatment. In one embodiment, the adult subject achieves an ACR70 response after treatment for at least twelve weeks (e.g., at week 12 of treating). In certain embodiments, the adult subject achieves an ACR20 response, an ACR50 response, and/or an ACR70 response following treatment for at least twelve weeks (e.g., at week 12 of treating).

[00587] In one embodiment, the adult subject receiving the treatment achieves an ACR20 response after treatment for at least 8 weeks (e.g., at week 8 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR20 response after treatment for at least 6 weeks (e.g., at week 6 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR20 response after treatment for at least 4 weeks (e.g., at week 4 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR20 response after treatment for at least 2 weeks (e.g., at week 2 of treating).

[00588] In one embodiment, the adult subject receiving the treatment achieves an ACR50 response after treatment for at least 8 weeks (e.g., at week 8 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR50 response after treatment for at least 6 weeks (e.g., at week 6 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR50 response after treatment for at least 4 weeks (e.g., at week 4 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR50 response after treatment for at least 2 weeks (e.g., at week 2 of treating).

[00589] In one embodiment, the adult subject receiving the treatment achieves an ACR70 response after treatment for at least 8 weeks (e.g., at week 8 of treating). In another embodiment, the adult subject receiving the treatment achieves an ACR70 response after treatment for at least 6 weeks (e.g., at week 6 of treating). In another embodiment, the adult

subject receiving the treatment achieves an ACR70 response after treatment for at least 4 weeks (e.g., at week 4 of treating).

[00590] In one embodiment, the adult subject receiving the treatment achieves a change in DAS28 score after treatment. In one embodiment, the change in DAS score is a decrease in DAS28(CRP) after treatment, as compared to baseline (i.e., DAS28(CRP) prior to treatment). In one embodiment, the adult subject achieves a decrease in DAS28 score as compared to baseline after treatment for at least twelve weeks (e.g., at week 12 of treating). In one embodiment, the adult subject achieves a decrease in DAS28(CRP) as compared to baseline after treatment for at least 12 weeks (e.g., at week 12 of treating). In another embodiment, the adult subject achieves a decrease in DAS28(CRP) as compared to baseline after treatment for at least 8 weeks (e.g., at week 8 of treating). In another embodiment, the adult subject achieves a decrease in DAS28(CRP) as compared to baseline after treatment for at least 6 weeks (e.g., at week 6 of treating). In another embodiment, the adult subject achieves a decrease in DAS28(CRP) as compared to baseline after treatment for at least 4 weeks (e.g., at week 4 of treating). In another embodiment, the adult subject achieves a decrease in DAS28(CRP) as compared to baseline after treatment for at least 2 weeks (e.g., at week 2 of treating).

[00591] In another embodiment, the adult subject receiving the treatment achieves a low disease activity (LDA) score or clinical remission after treatment. In one embodiment, the LDA score or clinical remission is measured as a DAS28 score (in particular, DAS28(CRP)) of 3.2 or less. In another embodiment, the LDA score or clinical remission is measured as a DAS28(CRP) of less than 2.6. In another embodiment, the LDA score or clinical remission is assessed using Clinical Disease Activity Index (CDAI) criteria. In one embodiment, the adult subject achieves a CDAI score of 10 or less after treatment. In another embodiment, the adult subject achieves a CDAI score of 2.8 or less after treatment. In one embodiment, the adult subject achieves the LDA score or clinical remission after treatment for at least 12 weeks (e.g., at week 12 of treating). In one embodiment, the adult subject achieves the LDA score or clinical remission after treatment for at least 8 weeks (e.g., at week 8 of treating). In one embodiment, the adult subject achieves the LDA score or clinical remission after treatment for at least 6 weeks (e.g., at week 6 of treating). In one embodiment, the adult subject achieves the LDA score or clinical remission after treatment for at least 4 weeks (e.g., at week 4 of treating). In one embodiment, the adult subject achieves the LDA score or clinical remission after treatment for at least 2 weeks (e.g., at week 2 of treating).

[00592] In one embodiment, the adult subject receiving the treatment achieves a change in mean modified Total Sharp Score (mTSS). In one embodiment, the adult subject receiving the treatment achieves a change in mTSS after treatment for at least twelve weeks (e.g., at week 12 of treating), or after treatment for at least twenty-four weeks (e.g., at week 24 of treating). In one embodiment, mTSS may be determined by scoring x-rays of the hand/wrist and feet joints for erosions and joint space narrowing. The erosion score and narrowing score are added to determine the total score.

[00593] In one embodiment, the adult subject receiving the treatment achieves a change in HAQ-DI score. In one embodiment, the adult subject receiving the treatment achieves a change in HAQ-DI score after treatment for at least twelve weeks (e.g., at week 12 of treating).

[00594] In one embodiment, the adult subject receiving the treatment achieves a change in Short Form 36 (SF-36) physical component score (PCS). In one embodiment, the adult subject receiving the treatment achieves a change in SF-36 PCS after treatment for at least twelve weeks (e.g., at week 12 of treating). SF-36 is a 36 item participant questionnaire with questions relating to participant health and daily activities.

[00595] In one embodiment, the adult subject receiving the treatment achieves a clinical remission (CR). In one embodiment, the adult subject receiving the treatment achieves a CR after treatment for at least twelve weeks (e.g., at week 12 of treating). In one embodiment, CR is determined based on DAS28 C-Reactive Protein (DAS28(CRP)) response rate. In one embodiment, CR is a DAS28(CRP) score of less than 2.6.

[00596] In one embodiment, the adult subject receiving the treatment achieves a change in functional assessment of chronic illness therapy (FACIT-F). In one embodiment, the adult subject receiving the treatment achieves a change in FACIT-F after treatment for at least twelve weeks (e.g., at week 12 of treating). FACIT-F is a participant questionnaire with 13 indexes rated on a 5 point scale. The indexes relate to the participant's level of fatigue during the past seven days.

[00597] In one embodiment, the adult subject receiving the treatment achieves a change in work instability score for rheumatoid arthritis (RA-WIS). In one embodiment, the adult subject receiving the treatment achieves a change in RA-WIS after treatment for at least twelve weeks (e.g., at week 12 of treating). RA-WIS is a participant questionnaire containing 23 questions relating to the participant's functioning in their work environment.

[00598] In one embodiment, the adult subject receiving the treatment achieves a change in morning stiffness severity. In one embodiment, the adult subject receiving the treatment achieves a change in morning stiffness severity after treatment for at least twelve weeks (e.g., at week 12 of treating). Morning stiffness severity is determined by the Patient's Assessment of Severity and Duration of Morning Stiffness questionnaire.

[00599] In one embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent to the subject, wherein the subject achieves an ACR20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR70 response at week 12 of treating. In one embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the

subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00600] In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to

the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR70 response at week 12 of treating. In another embodiment, the subject achieves an ACR70 response at week 8 of treating. In another embodiment, the subject achieves an ACR70 response at week 6 of treating. In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 15 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00601] In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit

dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR70 response at week 12 of treating. In another embodiment, the subject achieves an ACR70 response at week 8 of treating. In another embodiment, the subject achieves an ACR70 response at week 6 of treating. In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 24 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00602] In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In another embodiment, the subject achieves an ACR50 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR70 response at week 12 of treating. In another embodiment, the subject achieves an ACR70 response at week 8 of treating. In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as

compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 30 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00603] In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves an ACR70 response at week 12 of treating. In another embodiment, the subject achieves an ACR70 response at week 8 of treating. In another embodiment, the subject achieves an ACR70 response at week 6 of treating. In another

embodiment, the subject achieves an ACR70 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 45 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00604] In another embodiment, the adult subject is a subject who has had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs). In one embodiment, the DMARD is a conventional synthetic DMARD (csDMARD). In another embodiment, the DMARD is a biologic DMARD (bDMARD). Examples of csDMARDs include, but are not limited to, methotrexate (MTX), sulfasalazine, hydroxychloroquine, chloroquine, leflunomide, and azathioprine. Examples of bDMARDs include, but are not limited to, tocilizumab such as ACTEMRA™, etanercept such as p75TNFR1gG (ENBREL™ brand etanercept), adalimumab (such as HUMIRA™ brand adalimumab), and golimumab such as SIMPONI™ (golimumab). In one embodiment, the csDMARD is MTX. In one embodiment, the bDMARD is an anti-TNF biologic. An inadequate response or intolerance to one or more DMARDs can be measured using any of the indices described herein (e.g., failure to achieve an ACR20 response). In one embodiment, a subject having an inadequate response to a DMARD is a subject who does not achieve reduced disease activity, does not achieve an

improvement in physical function, exhibits no evidence of stopping disease progression, or who experiences disease relapse after treatment with the DMARD. In one embodiment, a subject having an inadequate response to a DMARD is a subject who does not achieve an ACR20 response after treatment with the DMARD. In one embodiment, a subject having an inadequate tolerance (intolerance) to a DMARD is a subject who experiences toxicity or complicating co-morbidities after treatment with the DMARD.

[00605] In one embodiment, the adult subject is a subject who has had an inadequate response to stable methotrexate therapy. In one embodiment, the adult subject received methotrexate therapy for at least three months prior to treatment. In another embodiment, the adult subject received a stable dose of methotrexate of about 7.5 to about 25 mg per week for at least four weeks prior to treatment. In another embodiment, the adult subject is administered a stable dose of methotrexate (e.g., from about 7.5 to about 25 mg per week) during treatment with Compound 1. In another embodiment, the adult subject received a supplement of folic acid for at least four weeks prior to treatment. In another embodiment, the adult subject is administered a supplement of folic acid during treatment.

[00606] In one embodiment, the adult subject is a subject who has had an inadequate response or intolerance to at least one anti-TNF therapy. Anti-TNF biologic agents are described elsewhere herein, and include TNF antagonists such as chimeric, humanized or human TNF antibodies, adalimumab (such as HUMIRA™ brand adalimumab), infliximab such as CA2 (REMICADE™ brand infliximab), golimumab such as SIMPONI™ (golimumab), certolizumab pegol such as CIMZIA™, tocilizumab such as ACTEMRA™, CDP 571, and soluble p55 or p75 TNF receptors, derivatives, thereof, etanercept such as p75TNFR1gG (ENBREL™ brand etanercept) or p55TNFR1gG (lenercept). In one embodiment, the adult subject received methotrexate therapy for at least three months prior to treatment. In another embodiment, the adult subject received a stable dose of methotrexate of about 7.5 to about 25 mg per week for at least four weeks prior to treatment. In another embodiment, the adult subject is administered a stable dose of methotrexate (e.g., from about 7.5 to about 25 mg per week) during treatment with Compound 1. In another embodiment, the adult subject has been treated with at least one anti-TNF biologic agent for at least three months prior to treatment with Compound 1. In another embodiment, the adult subject received a supplement of folic acid for at least four weeks prior to treatment. In another embodiment, the adult subject is administered a supplement of folic acid during treatment

[00607] In certain embodiments, the adult subject, who has had an inadequate response or tolerance to one or more DMARDS (including methotrexate and/or an anti-TNF biologic agent), achieves an ACR20 response, an ACR50 response, an ACR70 response, and/or a decrease in DAS28(CRP) as compared to baseline following treatment for at least twelve weeks (e.g., at week 12 of treating), and/or following treatment for at least 8 weeks (e.g., at week 8 of treating), and/or following treatment for at least 6 weeks (e.g., at week 6 of treating), and/or following treatment for at least 4 weeks (e.g., at week 4 of treating), and/or following treatment for at least 2 weeks (e.g., at week 2 of treating).

[00608] For instance, in one embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 70 response at week 12 of treating. In one

embodiment, the method or use comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00609] In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to

the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 70 response at week 12 of treating. In another embodiment, the subject achieves an ACR70 response at week 8 of treating. In another embodiment, the subject achieves an ACR70 response at week 6 of treating. In one embodiment, the method or use comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 15 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00610] In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In another embodiment, the subject achieves an ACR50 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 70 response at week 12 of treating. In one embodiment, the method or use comprises administering to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 24 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a

decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 24 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00611] In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating. In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In another embodiment, the subject achieves an ACR50 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit

dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 70 response at week 12 of treating. In one embodiment, the method or use comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 30 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00612] In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 20 response at week 12 of treating. In another embodiment, the subject achieves an ACR20 response at week 8 of treating. In another embodiment, the subject achieves an ACR20 response at week 6 of treating.

In another embodiment, the subject achieves an ACR20 response at week 4 of treating. In another embodiment, the subject achieves an ACR20 response at week 2 of treating. In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 50 response at week 12 of treating. In another embodiment, the subject achieves an ACR50 response at week 8 of treating. In another embodiment, the subject achieves an ACR50 response at week 6 of treating. In another embodiment, the subject achieves an ACR50 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves an ACR 70 response at week 12 of treating. In another embodiment, the subject achieves an ACR70 response at week 8 of treating. In another embodiment, the subject achieves an ACR70 response at week 6 of treating. In another embodiment, the subject achieves an ACR70 response at week 4 of treating. In one embodiment, the method or use comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, wherein the subject has had an inadequate response or intolerance to one or more DMARDS, and the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 12 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 8 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 6 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 4 of treating. In another embodiment, the subject achieves a decrease in DAS28(CRP) as compared to baseline at week 2 of treating. In one embodiment, the method or use comprises administering about 45 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt

thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00613] In another embodiment, the adult subject is also administered a csDMARD or a bDMARD in a combination therapy, as described hereinafter. In certain embodiments, the DMARD is MTX. In certain embodiments, the adult subject receiving the combination therapy achieves an ACR20 response, an ACR50 response, an ACR70 response, and/or a decrease in DAS28(CRP) as compared to baseline following treatment. In particular embodiments, the adult subject receiving the combination therapy achieves an ACR20 response, an ACR50 response, an ACR70 response, and/or a decrease in DAS28(CRP) as compared to baseline at week 12 of treating, and/or at week 8 of treating, and/or at week 6 of treating, and/or at week 4 of treating, and/or at week 2 of treating. In one embodiment, the adult subject receiving the combination therapy is administered about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent. In one embodiment, the adult subject receiving the combination therapy is administered about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent. In one embodiment, the adult subject receiving the combination therapy is administered about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent. In one embodiment, the adult subject receiving the combination therapy is administered about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent. In one embodiment, the method comprises administering

about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of the solid state form to the subject. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form is in a once daily extended release formulation. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00614] In another embodiment, any of the methods of treating an adult subject having moderate to severely active rheumatoid arthritis described herein may further comprises alleviating at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity. In another embodiment, the arthritis is further treated by alleviating at least one symptom selected from the group consisting of joint distortion, swelling, joint deformation, ankyloses on flexion, and severely impaired movement.

[00615] In another embodiment, the present disclosure relates to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis. The method comprises administering to the subject a therapeutically effective amount of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 (e.g., a crystalline hydrate or a crystalline anhydrate) as described herein, such that the structural damage in the adult subject is inhibited or lessened. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, such that the structural damage in the adult subject is inhibited or lessened. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of a solid state form of Compound 1, such that the structural damage in the adult subject is inhibited or lessened. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered to the subject orally QD (once daily). In one embodiment, the structural damage is selected from the group consisting of loss of

bone and/or cartilage, bone erosion, joint space narrowing as measured by radiography, and combinations thereof. In one embodiment, the structural damaged is inhibited or lessened when the structural damage is reduced by at least 20%, or at least 25%, or at least 30%, or at least 50%. In other embodiments, structural damage is inhibited or lessened when there is no further radiographic progression of the structural damage. In certain embodiments, structural joint damage can be assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and Joint Space Narrowing (JSN) score, for example, at week 12 compared to baseline. In another aspect, the disclosure relates to a solid state form (and in particular a crystalline hydrate) of Compound 1, as described in the present disclosure, for use in treatment of structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is a hemihydrate. In one embodiment, the hemihydrate is Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is Freebase Anhydrate Form D. In one embodiment, the stolid state form is Tartrate Hydrate. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is in a once daily extended release formulation. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is in a once daily extended release formulation, and the formulation delivers about 7.5 mg or about 15 mg or about 30 mg or about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) orally QD (once daily).

[00616] In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 (e.g., a crystalline hydrate or crystalline anhydrate), as described in the present disclosure for use in treatment of structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, such that the structural damage in the adult subject is inhibited or lessened, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is a hemihydrate. In one embodiment, the hemihydrate is Freebase Hydrate Form C. In one

embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhydrate is Freebase Anhydrate Form D. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the formulation delivers about 7.5 mg or about 15 mg or about 30 mg or about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) or a solid state form of Compound 1 orally QD (once daily).

[00617] In one embodiment, the present disclosure is directed to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, such that the structural damage in the adult subject is inhibited or lessened. In one embodiment, the method comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, for use in treatment of structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, such that the structural damage in the adult subject is inhibited or lessened, the use comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the structural damage is selected from the

group consisting of loss of bone and/or cartilage, bone erosion, joint space narrowing as measured by radiography, and combinations thereof.

[00618] In one embodiment, the present disclosure is directed to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, the method comprising administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, such that the structural damage in the adult subject is inhibited or lessened. In one embodiment, the method comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, for use in treatment of structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, such that the structural damage in the adult subject is inhibited or lessened, the use comprising administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the structural damage is selected from the group consisting of loss of bone and/or cartilage, bone erosion, joint space narrowing as measured by radiography, and combinations thereof.

[00619] In one embodiment, the present disclosure is directed to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid

arthritis, the method comprising administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, such that the structural damage in the adult subject is inhibited or lessened. In one embodiment, the method comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, for use in treatment of structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, such that the structural damage in the adult subject is inhibited or lessened, the use comprising administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the structural damage is selected from the group consisting of loss of bone and/or cartilage, bone erosion, joint space narrowing as measured by radiography, and combinations thereof.

[00620] In one embodiment, the present disclosure is directed to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, the method comprising administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent, such that the structural damage in the adult subject is inhibited or lessened. In one

embodiment, the method comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, for use in treatment of structural damage associated with rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, such that the structural damage in the adult subject is inhibited or lessened, the use comprising administering to the subject 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Comound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the structural damage is selected from the group consisting of loss of bone and/or cartilage, bone erosion, joint space narrowing as measured by radiography, and combinations thereof.

[00621] In another embodiment, the present disclosure is directed to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderately to severely active rheumatoid arthritis. The method comprises administering to the subject a therapeutically effective amount of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 (e.g., a crystalline hydrate or a crystalline anhydrate) as described herein. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent. In one embodiment, the method comprises administering to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule)

of a solid state form of Compound 1. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered to the subject orally QD (once daily). In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form (and in particular a crystalline hydrate) of Compound 1, as described in the present disclosure, for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the use comprising administering to the subject a therapeutically effective amount of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form (and in particular a crystalline hydrate) of Compound 1. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the formulation delivers about 7.5 mg or about 15 mg or about 30 mg or about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) or the solid state form of Compound 1 to the subject orally QD (once daily). In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhdyrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate.

[00622] In one embodiment, the present disclosure is directed to a method of reducing the signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent. In one embodiment, the method comprises administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the use comprising administering to the subject about 7.5 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1

freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is a hemihydrate. In one embodiment, the hemihydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation, and the formulation delivers about 7.5 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) or the solid state form of Compound 1 orally QD (once daily) to the subject.

[00623] In one embodiment, the present disclosure is directed to a method of reducing the signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent. In one embodiment, the method comprises administering to the subject about 15 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the use comprising administering to the subject, about 15 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is a hemihydrate. In one embodiment, the hemihydrate is Freebase Hydrate Form C. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one

embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation, and the formulation delivers about 15 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) or the solid state form of Compound 1 orally QD (once daily) to the subject.

[00624] In another embodiment, the present disclosure is directed to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderately to severely active rheumatoid arthritis. The method comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent. In one embodiment, the method comprises administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the use comprising administering to the subject about 30 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is a hemihydrate. In one embodiment, the hemihydrate is Freebase Hydrate Form C. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 (freebase) or the crystalline hydrate is in a once

daily extended release formulation. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation, and the formulation delivers about 30 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) or the solid state form of Compound 1 orally QD (once daily) to the subject.

[00625] In one embodiment, the present disclosure is directed to a method of reducing the signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderately to severely active rheumatoid arthritis, the method comprising administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent. In one embodiment, the method comprises administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In another aspect, the disclosure relates to Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to moderate to severely active rheumatoid arthritis, the use comprising administering to the subject about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1. In one embodiment, the solid state form is a crystalline hydrate. In one embodiment, the crystalline hydrate is the Freebase Hydrate Form B. In one embodiment, the crystalline hydrate is a hemihydrate. In one embodiment, the hemihydrate is the Freebase Hydrate Form C. In one embodiment, the solid state form is a crystalline anhdyrate. In one embodiment, the crystalline anhydrate is the Freebase Anhydrate Form D. In one embodiment, the solid state form is the Tartrate Hydrate. In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is administered orally QD (once daily). In one embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 is in a once daily extended release formulation, and the formulation delivers about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound

1 (freebase equivalent) or the solid state form of Compound 1 orally QD (once daily) to the subject.

[00626] In another aspect, the disclosure relates to a solid state form (and in particular a crystalline hydrate) of Compound 1, as described in the present disclosure, for use in reducing signs and symptoms of rheumatoid arthritis in an adult subject, particularly in a human subject suffering from or susceptible to rheumatoid arthritis.

[00627] In another embodiment, any of the methods of reducing signs and symptoms of rheumatoid arthritis described herein may further comprises alleviating at least one symptom selected from the group consisting of bone erosion, cartilage erosion, inflammation, and vascularity. In another embodiment, the arthritis is further treated by alleviating at least one symptom selected from the group consisting of joint distortion, swelling, joint deformation, ankyloses on flexion, and severely impaired movement.

[00628] In another embodiment, the Compound 1 freebase or a pharmaceutically acceptable salt thereof and/or solid state forms of Compound 1 used in any of the methods set forth herein may be administered to the subject in a once daily extended release solid oral dosage form. In particular, in one embodiment, the methods comprise once daily administration to the subject of an extended release (e.g., modified release) solid oral dosage form comprising the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1. In one aspect, the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 hours to about 24 hours following entry of the dosage form into a use environment. In one embodiment, the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment. The term "entry into a use environment" refers to contact of the dosage form with gastric fluids of the subject to whom it is administred. As used herein, the term "release rate" refers to the percentage of the active ingredient (e.g., Compound 1 or a solid state form of Compound 1) in the dosage form that is released in the given time period, and under the specified conditions. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg or about 15 mg or

about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of Compound 1 freebase equivalent. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), per day of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the pharmaceutically acceptable polymeric carrier is a release control polymer, as set forth herein.

[00629] Thus, in one aspect, the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Comound 1 for from about 4 hours to about 24 hours. In one embodiment, the dosage form releases the active ingredient (i.e., Compound 1 or a solid state form of Compound 1), at a release rate of not more than about 25%, or from about 10% to about 25%, or from about 15% to about 20%, or about 20% after passage of about 1 hour following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 40%, or from about 20% to about 40%, or from about 25% to about 35% after passage of about 2 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a relase rate of not more than about 60%, or from about 30% to about 60%, or from about 40% to about 60%, or from about 45% to about 55% after passage of about 4 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 70% or from about 40% to about 70%, or from about 55% to about 70% after passage of about 6 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 80% or from about 55% to about 80%, or from about 60% to about 80% after passage of about 6 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 80%, or not less than about 50%, or not less than about 60%, or not less than about 70%, or not less than about 75%, or from about 50% to about 80%, or from about 60% to about 80%, or from about 65% to about 80% after passage of about 8 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not less than about 55%, or not less than about 60% or not less than about 70%, or not less than about 80%, or not less than about 85%, or from about 55% to about 90%, or from about 70% to about 90% after passage of about 10 hours following entry into the use environment. In

one embodiment, the dosage form releases the active ingredient at a release rate of not less than about 65%, or not less than about 70%, or not less than about 80%, or not less than about 90%, or from about 65% to about 99%, or from about 80% to about 99%, or from about 90% to about 99% after passage of about 16 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not less than about 70%, or not less than about 80%, or not less than about 90%, or from about 70% to 100%, or from about 80% to 100% after passage of about 20 hours following entry into the use environment. In one aspect, the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment, from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00630] In one embodiment, the present disclosure is directed to a method of treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus, the method comprising once daily administration to a subject suffering from or susceptible to the condition, of an extended release solid oral dosage form comprising about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In

one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00631] In another aspect, the disclosure is directed to an extended release solid oral dosage form comprising Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus, the use comprising once daily administration to a subject suffering from or susceptible to the condition, of the extended release solid oral dosage form, wherein the solid dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase, or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use

environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00632] In another embodiment, the disclosure is directed to a method of treating an adult subject having moderate to severely active rheumatoid arthritis, the method comprising once daily administration to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, of an extended release solid oral dosage form comprising about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment. In one embodiment, the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating.

[00633] In another aspect, the disclosure is directed to an extended release solid oral dosage form comprising Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treating an adult subject having moderate to severely

active rheumatoid arthritis, the use comprising once daily administration to the subject, particularly a subject suffering from or susceptible to moderately to severely active rheumatoid arthritis, of the extended release solid oral dosage form, wherein the solid dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase or a pharmaceutically acceptable salt thereof, or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment. In one embodiment, the subject has symptoms selected from the group consisting of at least 6 swollen joints, at least 6 tender joints, and combinations thereof prior to treating.

[00634] In one embodiment, the disclosure is directed to a method of treating structural damage associated with rheumatoid arthritis in an adult subject, the method comprising once daily administration to the subject, particularly a human subject suffering from or susceptible to rheumatoid arthritis, of an extended release solid oral dosage form comprising about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or

about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase or a pharmaceutically acceptable salt thereof equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment,t the solid state form is Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00635] In another aspect, the disclosure is directed to an extended release solid oral dosage form comprising Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in treating structural damage associated with rheumatoid arthritis in an adult subject, the use comprising once daily administration to the subject, particularly a subject suffering from or susceptible to structural damage associated with rheumatoid arthritis, of the extended release solid oral dosage form, wherein the solid dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase, or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically

acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment,t the solid state form is Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00636] In one embodiment, the disclosure is directed to a method of reducing signs and symptoms of rheumatoid arthritis in an adult subject, the method comprising once daily administration to the subject, particularly a human subject suffering from or susceptible to moderately to severely active rheumatoid arthritis, of an extended release solid oral dosage form comprising about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the solid state form is

Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00637] In another aspect, the disclosure is directed to an extended release solid oral dosage form comprising Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 for use in reducing signs and symptoms associated with rheumatoid arthritis in an adult subject, the use comprising once daily administration to the subject, particularly a subject suffering from or susceptible to rheumatoid arthritis, of the extended release solid oral dosage form, wherein the solid dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule) of Compound 1 freebase, or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in an amount sufficient to deliver to the subject about 7.5 mg, or about 15 mg, or about 30 mg, or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of Compound 1 freebase equivalent, and a pharmaceutically acceptable polymeric carrier substantially contributing to the modification of the release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1, wherein the dosage form sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 to about 24 hours following entry of the dosage form into a use environment, wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following said entry into said use environment. In one embodiment, the dosage form comprises about 7.5 mg or about 15 mg or about 30 mg or about 45 mg, per unit dosage form (e.g., per tablet or capsule), of a solid state form of Compound 1. In one embodiment, the solid state form is Freebase Hydrate Form B. In one embodiment, the solid state form is Freebase Hydrate Form C. In one embodiment, the solid state form is Freebase Anhydrate Form D. In one embodiment, the solid state form is Tartrate Hydrate. In one embodiment, the dosage form further has a release rate of from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and/or from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00638] In the foregoing methods, in one embodiment, the pharmaceutically acceptable polymeric carrier comprises a release control polymer. In one embodiment, the release control polymer is hydroxypropylmethyl cellulose. In one embodiment, the dosage form comprises a pH modifier. In one embodiment, the pH modifier is tartaric acid. In one embodiment, the dosage form comprises from about 10 w/w% to about 35 w/w% tartaric acid. In one embodiment, the dosage form comprises about 10 w/w% tartaric acid. In one embodiment, the dosage form comprises about 20 w/w% tartaric acid. In one embodiment, the dosage form comprises about 30 w/w% tartaric acid.

[00639] In another embodiment the methods of the present disclosure further comprise administering Compound 1 or a solid state form thereof for at least 8 weeks. In another embodiment, the methods of the present disclosure comprise administering Compound 1 or a solid state form thereof for at least 12 weeks.

[00640] In another embodiment, the present disclosure relates to the use of a solid state form of Compound 1 for treating a condition as described in the various embodiments of the present disclosure.

[00641] In another embodiment, the present disclosure relates to a solid state form of Compound 1 for use in treatment of a condition as described in the various embodiments of the present disclosure.

V. Combination Therapy and Fixed-Dose Combinations

[00642] The present disclosure further relates to (i) methods of treatment and uses as previously described that further comprise the administration of one or more additional therapeutic agents (*i.e.*, combination therapies), and (ii) pharmaceutical compositions as previously described that further comprise one or more additional therapeutic agents (*i.e.*, fixed-dose combinations). When administered to a subject in combination with one or more additional therapeutic agents, the solid state form of Compound 1 and the additional therapeutic agent(s) can be administered as separate dosage forms or as a single dosage form comprising the solid state form of Compound 1 and the additional therapeutic agent(s). If administered as a separate dosage form, the additional therapeutic agent may be administered either simultaneously with, or sequentially with, the dosage form comprising the solid state form of Compound 1.

[00643] For example, the solid state forms of the present disclosure may be administered in a pharmaceutically acceptable form either alone or in combination with one or more

additional agents that modulate a mammalian immune system or with anti-inflammatory agents. These agents may include but are not limited to cyclosporin A (*e.g.*, SANDIMMUNE® or NEORAL®, rapamycin, FK-506 (tacrolimus), leflunomide, deoxyspergualin, mycophenolate (*e.g.*, CELLCEPT®), azathioprine (*e.g.*, IMURAN®), daclizumab (*e.g.*, ZENAPAX®), OKT3 (*e.g.*, ORTHOCLONE®), AtGam, aspirin, acetaminophen, aminosalicylate, ciprofloxacin, corticosteroid, metronidazole, probiotic, tacrolimus, ibuprofen, naproxen, piroxicam, and anti-inflammatory steroids (*e.g.*, prednisolone or dexamethasone). In certain embodiments, the one or more additional agents are selected from the group consisting of aspirin, acetaminophen, aminosalicylate, ciprofloxacin, corticosteroid, cyclosporine, metronidazole, probiotic, tacrolimus, ibuprofen, naproxen, piroxicam, prednisolone, dexamethasone, anti-inflammatory steroid, methotrexate, chloroquine, azathioprine, hydroxychloroquine, penicillamine, sulfasalazine, leflunomide, tocilzumab, anakinra, abatacept, certolizumab pegol, golimumab, vedolizumab, natalizumab, ustekinumab, rituximab, efalizumab, belimumab, etanercept, infliximab, adalimumab, and immune modulator (*e.g.*, activator) for CD4+CD25+ T_{reg} cells.

[00644] Non-limiting examples of therapeutic agents for rheumatoid arthritis with which a compound of the invention can be combined include the following: cytokine suppressive anti-inflammatory drug(s) (CSAIDs); antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IL-21, IL-23, interferons, EMAP-II, GM-CSF, FGF, and PDGF. Compounds of the invention can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD80 (B7.1), CD86 (B7.2), CD90, CTLA or their ligands including CD154 (gp39 or CD40L). Combinations of therapeutic agents may interfere at different points in the autoimmune and subsequent inflammatory cascade. Such examples may include TNF antagonists like chimeric, humanized or human TNF antibodies, adalimumab (such as HUMIRA™ brand adalimumab), infliximab such as CA2 (REMICADE™ brand infliximab), golimumab such as SIMPONI™ (golimumab), certolizumab pegol such as CIMZIA™, tocilizumab such as ACTEMRA™, CDP 571, and soluble p55 or p75 TNF receptors, derivatives, thereof, etanercept such as p75TNFR1gG (ENBREL™ brand etanercept) or p55TNFR1gG (lenercept), and also TNFα converting enzyme (TACE) inhibitors; similarly IL-1 inhibitors (Interleukin-1-converting enzyme inhibitors, IL-1RA *etc.*) may be effective for the same reason. Other combinations include Interleukin 11.

[00645] The solid state form may also be combined with nonbiologic DMARDS or other agents, such as methotrexate, 6-mercaptopurine, azathioprine sulphasalazine, mesalazine,

olsalazine chloroquinine / hydroxychloroquine, pencillamine, aurothiomalate (intramuscular and oral), azathioprine, cochicine, corticosteroids (oral, inhaled and local injection), beta-2 adrenoreceptor agonists (salbutamol, terbutaline, salmeteral), xanthines (theophylline, aminophylline), cromoglycate, nedocromil, ketotifen, ipratropium and oxitropium, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as IL-1 (*e.g.*, NIK, IKK, p38 or MAP kinase inhibitors), IL-1β converting enzyme inhibitors, T-cell signalling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, and 6-mercaptopurines. The solid state form may also be combined with methotrexate.

[00646] Non-limiting examples of therapeutic agents for inflammatory bowel disease (IBD) with which the solid state form can be combined may include (but are not limited to) the following: budenoside; epidermal growth factor; corticosteroids; cyclosporin, sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1β monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IL-23, EMAP-II, GM-CSF, FGF, and PDGF; cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands; methotrexate; cyclosporine; FK506; rapamycin; mycophenolate mofetil; leflunomide; NSAIDs, for example, ibuprofen; corticosteroids such as prednisolone; phosphodiesterase inhibitors; adenosine agonists; antithrombotic agents; complement inhibitors; adrenergic agents; agents which interfere with signalling by proinflammatory cytokines such as TNFα or IL-1 (*e.g.*, NIK, IKK, or MAP kinase inhibitors); IL-1β converting enzyme inhibitors; TNFα converting enzyme inhibitors; T-cell signalling inhibitors such as kinase inhibitors; metalloproteinase inhibitors; sulfasalazine; azathioprine; 6-mercaptopurines; angiotensin converting enzyme inhibitors; soluble cytokine receptors and derivatives thereof (*e.g.* soluble p55 or p75 TNF receptors, sIL-1RI, sIL-1RII, sIL-6R) and anti-inflammatory cytokines (*e.g.*, IL-4, IL-10, IL-11, IL-13 and TGFβ). The solid state form may also be combined with methotrexate.

[00647] Examples of therapeutic agents for Crohn's disease with which the solid state form can be combined include the following: TNF antagonists, for example, anti-TNF

antibodies, adalimumab (such as HUMIRA™ brand adalimumab), infliximab such as CA2 (REMICADE™ brand infliximab), certolizumab pegol such as CIMZIA™, golimumab such as SIMPONI™ (golimumab), CDP 571, TNFR-Ig constructs, etanercept such as p75TNFRIgG (ENBREL™ brand etanercept) and lenercept such as p55TNFRIgG (Lenercept™) inhibitors and PDE4 inhibitors.

[00648] The solid state form can be combined with corticosteroids, for example, budenoside and dexamethasone; sulfasalazine, 5-aminosalicylic acid; olsalazine; and agents which interfere with synthesis or action of proinflammatory cytokines such as IL-1, for example, IL-1β converting enzyme inhibitors and IL-1ra; T cell signaling inhibitors, for example, tyrosine kinase inhibitors; 6-mercaptopurine; IL-11; mesalamine; prednisone; azathioprine; mercaptopurine; methylprednisolone sodium succinate; diphenoxylate/atrop sulfate; loperamide hydrochloride; methotrexate; omeprazole; folate; ciprofloxacin/dextrose-water; hydrocodone bitartrate/apap; tetracycline hydrochloride; fluocinonide; metronidazole; thimerosal/boric acid; cholestyramine / sucrose; ciprofloxacin hydrochloride; hyoscyamine sulfate; meperidine hydrochloride; midazolam hydrochloride; oxycodone HCl / acetaminophen; promethazine hydrochloride; sodium phosphate; sulfamethoxazole / trimethoprim; celecoxib; polycarbophil; propoxyphene napsylate; hydrocortisone; multivitamins; balsalazide disodium; codeine phosphate/apap; colesevelam HCl; cyanocobalamin; folic acid; levofloxacin; methylprednisolone; natalizumab and interferon-gamma.

[00649] Non-limiting examples of therapeutic agents for multiple sclerosis (MS) with which the solid state form can be combined include the following: corticosteroids; prednisolone; methylprednisolone; azathioprine; cyclophosphamide; cyclosporine; methotrexate; 4-aminopyridine; tizanidine; interferon-β1a (AVONEX®; Biogen); interferon-β1b (BETASERON®; Chiron/Berlex); interferon α-n3) (Interferon Sciences/Fujimoto), interferon-α (Alfa Wassermann/J&J), interferon β1A-IF (Serono/Inhale Therapeutics), Peginterferon α 2b (Enzon/Schering-Plough), Copolymer 1 (Cop-1; COPAXONE®; Teva Pharmaceutical Industries, Inc.); hyperbaric oxygen; intravenous immunoglobulin; cladribine; antibodies to or antagonists of other human cytokines or growth factors and their receptors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-23, IL-15, IL-16, EMAP-II, GM-CSF, FGF, and PDGF. A compound of the invention can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD19, CD20, CD25, CD28, CD30, CD40, CD45, CD69, CD80, CD86, CD90 or their ligands. The solid state form may also be combined with agents such as methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil, leflunomide, an S1P1

agonist, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adensosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNFα or IL-1 (*e.g.*, NIK, IKK, p38 or MAP kinase inhibitors), IL-1β converting enzyme inhibitors, TACE inhibitors, T-cell signaling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (*e.g.*, soluble p55 or p75 TNF receptors, sIL-1RI, sIL-1RII, sIL-6R) and anti-inflammatory cytokines (*e.g.* IL-4, IL-10, IL-13 and TGFβ). Examples of therapeutic agents for multiple sclerosis in which a compound of the invention can be combined to include interferon-β, for example, IFNβ1a and IFNβ1b; copaxone, corticosteroids, caspase inhibitors, for example inhibitors of caspase-1, IL-1 inhibitors, TNF inhibitors, and antibodies to CD40 ligand and CD80.

[00650] The solid state form may also be combined with agents, such as alemtuzumab, dronabinol, daclizumab, mitoxantrone, xaliproden hydrochloride, fampridine, glatiramer acetate, natalizumab, sinnabidol, α-immunokine NNSO3, ABR-215062, AnergiX.MS, chemokine receptor antagonists, BBR-2778, calagualine, CPI-1189, LEM (liposome encapsulated mitoxantrone), THC.CBD (cannabinoid agonist), MBP-8298, mesopram (PDE4 inhibitor), MNA-715, anti-IL-6 receptor antibody, neurovax, pirfenidone allotrap 1258 (RDP-1258), sTNF-R1, talampanel, teriflunomide, TGF-beta2, tiplimotide, VLA-4 antagonists (for example, TR-14035, VLA4 Ultrahaler, Antegran-ELAN/Biogen), interferon gamma antagonists and IL-4 agonists.

[00651] Non-limiting examples of therapeutic agents for ankylosing spondylitis (AS) with which the solid state form can be combined include the following: ibuprofen, diclofenac, misoprostol, naproxen, meloxicam, indomethacin, diclofenac, celecoxib, rofecoxib, sulfasalazine, methotrexate, azathioprine, minocyclin, prednisone, and anti-TNF antibodies, adalimumab (such as HUMIRA™ brand adalimumab), infliximab such as CA2 (REMICADE™ brand infliximab), CDP 571, TNFR-Ig constructs, etanercept such as p75TNFRIgG (ENBREL™ brand etanercept) and lenercept such as p55TNFRIgG (LENERCEPT™).

[00652] Non-limiting examples of therapeutic agents for psoriasis (Ps, such as moderate to severe plaque psoriasis) with which the solid state form can be combined include the following: calcipotriene, clobetasol propionate, triamcinolone acetonide, halobetasol propionate, tazarotene, methotrexate, fluocinonide, betamethasone diprop augmented, fluocinolone

acetonide, acitretin, tar shampoo, betamethasone valerate, mometasone furoate, ketoconazole, pramoxine/fluocinolone, hydrocortisone valerate, flurandrenolide, urea, betamethasone, clobetasol propionate/emoll, fluticasone propionate, azithromycin, hydrocortisone, moisturizing formula, folic acid, desonide, pimecrolimus, coal tar, diflorasone diacetate, etanercept folate, lactic acid, methoxsalen, hc/bismuth subgal/znox/resor, methylprednisolone acetate, prednisone, sunscreen, halcinonide, salicylic acid, anthralin, clocortolone pivalate, coal extract, coal tar/salicylic acid, coal tar/salicylic acid/sulfur, desoximetasone, diazepam, emollient, fluocinonide/emollient, mineral oil/castor oil/na lact, mineral oil/peanut oil, petroleum/isopropyl myristate, psoralen, salicylic acid, soap/tribromsalan, thimerosal/boric acid, celecoxib, infliximab, cyclosporine, alefacept, efalizumab, tacrolimus, pimecrolimus, PUVA, UVB, sulfasalazine, ABT-874, ustekinamab, and adalimumab (such as HUMIRA™ brand adalimumab).

[00653] Non-limiting examples of therapeutic agents for psoriatic arthritis (PsA) with which the solid state form can be combined include the following: methotrexate, etanercept, rofecoxib, celecoxib, folic acid, sulfasalazine, naproxen, leflunomide, methylprednisolone acetate, indomethacin, hydroxychloroquine sulfate, prednisone, sulindac, betamethasone diprop augmented, infliximab, methotrexate, folate, triamcinolone acetonide, diclofenac, dimethylsulfoxide, piroxicam, diclofenac sodium, ketoprofen, meloxicam, methylprednisolone, nabumetone, tolmetin sodium, calcipotriene, cyclosporine, diclofenac sodium/misoprostol, fluocinonide, glucosamine sulfate, gold sodium thiomalate, hydrocodone bitartrate/apap, ibuprofen, risedronate sodium, sulfadiazine, thioguanine, valdecoxib, alefacept, adalimumab (such as HUMIRA™ brand adalimumab), and efalizumab.

[00654] Examples of therapeutic agents for SLE (Lupus) with which the solid state form can be combined include the following: NSAIDS, for example, diclofenac, naproxen, ibuprofen, piroxicam, indomethacin; COX2 inhibitors, for example, celecoxib, rofecoxib, valdecoxib; anti-malarials, for example, hydroxychloroquine; steroids, for example, prednisone, prednisolone, budenoside, dexamethasone; cytotoxics, for example, azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate; inhibitors of PDE4 or purine synthesis inhibitor, for example CELLCEPT®. The solid state form may also be combined with agents such as sulfasalazine, 5-aminosalicylic acid, olsalazine, IMURAN® and agents which interfere with synthesis, production or action of proinflammatory cytokines such as IL-1, for example, caspase inhibitors like IL-1β converting enzyme inhibitors and IL-1ra. The solid state form may also be used with T cell signaling inhibitors, for example, tyrosine kinase inhibitors; or molecules that

target T cell activation molecules, for example, CTLA-4-IgG or anti-B7 family antibodies, anti-PD-1 family antibodies. The solid state form can be combined with IL-11 or anti-cytokine antibodies, for example, fonotolizumab (anti-IFNg antibody), or anti-receptor receptor antibodies, for example, anti-IL-6 receptor antibody and antibodies to B-cell surface molecules. The solid state form may also be used with LJP 394 (abetimus), agents that deplete or inactivate B-cells, for example, Rituximab (anti-CD20 antibody), lymphostat-B (anti-BlyS antibody), TNF antagonists, for example, anti-TNF antibodies, adalimumab (such as HUMIRA™ brand adalimumab), infliximab such as CA2 (REMICADE™ brand infliximab), CDP 571, TNFR-Ig constructs, etanercept such as p75TNFRIgG (ENBREL™ brand etanercept) and lenercept such as p55TNFRIgG (LENERCEPT™).

[00655] The solid state form may also be combined with an immune modulator for CD4+CD25+ T_{reg} cells. T_{reg} cells are essential for maintaining normal immune homeostasis. In patients with autoimmune diseases, reduced numbers or functional impairment of T_{reg} cells has been observed, leading to loss of this finely-tuned mechanism. A humanized agonistic monoclonal antibody, BT-061, binds to a unique epitope of human CD4, and induces T_{reg}-specific signaling events that lead to their functional activation. Pre-clinical data using isolated T_{reg} cells and rheumatoid arthritis synovial fluid indicate that BT-061 leads to suppression of CD4+ and CD8+ T effector cell proliferation, reduction of the expression of pro-inflammatory cytokines, and increase in the production of the anti-inflammatory cytokine TGFβ. Thus similar immune modulators for CD4+CD25+ T_{reg} cells can also be co-administered with a compound of the invention for treating any of the inflammatory disease / disorder, or an autoimmune disease / disorder described herein, including but not limited to rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, systemic lupus erythematosus, lupus nephritis, diabetic nephropathy, dry eye syndrome, Sjogren's syndrome, alopecia areata, vitiligo, or atopic dermatitis. In certain embodiments, the combination treats rheumatoid arthritis, Crohn's disease, psoriasis, or psoriatic arthritis, including moderately to severely active rheumatoid arthritis, Crohn's disease, psoriasis, or psoriatic arthritis. In certain embodiments, the rheumatoid arthritis, Crohn's disease, psoriasis, or psoriatic arthritis patient being treated has inadequately responded to or has discontinued therapy due to loss of response to or intolerance to a first line therapy (such as a DMARD, including methotrexate) or an anti-TNFα therapy.

[00656] In certain embodiments, the immune modulator has one or more (or all) of the following properties: (1) activates a subset of CD4+ T cells comprising CD4+CD25+ regulatory

T cells (T_{reg}), or CD4+CD25+ T_{reg} cells; (2) binds only to a special epitope of the human CD4 antigen (such as the IgG-like C2 type 1 domain of CD4), which said epitope of human CD4 may be bound by a mouse IgG1 anti-CD4 monoclonal antibody B-F5 or a humanized version thereof, such as the BT-061 hB-F5 antibody tregalizumab as described in U.S. Pat. No. 7,452,981 (including all sequences of the VH and VL chains disclosed therein); (3) provides an activation signal to naturally occurring T_{reg} cells but does not activate conventional T cells (*e.g.*, CD4+ T cells that are not activated in (1), CD8+ cytotoxic T cells, *etc.*); and (4) is not a depleting anti-CD4 antibody that depletes CD4+ T cells, and/or does not appreciably trigger ADCC or CDC.

VI. Pharmaceutical Compositions

[00657] The present disclosure further relates, in part, to compositions comprising Compound 1 or a pharmaceutically acceptable salt thereof, or one or more solid state forms of Compound 1. Although the solid state form may be administered alone or in the form of a pharmaceutical composition, administration generally will be in the form of a pharmaceutical composition. In some embodiments, the composition comprises Compound 1 or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1 in association with a pharmaceutically acceptable carrier. The preferred composition depends on the method of administration, and typically comprises one or more conventional pharmaceutically acceptable carriers, adjuvants, and/or vehicles (together referred to as "excipients"). Such compositions can be formulated for various routes of systemic or local delivery for example, by oral administration, topical administration, transmucosal administration, rectal administration, intravaginal administration, or administration by subcutaneous, intrathecal, intravenous, intramuscular, intraperitoneal, intranasal, intraocular or intraventricular injection.

[00658] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the compounds or salts are ordinarily combined with one or more excipients. If administered per os, the compounds or salts can be mixed with, for example, lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in, for example, a dispersion of the compound or salt in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise pH

modifiers, such as sodium citrate; magnesium or calcium carbonate or bicarbonate; tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and phosphoric acid and combinations thereof. Tablets and pills additionally can be prepared with enteric coatings.

[00659] Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions (including both oil-in-water and water-in-oil emulsions), solutions (including both aqueous and non-aqueous solutions), suspensions (including both aqueous and non-aqueous suspensions), syrups, and elixirs containing inert diluents commonly used in the art (*e.g.*, water). Such compositions also can comprise, for example, wetting, emulsifying, suspending, sweeting and flavoring agents.

[00660] Parenteral administration includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (*e.g.*, sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Acceptable vehicles and solvents include, for example, water, 1,3-butanediol, Ringer's solution, isotonic sodium chloride solution, bland fixed oils (*e.g.*, synthetic mono- or diglycerides), fatty acids (*e.g.*, oleic acid), dimethyl acetamide, surfactants (*e.g.*, ionic and non-ionic detergents), and/or polyethylene glycols.

[00661] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the excipients mentioned for use in the formulations for oral administration. A compound or salt of the invention can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various pH modifiers. The pH may be adjusted, if necessary, with a suitable acid, base, or pH modifier.

[00662] Suppositories for rectal administration can be prepared by, for example, mixing a compound or salt of the invention with a suitable nonirritating excipient that is solid at ordinary temperatures, but liquid at the rectal temperature, and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter; synthetic mono-, di-, or triglycerides, fatty acids, and/or polyethylene glycols.

[00663] Compound 1 or the solid state forms of the present disclosure can be formulated for administration topically to the skin or mucosa, *i.e.*, dermally or transdermally. Such administration can include the use, *e.g.*, of transdermal patches or iontophoresis devices.

[00664] Besides those representative dosage forms described above, pharmaceutically acceptable excipients and carriers are generally known to those skilled in the art and are thus included in the instant invention. Formulation of drugs is generally discussed in, for example, Hoover, J., Remington's Pharmaceutical Sciences (Mack Publishing Co., 1975) and Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems (Lippincott Williams & Wilkins, 2005).

[00665] Depending upon the route and frequency of administration, the pharmaceutical compositions of the present invention can contain, for example, from about 0.1 percent by weight to about 99 percent or more by weight of the active ingredient. The amount of active ingredient contained in the dosage unit composition employed for adult human treatment generally can range, for example, from about 0.01 mg to about 3000 mg. For the therapeutic uses described in this application, the amount of active ingredient contained in the dosage unit composition generally will be in the range, for example, from about 0.1 mg to about 1000 mg. In one embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 500 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 250 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 100 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 50 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 45 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 30 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 25 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 24 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 15 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 10 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 1 mg to about 7.5 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 10 mg to about 20 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 20

mg to about 30 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 30 mg to about 40 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 7.5 mg to about 45 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is in a range from about 15 mg to about 30 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 3 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 6 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 7.5 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 12 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 15 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 18 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 24 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 30 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 36 mg. In another embodiment, the amount of active ingredient contained in the dosage unit composition is about 45 mg.

[00666] In one embodiment, the active ingredient contained in the dosage unit composition is Compound 1, or a pharmaceutically acceptable salt thereof. In one embodiment, the target or label amount of active ingredient (e.g., Compound 1) provided for inclusion in the compositions of the present disclosure refers to the amount of Compound 1 freebase. For instance, as discussed herein, Compound 1 may be prepared in several solid state forms including Amorphous Freebase, crystalline solvates and hydrates (e.g., Freebase Solvate Form A, Freebase Hydrate Form B), crystalline hemihydrates (e.g., Freebase Hydrate Form C), crystalline anhydrate (e.g., Freebase Anhydrate Form D), crystalline tartrate (e.g., Tartrate Hydrate), crystalline hydrochloride (e.g., Hydrochloride Solvate Form AA, Hydrochloride Solvate Form BB, Hydrochloride Solvate Form CC), and crystalline L-maleate (e.g., L-Maleate Form AAA, L-Maleate Form BBB, L-Maleate Form CCC). It should be understood that in embodiments, where the dosage unit composition comprises, e.g., a solvate, hydrate, hemihydrate, tartrate, hydrochloride, or L-maleate of Compound 1, the amount of solvate, hydrate, hemihydrate, tartrate, hydrochloride, or L-maleate of Compound 1 present in the dosage unit composition may be slightly higher than the target amount of Compound 1 (active

ingredient), and preferably will be present in the dosage unit composition in an amount sufficient to deliver the target amount of Compound 1 freebase equivalent to a subject. For example, if the target amount of Compound 1 (active ingredient) in a dosage unit composition is 15 mg, a dosage unit composition comprising, for example, Freebase Hydrate Form C, may comprise the Freebase Hydrate Form C in an amount sufficient to deliver 15 mg of the Compound 1 freebase equivalent.

[00667] In one embodiment, the pharmaceutical composition is a tablet dosage form. In one aspect, the tablet is coated with a pharmaceutically acceptable polymer.

[00668] In one embodiment, tablet is a controlled-release formulation, such as an extended release tablet dosage form (also referred to herein as a modified release or sustained release formulation). Such formulations permit the sustained release of the active ingredient over an extended period of time, as compared to immediate release solid dosage forms, which permit the release of most or all of the active ingredient over a short period of time (e.g., typically around 60 minutes or less). In one aspect, the tablet comprises an active ingredient and at least one additive selected from the group consisting of a release control polymer, a filler, a glidant, a lubricant (e.g., for use in compacting the granules), a pH modifier, a surfactant, and combinations thereof. In one aspect, the tablet comprises an active ingredient, a release control polymer, a filler, a glidant, and a lubricant. In one aspect, the tablet comprises an active ingredient, a release control polymer, a filler, a glidant, a lubricant, and a pH modifier.

[00669] In certain embodiments, the release control polymer will be a hydrophilic polymer. Examples of suitable release control polymers include, but are not limited to a cellulose derivative with a viscosity of between 1000 and 150,000 mPA-s, hydroxypropylmethyl cellulose (e.g., Hypromellose 2208 or controlled release grades of hydroxypropylmethyl cellulose, including the E, F, and K series), copolymers of acrylic acid crosslinked with a polyalkenyl polyether (e.g., Carbopol® polymers), hydroxypropyl cellulose, hydroxyethyl cellulose, non-ionic homopolymers of ethylene oxide (e.g., Polyox™), water soluble natural gums of polysaccharides (e.g., xanthan gum, alginate, locust bean gum, etc.), crosslinked starch, polyvinyl acetates, polyvinylpyrrolidone, mixtures of polyvinyl acetates and polyvinyl pyrrolidone, and combinations thereof. In one embodiment, the release control polymer is selected from the group consisting of hydroxypropylmethyl cellulose, copolymers of acrylic acid crosslinked with a polyalkenyl polyether (e.g., Carbopol® polymers), and combinations thereof. Examples of suitable fillers ("bulking agents") include, but are not limited to, microcrystalline cellulose (e.g., Avicel® PH 101; Avicel® PH 102;), mannitol (e.g.,

Pearlitol® 100 SD or Pearlitol® 200 SD), lactose, sucrose, sorbitol, and the like. In one embodiment, the filler is selected from the group consisting of microcrystalline cellulose, mannitol, and combinations thereof. Examples of suitable glidants include, but are not limited to, silicone dioxide (e.g., colloidal silicon dioxide), calcium silicate, magnesium silicate, talc, and combinations thereof. In one embodiment, the glidant is colloidal silicone dioxide. Examples of suitable lubricants include, but are not limited to, polyethylene glycol (e.g., having a molecular weight of from 1000 to 6000), magnesium stearate, calcium stearate, sodium stearyl fumarate, talc, and the like. In one embodiment, the lubricant is magnesium stearate. Examples of suitable pH modfiers include, but are not limited to, organic acids, such as tartaric acid, citric acid, succinic acid, fumaric acid; sodium citrate; magnesium or calcium carbonate or bicarbonate; and combinations thereof. In one embodiment, the pH modifier is tartaric acid. Examples of suitable surfactants include sodium lauryl sulfate.

[00670] In one embodiment, the pharmaceutical composition comprises from about 10 w/w% to about 35 w/w% of a pH modifier, and in particular, tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, or combinations thereof. In other embodiments, the formulation comprises from about 20 w/w% to about 35 w/w%, or from about 20 w/w% to about 30 w/w%, or from about 20 w/w% to about 25 w/w%, or about 10 w/w%, about 15 w/w.%, about 20 w/w%, about 25 w/w% or about 30 w/w% pH modifier. In one embodiment, the pH modifier is tartaric acid.

[00671] As discussed herein, sustained peak plasma concentrations can theoretically be achieved by means of sustained release matrix systems. However, when such systems are made of hydrophilic polymers, such as HPMC, they seldom provide pH independent drug release of pH-dependent soluble drugs, and they are normally incapable of attaining zero-order release except for practically insoluble drugs. Unexpectedly, is has now been discovered that when a pH modifier, such as tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, or combinations thereof, is used in a hydrophilic sustained release matrix system, it allows Compound 1 or a pharmaceutically acceptable salt or solid state form thereof to be released at a steady rate regardless of the pH of the environment. In an unexpected finding, it was discovered that as a tablet containing the hydrophilic polymer matrix system erodes, Compound 1 reacts with the HPMC, creating a thicker gel layer which slows the release of Compound 1 from the tablet. The resulting gel layer provides an environment suitable for Compound 1 to dissolve.

[00672] Thus, in one embodiment, the pharmaceutical composition of the present disclosure exhibits a pH-independent release of the active ingredient (Compound 1).

Advantageously, it has been discovered that including organic acids, such as a tartaric acid, in the composition as a pH modifier improves the release profile, and results in a pH independent release of the active ingredient. Without wishing to be bound to any particular theory, it is believed that the pH modifier and hydrophilic polymer create a microenvironment in which the active ingredient dissolves, and then is released. The release from the microenvironment occurs at approximately the same rate, regardless of pH. This is particularly advantageous, since the pH of the gastrointestinal tract may vary significantly from the stomach (e.g., pH of about 1.5-3), to the duodenum (e.g., pH of about 4-5), to the lower part of the small intestines (e.g., pH of about 6.5-7.5).

[00673] Thus, in one embodiment, the pharmaceutical composition is an extended release formulation comprising Compound 1, or a pharmaceutically acceptable salt or solid state form thereof, a hydrophilic polymer, and a pH modifier, wherein the hydrophilic polymer, in contact with water, forms a gel layer that provides an environment suitable for Compound 1, or a pharmaceutically acceptable salt or solid state form thereof, to dissolve. In some embodiments, the environment suitable for Compound 1, or a pharmaceutically acceptable salt or solid state form thereof, to dissolve has a pH equal to or less than about 3.8 at 37°C. In some such embodiments, the environment has a pH of from about 1.5 to about 3.7, or from about 2.0 to about 3.7, or from about 2.5 to about 3.6, or from about 3.0 to about 3.6, or from about 3.0 to about 3.5.

[00674] In one such embodiment, the environment suitable for Compound 1, or a pharmaceutically acceptable salt or solid state form thereof, to dissolve is as set forth above, and the extended release formulation comprises from about 10 w/w% to about 35 w/w% of a pH modifier, and in particular, tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, or combinations thereof. In other embodiments, the formulation comprises from about 20 w/w% to about 35 w/w%, or from about 20 w/w% to about 30 w/w%, or from about 20 w/w% to about 25 w/w%, or about 10 w/w%, about 15w/w%, about 20 w/w%, about 25 w/w% or about 30 w/w% pH modifier. In any of these embodiments, the pH modifier may be selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and combinations thereof. In one such embodiment, the pH modifier is selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, and combinations thereof. In one such embodiment, the pH modifier is selected from the group consisting of tartaric acid and fumaric acid. In one embodiment, the pH motifier is tartaric acid. In one embodiment, the pH modifier is fumaric acid or citric acid. The weight % tartaric acid set forth herein is by weight of the

uncoated composition (e.g., uncoated tablet). In any of the foregoing embodiments, the hydrophilic polymer may be a cellulose derivative with a viscosity of between 1000 and 150,000 mPA-s. In one embodiment, the hydrophilic polymer is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, and mixtures or combinations thereof. In one embodiment, the hydrophilic polymer is hydroxypropylmethyl cellulose. In one embodiment, the hydrophilic polymer is hydroxypropylmethyl cellulose Grade E, F, or K. In one embodiment, the hydrophilic polymer is Hypromellose 2208.

[00675] In one embodiment, the tablet is a compressed and/or milled tablet. For example, in some embodiments, the tablet is formed by blending the composition components (e.g., including the active ingredient and at least one pharmaceutically acceptable carrier). The composition can then be either directly compressed, or one or more of the composition components can be granulated prior to compression. In one embodiment, milling is performed using a mill fitted with any suitable size screen (e.g., a fitted with a screen size of from about 600 to about 1400 μm or about 610 μm or about 1397 μm). Compression can be done in a tablet press, such as in a steel die between two moving punches.

[00676] In other embodiments, the compressed and/or milled tablet is formulated using a wet granulation process. Use of wet granulation helps reduce and/or eliminate sticking that may occur when compression without wet granulation (e.g., direct compression) is used to formulate the tablets. In one embodiment, the wet granulation process may include the following steps: (a) combining the active ingredient (e.g., Compound 1 or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1) and at least a portion of one additional composition component to form a dry granulation mixture; (b) contacting the dry granulation mixture with a granulation fluid to form a wet granulation mixture; (c) drying the wet granulation mixture to form a granulated material; (d) milling the granulated material to form a milled granulated material; (e) combining the milled granulation material with the remaining composition components; and (f) compressing the composition into the solid dosage unit (e.g., a tablet).

[00677] In step (a) of this process, the active ingredient may be combined with, for example, a portion of the release control polymer (e.g., HPMC), a portion of the filler (e.g., microcrystalline cellulose, such as Avicel® PH101), or both a portion of the release control polymer and a portion of the filler to form the dry granulation mixture. Any suitable porition of the release control polymer may be used in step (a). In one embodiment, th from about 5 to 10 wt.% or from about 6 to 8 wt.% of the total amount of the release control polymer in the composition is used in step (a).

[00678] In certain embodiments, the granulation fluid used in step (b) may comprise water, a suitable solvent (e.g., ethanol, isopropanol, etc.), or combinations thereof. In one embodiment, the granulation fluid comprises water. In one embodiment, the active ingredient may be combined with a portion of the filler, while a portion of the release control polymer (e.g., HPMC) is dissolved in a liquid, such as water, to form the granulation fluid. In one embodiment, the granulation fluid is sprayed on the dry granulation mixture.

[00679] The dried granulation material may be milled using, for example, a comill fit with any suitable screen size. In one embodiment, the screen size is from about 600 to about 900 microns, or from about 610 to about 813 microns. In one embodiment, the granulated material is milled using a comill fitted with a 610 μm screen. In one embodiment, the granulated material is milled using a comill fitted with a 813 μm screen.

[00680] In step (e), the milled granulation material is combined with any remaining composition components, such as any remaining filler (e.g., microcrystalline cellulose, such as Avicel® PH102), any remaining release control polymer, glidants, lubricants, pH modifiers, surfactants, and the like. In one embodiment, the filler and/or release control polymer included in the granulated material may be the same or different than the filler and/or release control polymer added in step (e). For instance, in one embodiment, the filler included in the granulated material (e.g., Avicel®PH101) may have a smaller particle size distribution than the filler added in step (e) (e.g., Avicel®PH102).

[00681] In one embodiment, the composition may be sieved, and the sieved composition blended, for example, after step (e), and prior to compressing the composition (step (f)). In one embodiment, the formulation is sieved prior to addition of any lubricant. In one embodiment, the pH modifier (e.g., tartaric acid) is optionally milled prior to combining with the granulated material.

[00682] In one embodiment, the present disclosure is directed to a process for preparing a pharmaceutical composition, the process comprising: (a) combining an active ingredient (e.g., Compound 1 or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1) and at least a portion of one additional composition component to form a dry granulation mixture; (b) contacting the dry granulation mixture with a granulation fluid to form a wet granulation mixture; (c) drying the wet granulation mixture to form a granulated material; (d) milling the granulated material to form a milled granulated material; (e) combining the milled granulation material with the remaining composition components; and (f) compressing the composition to form the pharmaceutical composition. In one embodiment, the method further

optionally comprises coating the pharmaceutical composition. In one embodiment, the disclosure is directed to a pharmaceutical composition prepared by this wet granulation process. In one embodiment, the pharmaceutical composition is a tablet. In one embodiment, the pH modifier (e.g., tartaric acid) is optionally milled prior to compressing. In one embodiment, the solid state form is Freebase Hydrate Form C.

[00683] In some embodiments, the compressed and/or milled tablet comprises a crystalline solid state form of Compound 1. In one embodiment, the crystalline solid state form is a crystalline hydrate. In one embodiment, the crystalline solid state form is Freebase Hydrate Form C. Advantageously, it has been discovered that crystalline Freebase Hydrate Form C is stable under mechanical processing, and exhibits minimal issues upon milling. In other embodiments, the crystalline solid state form is a crystalline anhydrate. In one embodiment, the crystalline anhydrate is Freebase Anhydrate Form D.

[00684] In some embodiments, the pharmaceutical composition is a compressed and/or milled tablet comprising Compound 1, wherein at least about 75% by weight of the Compound 1 present in the tablet is Freebase Hydrate Form C. In one aspect, at least 80% by weight is the Freebase Hydrate Form C. In another aspect, at least 85% by weight is the Freebase Hydrate Form C. In another aspect, at least 90% by weight is the Freebase Hydrate Form C. In another aspect, at least 95% by weight is the Freebase Hydrate Form C. In another aspect, at least 96% by weight is the Freebase Hydrate Form C. In another aspect, at least 97% by weight is the Freebase Hydrate Form C. In another aspect, at least 98% by weight is the Freebase Hydrate Form C. In another aspect, at least 99% by weight is the Freebase Hydrate Form C.

[00685] In some embodiments, the pharmaceutical composition is a compressed and/or milled tablet comprising Compound 1, wherein at least about 75% by weight of the Compound 1 present in the tablet is the Amorphous Freebase. In one aspect, at least 80% by weight is the Amorphous Freebase. In another aspect, at least 85% by weight is the Amorphous Freebase. In another aspect, at least 90% by weight is the Amorphous Freebase. In another aspect, at least 95% by weight is the Amorphous Freebase. In another aspect, at least 96% by weight is the Amorphous Freebase. In another aspect, at least 97% by weight is the Amorphous Freebase. In another aspect, at least 98% by weight is the Amorphous Freebase. In another aspect, at least 99% by weight is the Amorphous Freebase.

[00686] In some embodiments, the pharmaceutical composition is a compressed and/or milled tablet comprising Compound 1, wherein at least about 75% by weight of the Compound 1 present in the tablet is the Freebase Hydrate Form B. In one aspect, at least 80% by weight is

the Freebase Hydrate Form B. In another aspect, at least 85% by weight is the Freebase Hydrate Form B. In another aspect, at least 90% by weight is the Freebase Hydrate Form B. In another aspect, at least 95% by weight is the Freebase Hydrate Form B. In another aspect, at least 96% by weight is the Freebase Hydrate Form B. In another aspect, at least 97% by weight is the Freebase Hydrate Form B. In another aspect, at least 98% by weight is the Freebase Hydrate Form B. In another aspect, at least 99% by weight is the Freebase Hydrate Form B.

[00687] In some embodiments, the pharmaceutical composition is a compressed and/or milled tablet comprising Compound 1, wherein at least about 75% by weight of the Compound 1 present in the tablet is Freebase Anhydrate Form D. In one aspect, at least 80% by weight is the Freebase Anhydrate Form D. In another aspect, at least 85% by weight is the Freebase Anhydrate Form D. In another aspect, at least 90% by weight is the Freebase Anhydrate Form D. In another aspect, at least 95% by weight is the Freebase Anhydrate Form D. In another aspect, at least 96% by weight is the Freebase Anhydrate Form D. In another aspect, at least 97% by weight is the Freebase Anhydrate Form D. In another aspect, at least 98% by weight is the Freebase Anhydrate Form D. In another aspect, at least 99% by weight is the Freebase Anhydrate Form D.

[00688] In some embodiments, the pharmaceutical composition is a compressed and/or milled tablet comprising Compound 1, wherein at least about 75% by weight of the Compound 1 present in the tablet is the crystalline tartrate. In one aspect, at least 80% by weight is the crystalline tartrate. In another aspect, at least 85% by weight is the crystalline tartrate. In another aspect, at least 90% by weight is the crystalline tartrate. In another aspect, at least 95% by weight is the crystalline tartrate. In another aspect, at least 96% by weight is the crystalline tartrate. In another aspect, at least 97% by weight is the crystalline tartrate. In another aspect, at least 98% by weight is the crystalline tartrate. In another aspect, at least 99% by weight is the crystalline tartrate.

[00689] In one embodiment, the pharmaceutical composition is a tablet comprising a solid state form of Compound 1 and a pharmaceutically acceptable carrier, wherein the tablet is prepared by compressing the solid state form of Compound 1 and the pharmaceutically acceptable carrier. In one embodiment, the solid state form of Compound 1 is milled prior to compressing. In one embodiment, the solid state form is Freebase Hydrate Form C.

[00690] In some embodiments, the tablet further comprises a film coat. A film coat on the tablet further may contribute to the ease with which it can be swallowed. A film coat can also improve taste and provides an elegant appearance. In certain embodiments, the film-coat

includes a polymeric film-forming material such as hydroxypropyl methylcellulose, hydroxypropylcellulose, and acrylate or methacrylate copolymers. Besides a film-forming polymer, the film-coat may further comprise a plasticizer, e.g. polyethylene glycol, a surfactant, e.g. polysorbates, and optionally a pigment, e.g. titanium dioxide or iron oxides. The film-coating may also comprise talc as anti-adhesive. In one embodiment, the film coat accounts for less than 5% by weight of a pharmaceutical composition of the present invention.

[00691] In another embodiment, the pharmaceutical composition is a capsule dosage form.

[00692] In another embodiment, the pharmaceutical composition comprises a crystalline hydrate of Compound 1, wherein at least about 75% by weight of Compound 1 present in the composition is the crystalline hydrate of Compound 1. In one aspect, at least 80% by weight is the crystalline hydrate. In another aspect, at least 85% by weight is the crystalline hydrate. In another aspect, at least 90% by weight is the crystalline hydrate. In another aspect, at least 95% by weight is the crystalline hydrate. In another aspect, at least 96% by weight is the crystalline hydrate. In another aspect, at least 97% by weight is the crystalline hydrate. In another aspect, at least 98% by weight is the crystalline hydrate. In another aspect, at least 99% by weight is the crystalline hydrate. In another aspect, the crystalline hydrate is the Freebase Hydrate Form C.

[00693] In another embodiment, the pharmaceutical composition comprises a crystalline tartrate of Compound 1, wherein at least about 75% by weight of Compound 1 present in the composition is the crystalline tartrate of Compound 1. In one aspect, at least 80% by weight is the crystalline tartrate. In another aspect, at least 85% by weight is the crystalline tartrate. In another aspect, at least 90% by weight is the crystalline tartrate. In another aspect, at least 95% by weight is the crystalline tartrate. In another aspect, at least 96% by weight is the crystalline tartrate. In another aspect, at least 97% by weight is the crystalline tartrate. In another aspect, at least 98% by weight is the crystalline tartrate. In another aspect, at least 99% by weight is the crystalline tartrate. In another aspect, the crystalline hydrate is the Tartrate Hydrate. In one embodiment, the pharmaceutical composition comprises a crystalline tartrate of Compound 1, from about 10 w/w% to about 35 w/w% of an organic acid selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and combinations thereof, and a pharmaceutically acceptable carrier. In one embodiment, the crystalline hydrate is the Tartrate Hydrate.

[00694] In another embodiment, the pharmaceutical composition comprises the Amorphous Freebase, wherein at least about 75% by weight of Compound 1 present in the

composition is the Amorphous Freebase. In one aspect, at least 80% by weight is the Amorphous Freebase. In another aspect, at least 85% by weight is the Amorphous Freebase. In another aspect, at least 90% by weight is the Amorphous Freebase. In another aspect, at least 95% by weight is the Amorphous Freebase. In another aspect, at least 96% by weight is the Amorphous Freebase. In another aspect, at least 97% by weight is the Amorphous Freebase. In another aspect, at least 98% by weight is the Amorphous Freebase. In another aspect, at least 99% by weight is the Amorphous Freebase.

[00695] In another embodiment, the pharmaceutical composition comprises a crystalline anhydrate of Compound 1, wherein at least about 75% by weight of Compound 1 present in the composition is the crystalline anhydrate of Compound 1. In one aspect, at least 80% by weight is the crystalline anhydrate. In another aspect, at least 85% by weight is the crystalline anhydrate. In another aspect, at least 90% by weight is the crystalline anhydrate. In another aspect, at least 95% by weight is the crystalline anhydrate. In another aspect, at least 96% by weight is the crystalline anhydrate. In another aspect, at least 97% by weight is the crystalline anhydrate. In another aspect, at least 98% by weight is the crystalline anhydrate. In another aspect, at least 99% by weight is the crystalline anhydrate. In another aspect, the crystalline anhydrate is the Freebase Anhydrate Form D.

[00696] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, and a pharmaceutically acceptable carrier, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00697] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, a pharmaceutically acceptable carrier, and a pH modifier, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In one embodiment, the pharmaceutical composition comprises from about 10 wt% to about 30 wt. % of the pH modifier. In one embodiment, the pH modifier is tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00698] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of a solid state form of Compound 1, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00699] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form B, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00700] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Amorphous Freebase, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00701] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Anhydrate Form D, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00702] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00703] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00704] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 20 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00705] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 30 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00706] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, and a pharmaceutically acceptable carrier, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00707] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, a pharmaceutically acceptable carrier, and a pH modifier, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In one embodiment, the pharmaceutical composition comprises from about 10 wt% to about 30 wt. % of the pH modifier. In one embodiment, the pH modifier is tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00708] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of a solid state form of Compound 1, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00709] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form B, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00710] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Amorphous Freebase, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00711] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Anhydrate Form D, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00712] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00713] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00714] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 20 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00715] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically

acceptable carrier, and about 30 w/w% of tartaric acid. In some such embodiments, the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule).

[00716] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 7.5 mg or about 15 mg or about 30 mg or about 45 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, and a pharmaceutically acceptable carrier, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that sustains release of the Compound 1 freebase or a pharmaceutically acceptable salt thereof or the solid state form of Compound 1 for from about 4 hours to about 24 hours following entry of the dosage form into a use environment, and wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment. In some such embodiments, the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment, from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment. In some embodiments, the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D,

[00717] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of a solid state form of Compound 1, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D, and the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that sustains release of the Compound 1 freebase or the solid state form of Compound 1 for from about 4 hours to about 24 hours following entry of the dosage form into a use environment, and wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment. In some such embodiments, the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment, from about 50% to

about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00718] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that sustains release of the Compound 1 freebase or the solid state form of Compound 1 for from about 4 hours to about 24 hours following entry of the dosage form into a use environment, and wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment, from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00719] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of a solid state form of Compound 1, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w % of tartaric acid, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D, and the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that sustains release of the Compound 1 freebase or the solid state form of Compound 1 for from about 4 hours to about 24 hours following entry of the dosage form into a use environment, and wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment. In some such embodiments, the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment, from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00720] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w % to about 35 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that sustains release of the Compound 1 freebase or the solid state form of Compound 1 for from about 4 hours to about 24 hours following entry of the dosage form into a use environment, and wherein the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment, from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00721] In some of the foregoing embodiments, the dosage form releases the active ingredient (i.e., Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1), at a release rate of not more than about 25%, or from about 10% to about 25%, or from about 15% to about 20%, or about 20% after passage of about 1 hour following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 40%, or from about 20% to about 40%, or from about 25% to about 35% after passage of about 2 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a relase rate of not more than about 60%, or from about 30% to about 60%, or from about 40% to about 60%, or from about 45% to about 55% after passage of about 4 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 70% or from about 40% to about 70%, or from about 55% to about 70% after passage of about 6 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 80% or from about 55% to about 80%, or from about 60% to about 80% after passage of about 6 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not more than about 80%, or not less than about 50%, or not less than about 60%, or not less than about 70%, or not less than about 75%, or from about 50% to about 80%, or from about 60% to about 80%, or from about 65% to about 80% after passage of about 8 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not less than

about 55%, or not less than about 60% or not less than about 70%, or not less than about 80%, or not less than about 85%, or from about 55% to about 90%, or from about 70% to about 90% after passage of about 10 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not less than about 65%, or not less than about 70%, or not less than about 80%, or not less than about 90%, or from about 65% to about 99%, or from about 80% to about 99%, or from about 90% to about 99% after passage of about 16 hours following entry into the use environment. In one embodiment, the dosage form releases the active ingredient at a release rate of not less than about 70%, or not less than about 80%, or not less than about 90%, or from about 70% to 100%, or from about 80% to 100% after passage of about 20 hours following entry into the use environment. In one aspect, the dosage form has a release rate of not more than about 60% after passage of about 4 hours following entry of the dosage form into a use environment, from about 50% to about 80% after passage of about 8 hours following entry of the dosage form into a use environment, from about 55% to about 90% after passage of about 10 hours following entry of the dosage form into a use environment, and from about 70% to 100% after passage of about 20 hours following entry of the dosage form into a use environment.

[00722] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 7.5 mg or about 15 mg or about 30 mg or about 45 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, and a pharmaceutically acceptable carrier, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that, when added to a test medium comprising 900 mL of 50 mM pH 6.8 sodium phosphate buffer at 37°C + 0.5°C in a standard USP rotating paddle apparatus when the paddles are rotated at 75 rpm ± 4%, dissolves not more than about 60% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 4 hours, from about 50% to about 80% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 8 hours, from about 55% to about 90% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 10 hours, and from about 70% to 100% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 20 hours.

[00723] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of a solid state form of Compound 1, a pharmaceutically

acceptable carrier, and from about 10 wt% to about 30 wt% of tartaric acid, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that, when added to a test medium comprising 900 mL of 50 mM pH 6.8 sodium phosphate buffer at 37°C ± 0.5°C in a standard USP rotating paddle apparatus when the paddles are rotated at 75 rpm ± 4%, dissolves not more than about 60% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 4 hours, from about 50% to about 80% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 8 hours, from about 55% to about 90% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 10 hours, and from about 70% to 100% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 20 hours.

[00724] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 wt% to about 30 wt% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that, when added to a test medium comprising 900 mL of 50 mM pH 6.8 sodium phosphate buffer at 37°C ± 0.5°C in a standard USP rotating paddle apparatus when the paddles are rotated at 75 rpm ± 4%, dissolves not more than about 60% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 4 hours, from about 50% to about 80% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 8 hours, from about 55% to about 90% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 10 hours, and from about 70% to 100% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 20 hours.

[00725] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of a solid state form of Compound 1, a pharmaceutically acceptable carrier, and from about 10 wt% to about 30 wt% of tartaric acid, wherein the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that, when added to a test medium comprising 900 mL of 50 mM pH 6.8 sodium phosphate buffer at 37°C ± 0.5°C in a standard USP rotating paddle apparatus when the paddles are rotated at 75 rpm ± 4%, dissolves not more than about 60% of Compound 1 freebase or the

solid state form of Compound 1 after passage of about 4 hours, from about 50% to about 80% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 8 hours, from about 55% to about 90% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 10 hours, and from about 70% to 100% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 20 hours.

[00726] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 wt% to about 30 wt% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) that, when added to a test medium comprising 900 mL of 50 mM pH 6.8 sodium phosphate buffer at 37°C ± 0.5°C in a standard USP rotating paddle apparatus when the paddles are rotated at 75 rpm ± 4%, dissolves not more than about 60% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 4 hours, from about 50% to about 80% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 8 hours, from about 55% to about 90% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 10 hours, and from about 70% to 100% of Compound 1 freebase or the solid state form of Compound 1 after passage of about 20 hours.

VII. Pharmacokinetic Parameters

15 mg Dosage Formulations

[00727] In certain embodiments, the methods of the present disclosure comprise administering to an adult subject (e.g., a human subject) Compound 1 (freebase), or a pharmaceutically acceptable salt thereof, or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject 15 mg of Compound 1 freebase equivalent. In one embodiment, the freebase or the hydrate is in a once daily extended release formulation.

[00728] Unless otherwise indicated, the following pharmacokinetic parameters are achieved after administration of a single 15 mg dose the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate (e.g., Freebase Hydrate Form C) to the adult subject, or after administration of a sufficient number of once-daily 15 mg doses to achieve a steady-state. By a single 15 mg dose, it is meant a single dosage unit containing an amount of freebase or pharmaceutically acceptable salt or crystalline hydrate sufficient to deliver to the subject 15 mg of Compound 1 freebase equivalent. In one embodiment, the single dosage unit is a once daily extended release formulation.

[00729] In certain embodiments, the administration of the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate to the adult subject achieves a mean C_{max} for Compound 1 of from about 25 to about 70 ng/mL, after a single 15 mg dose. In some embodiments, when administered to the adult subject, the Compound 1 (freebase) or the crystalline hydrate achieve a mean C_{max} for Compound 1 of from about 25.0 to about 60.0 ng/mL,or from about 25.0 to about 40.0 ng/mL, from about 25.0 to about 30.0 ng/mL, or about 25.0 to about 28.0 ng/mL, or about 25.0 to about 27.0 ng/mL, or about 27.0 to about 40.0 ng/mL, or about 27.0 to about 35.0 ng/mL, or about 27.0 to about 30.0 ng/mL, or about 27.0 to about 29.0 ng/mL, or about 28.0 to about 30.0 ng/mL, or about 29.0 to about 31.0 ng/mL, or about 30.0 to about 32.0 ng/mL, after a single 15 mg dose. In some embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{max} for Compound 1 of from about 26.0 to about 26.4 ng/mL, or from about 26.2 to about 26.6 ng/mL, or from about 26.4 to about 26.8 ng/mL, or from about 26.6 to about 27.0 ng/mL, or from about 26.8 to about 27.2 ng/mL, or from about 27.0 to about 27.4 ng/mL, or from about 27.2 to about 27.6 ng/mL, or from about 27.4 to about 27.8 ng/mL, or from about 27.6 to about 28.0 ng/mL, or from about 27.8 to about 28.2 ng/mL, or from about 28.0 to about 28.4 ng/mL, or from about 28.2 to about 28.6 ng/mL, or from about 28.4 to about 28.8 ng/mL, or from about 28.6 to about 29.0 ng/mL, or from about 28.8 to about 29.2 ng/mL, or from about 29.0 to about 29.4 ng/mL, or from about 29.2 to about 29.6 ng/mL, or from about 29.4 to about 29.8 ng/mL, or from about 29.6 to about 30.0 ng/mL, or from about 29.8 to about 30.2 ng/mL, or from about 30.0 to about 30.4 ng/mL, or from about 30.2 to about 30.6 ng/mL, or from about 30.4 to about 30.8 ng/mL, or from about 30.6 to about 31.0 ng/mL, or from about 30.8 to about 31.2 ng/mL, or from about 31.0 to about 31.4 ng/mL, or from about 31.2 to about 31.6 ng/mL, or from about 31.4 to about 31.8 ng/mL, or from about 31.6 to about 32.0 ng/mL, after a single 15 mg dose.

[00730] In some embodiments, when administered to the adult subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{max} for Compound 1 of about 26 ng/mL or about 32 ng/mL, after a single 15 mg dose. In other embodiments, when administered to the adult subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{max} for Compound 1 of about 37 ng/mL or about 40 ng/mL after a single 15 mg dose.

[00731] In certain embodiments, when the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is administered to the adult subject, the difference in the C_{max} for Compound 1 after a single 15 mg dose in the fed versus the fasted state is selected from about 30% or less, about 20% or less, and about 10% or less. As used herein, a subject in a "fed" state (also referred to herein as "non-fasting" state or "non-fasting conditions") is one who has consumed a standard or high-fat meal within about 30 minutes prior to administration of the drug. As used herein, a subject in a "fasted" state (also referred to herein as "fasting conditions") refers to a subject who has fasted for at least 10 hours prior to initial administration the drug, or, if the subject is being administered the drug over multiple days, refers to a subject who has fasted for at least two hours prior to each subsequent administration of the drug.

[00732] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 from about 1.0 to about 6.0 hours after a single 15 mg dose. In some embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 of from about 1.0 to about 5.0 hours, or from about 1.0 to about 4.0 hours, or from about 1.0 to about 3.0 hours, or from about 1.0 to about 2.0 hours, or from about 2.0 to about 6.0 hours, or from about 3.0 to about 6.0 hours, or from about 4.0 to about 6.0 hours, or from about 5.0 to about 6.0 hours, or from about 2.0 to about 5.0 hours, or from about 2.0 to about 4.0 hours, or from about 2.0 to about 3.0 hours, or from about 3.0 to about 4.0 hours, or from about 3.0 to about 5.0 hours, or from about 4.0 to about 5.0 hours, after a single 15 mg dose. In some embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 of from about 2.6 to about 3.0 hours, or from about 2.8 to about 3.2 hours, or from about 3.0 to about 3.4 hours, or from about 3.2 to about 3.6 hours, or from about 3.4 to about 3.8 hours, or from about 3.6 to about 4.0 hours, or from about 3.8 to about 4.2 hours, or from about 4.0 to about 4.4 hours, after a single 15 mg dose.

[00733] In other embodiments, when administered to the adult subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 of from about 1.0 to about 4.0 hours after a single 15 mg dose, or achieve a T_{max} for Compound 1 from about 1.5 to about 6.0 hours after a single 15 mg dose, or achieve a median T_{max} for Compound 1 of about 3.0 hours after a single

15 mg dose. In other embodiments, when administered to the adult subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 from about 3.0 to about 6.0 hours after a single 15 mg dose, or achieve a median T_{max} for Compound 1 of about 4.0 hours after a single 15 mg dose.

[00734] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to about 14.0 hours after a single 15 mg dose. In other embodiments, when administered to an adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to about 13.0 hours, or from about 10.0 to about 12.0 hours, or from about 10.0 to about 11.0 hours, or from about 11.0 to about 14.0 hours, or from about 11.0 to about 13.0 hours, or from about 11.0 to about 12.0 hours, or from about 12.0 to about 14.0 hours, or from about 12.0 to about 13.0 hours, or from about 13.0 to about 14.0 hours, after a single 15 mg dose. In other embodiments, when administered to an adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2}$ for Compound 1 of from about 12.0 to about 12.4 hours, or from about 12.2 to about 12.6 hours, or from about 12.4 to about 12.8 hours, or from about 12.6 to about 13.0 hours, or from about 12.8 to about 13.2 hours, or from about 13.0 to about 13.4 hours, or from about 13.4 to about 13.8 hours, or from about 13.6 to about 14.0 hours, after a single 15 mg dose. In other embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2}$ for Compound 1 of about 12.5 hours after a single 15 mg dose.

[00735] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 220 to about 450 ng·hours/mL after a single 15 mg dose. When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 220 to about 320 ng·hours/mL, or from about 220 to about 260 ng·hours/mL, or from about 220 to about 250 ng·hours/mL, or from about 220 to about 245 ng·hours/mL, or from about 230 to about 260 ng·hours/mL, or from about 230 to about 250 ng·hours/mL, or from about 230 to about 245 ng·hours/mL, or from about 240 to about 260 ng·hours/mL, or from about 240 to about 250 ng·hours/mL, or from about 242 to about 250

ng·hours/mL, or from about 240 to about 245 ng·hours/mL after a single 15 mg dose. When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 238 to about 240 ng·hours/mL, or from about 239 to about 241 ng·hours/mL, or from about 240 to about 242 ng·hours/mL, or from about 242 to about 244 ng·hours/mL, or from about 243 to about 245 ng·hours/mL, or from about 244 to about 246 ng·hours/mL, or from about 245 to about 247 ng·hours/mL, or from about 246 to about 248 ng·hours/mL, or from about 247 to about 249 ng·hours/mL after a single 15 mg dose.

[00736] When administered to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 240 to about 245 ng·hours/mL, or about 242 ng·hours/mL after a single 15 mg dose.

[00737] When administered to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_t for Compound 1 of about 227 ng·hours/mL after a single 15 mg dose, or achieve a mean AUC_{24} for Compound 1 of about 249 ng·hours/mL after a single 15 mg dose. When administered to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{24} for Compound 1 of about 305 ng·hours/mL or about 318 ng·hours/mL after a single 15 mg dose.

[00738] In certain embodiments, when the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is administered to the subject, the difference in the AUC_{inf} for Compound 1 after a 15 mg dose in the fed versus the fasted state is selected from about 30% or less, about 20% or less, and about 10% or less.

[00739] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{24} for Compound 1 of from about 1.4 to about 2.5 ng/mL after a single 15 mg dose. When administered to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{24} for Compound 1 of about 1.5 ng/mL or about 1.9 ng/mL after a single 15 mg dose. When administered to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{24} for Compound 1 of about 2.4 ng/mL.

[00740] When administered QD (once-daily) to the adult subject, in certain embodiments the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 55 ng/mL. When administered QD (once-daily) to the adult subject, in certain embodiments the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 38 ng/mL, or from about 27 to about 36 ng/mL, or from about 27 to about 34 ng/mL, or from about 27 to about 32 ng/mL, or from about 27 to about 30 ng/mL, or from about 29 to about 38 ng/mL, or from about 29 to about 36 ng/mL, or from about 29 to about 34 ng/mL, or from about 29 to about 32 ng/mL, or from about 30 to about 36 ng/mL, or from about 30 to about 34 ng/mL. When administered QD (once-daily) to the adult subject, in certain embodiments the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of from about 31.0 to about 31.4 ng/mL, or from about 31.2 to about 31.6 ng/mL, or from about 31.4 to about 31.8 ng/mL, or from about 31.6 to about 32.0 ng/mL, or from about 31.8 to about 32.2 ng/mL, or from about 32.0 to about 32.4 ng/mL, or from about 32.2 to about 32.6 ng/mL, or from about 32.4 to about 32.8 ng/mL, or from about 32.6 to about 33.0 ng/mL, or from about 32.8 to about 33.2 ng/mL,or from about 33.0 to about 33.4 ng/mL, or from about 33.2 to about 33.6 ng/mL, or from about 33.4 to about 33.8 ng/mL, or from about 33.6 to about 34.0 ng/mL, or from about 33.8 to about 34.2 ng/mL, or from about 34.0 to about 34.4 ng/mL, or from about 34.2 to about 34.6 ng/mL, or from about 34.4 to about 34.8 ng/mL, or from about 34.6 to about 35.0 ng/mL, or from about 34.8 to about 35.2 ng/mL, or from about 35.0 to about 35.4 ng/mL, or from about 35.2 to about 35.6 ng/mL, or from about 35.4 to about 35.8 ng/mL, or from about 35.6 to about 36.0 ng/mL, or from about 35.8 to about 36.2 ng/mL, or from about 36.0 to about 36.4 ng/mL, or from about 36.2 to about 36.6 ng/mL, or from about 36.4 to about 36.8 ng/mL, or from about 36.6 to about 37.0 ng/mL, or from about 36.8 to about 37.2 ng/mL, or from about 37.0 to about 37.4 ng/mL, or from about 37.2 to about 37.6 ng/mL, or from about 37.4 to about 37.8 ng/mL, or from about 37.6 to about 38.0 ng/mL.

[00741] When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of about 32 ng/mL. When administered QD (once-daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the

crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of about 36 ng/mL or about 37 ng/mL.

[00742] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 5.0 hours, or from about 1.5 to about 4.0 hours, or from about 1.5 to about 3.0 hours, or from about 1.5 to about 2.0 hours, or from about 2.0 to about 6.0 hours, or from about 3.0 to about 6.0 hours, or from about 4.0 to about 6.0 hours, or from about 2.0 to about 5.0 hours, or from about 2.0 to about 4.0 hours, or from about 2.0 to about 3.0 hours, or from about 3.0 to about 5.0 hours, or from about 3.0 to about 4.0 hours, or from about 4.0 to about 5.0 hours. In some embodiments, when administered QD (once-daily) to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ for Compound 1 of from about 2.6 to about 3.0 hours, or from about 2.8 to about 3.2 hours, or from about 3.0 to about 3.4 hours, or from about 3.2 to about 3.6 hours, or from about 3.4 to about 3.8 hours, or from about 3.6 to about 4.0 hours, or from about 3.8 to about 4.2 hours, or from about 4.0 to about 4.4 hours.

[00743] When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 4.0 hours, or achieve a median $T_{max,ss}$ for Compound 1 of about 2.5 hours. When administered QD (once-daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ for Compound 1 of from about 2.0 to about 6.0 hours, or achieve a median $T_{max,ss}$ for Compound 1 of about 4.0 hours.

[00744] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{trough} for Compound 1 of from about 2.5 to about 5.1 ng/mL. When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{trough} for Compound 1 of about 2.8 ng/mL. When administered QD (once-daily) to the adult subject under non-fasting conditions, in certain

embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{trough} for Compound 1 of from about 2.5 to about 5.1 ng/mL, or from about 2.5 to about 3.6 ng/mL, or achieve a mean C_{trough} for Compound 1 of about 2.6 ng/mL or about 3.2 ng/mL or about 3.6 ng/mL, or about 5.0 ng/mL.

[00745] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 325 ng·hours/mL. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 290 ng·hours/mL, or from about 240 to about 280 ng·hours/mL, or from about 240 to about 260 ng·hours/mL, or from about 250 to about 290 ng·hours/mL, or from about 250 to about 280 ng·hours/mL, or from about 260 to about 280 ng·hours/mL, or from about 270 to about 280 ng·hours/mL, or from about 275 to about 280 ng·hours/mL, or from about 279 to about 280 ng·hours/mL. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 244 ng·hours/mL, or from about 241 to about 245 ng·hours/mL, or from about 242 to about 246 ng·hours/mL, or from about 244 to about 248 ng·hours/mL, or from about 246 to about 250 ng·hours/mL, or from about 248 to about 252 ng·hours/mL, or from about 250 to about 254 ng·hours/mL, or from about 252 to about 256 ng·hours/mL, or from about 254 to about 258 ng·hours/mL, or from about 256 to about 260 ng·hours/mL, or from about 258 to about 262 ng·hours/mL, or from about 260 to about 264 ng·hours/mL, or from about 262 to about 266 ng·hours/mL, or from about 264 to about 268 ng·hours/mL, or from about 266 to about 270 ng·hours/mL, or from about 268 to about 272 ng·hours/mL, or from about 270 to about 274 ng·hours/mL, or from about 272 to about 276 ng·hours/mL, or from about 274 to about 278 ng·hours/mL, or from about 276 to about 280 ng·hours/mL.

[00746] When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of about 241 ng·hours/mL or about 279 ng·hours/mL. When administered QD (once-daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a

pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of about 317 ng•hours/mL or about 322 ng•hours/mL.

[00747] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.2 ng/mL. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.1 ng/mL, or from about 2.8 to about 3.0 ng/mL, or from about 2.8 to about 2.9 ng/mL, or from about 2.9 to about 3.2 ng/mL, or from about 2.9 to about 3.0 ng/mL, or from about 3.0 to about 3.2 ng/mL, or from about 3.0 to about 3.1 ng/mL, or from about 3.1 to about 3.2 ng/mL. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{min,ss}$ for Compound 1 of about 2.8 ng/mL or about 3.0 ng/mL, or about 3.1 ng/mL.

[00748] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{24,ss}$ for Compound 1 of from about 2.9 to about 3.2 hours. When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{24,ss}$ for Compound 1 of about 3.1 ng/mL. When administered QD (once-daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{24,ss}$ for Compound 1 of about 3.2 ng/mL.

[00749] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.5 hours. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.4 hours, or from about 9.4 to about 10.3 hours, or from about 9.4 to about 10.1 hours, or from about 9.4 to about 9.9 hours, or from about 9.5 to about 10.4 hours. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2,ss}$ for Compound 1

of from about 9.4 to about 9.8 hours, or from about 9.6 to about 10.0 hours, or from about 9.8 to about 10.2 hours, or from about 10.0 to about 10.4 hours, or from about 10.1 to about 10.5 hours. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2,ss}$ for Compound 1 of about 10.3 hours or about 9.4 hours or about 9.5 hours.

[00750] In certain embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean C_{max} for Compound 1 of from about 25 to about 70 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 6.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to about 14.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 220 to about 450 ng-hours/mL; (e) a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 55 ng/mL; (f) a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 325 ng-hours/mL; (g) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (h) a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.2 ng/mL; (i) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.5 hours; or combinations thereof.

[00751] In certain embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean C_{max} for Compound 1 of from about 25 to about 70 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 6.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to about 14.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 220 to about 450 ng-hours/mL; or combinations thereof, after a single 15 mg dose.

[00752] In certain embodiments, when administered QD (once daily) to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 55 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 325 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.2 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.5 hours; or combinations thereof.

[00753] In certain embodiments, when administered to the adult subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean C_{max} for Compound 1 of about 26 ng/mL or about 32 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 to about 4.0 hours, or from about 1.5 to

about 6.0 hours, or a median T_{max} for Compound 1 of about 3.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 12.5 hours; (d) a mean AUC_{inf} for Compound 1 of about 242 ng·hours/mL; or combinations thereof, after a single 15 mg dose.

[00754] In certain embodiments, when administered to the adult subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean C_{max} for Compound 1 of about 40 ng/mL; (b) a T_{max} for Compound 1 of from about 3.0 to about 6.0 hours, or a median T_{max} for Compound 1 of about 4.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 12.5 hours; or combinations thereof, after a single 15 mg dose.

[00755] In certain embodiments, when administered QD (once daily) to the adult subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate alternately or additionally may provide (a) a mean $C_{max,ss}$ for Compound 1 of about 32 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of about 279 ng·hours/mL; (c) a $T_{max,ss}$ for Compound 1 of about 1.5 to about 4.0 hours, or a median $T_{max,ss}$ for Compound 1 of about 2.5 hours; (d) a mean $C_{min,ss}$ for Compound 1 of about 3.0 ng/mL or about 3.1 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of about 9.5 hours or about 10.3 hours; or combinations thereof.

[00756] In certain embodiments, when administered QD (once daily) to the adult subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate alternately or additionally may provide (a) a mean $C_{max,ss}$ for Compound 1 of about 36 ng/mL or about 37 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of about 317 ng·hours/mL or about 322 ng·hours/mL; (c) a $T_{max,ss}$ for Compound 1 of about 2.0 to about 6.0 hours or a median $T_{max,ss}$ for Compound 1 of about 4.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of about 2.8 ng/mL or about 3.0 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of about 9.4 hours or about 9.5 hours or 10.3 hours; or combinations thereof.

[00757] In certain embodiments, the present disclosure is directed to pharmaceutical compositions comprising a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject 15 mg of Compound 1 freebase equivalent. In certain embodiments, the crystalline hydrate is Freebase Hydrate Form C. In one embodiment, the crystalline hydrate is in a once daily extended release formulation. In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 25 to about 70 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 6.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to

about 14.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 220 to about 450 ng-hours/mL; (e) a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 55 ng/mL; (f) a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 325 ng-hours/mL; (g) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (h) a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.2 ng/mL; (i) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.5 hours; or combinations thereof.

[00758] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 25 to about 70 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 6.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to about 14.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 220 to about 450 ng-hours/mL; or combinations thereof, after a single 15 mg dose.

[00759] In one embodiment, when administered QD (once daily) to the adult subject the pharmaceutical composition provides (a) a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 55 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 325 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.2 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.5 hours; or combinations thereof.

[00760] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject under fasting conditions, the pharmaceutical composition provides (a) a mean C_{max} for Compound 1 of about 26. ng/mL or about 32 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 to about 4.0 hours, or from about 1.5 to about 6.0 hours, or a median T_{max} for Compound 1 of about 3.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 12.5 hours; (d) a mean AUC_{inf} for Compound 1 of about 242 ng·hours/mL; or combinations thereof, after a single 15 mg dose. In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject under non-fasting conditions, the composition provides (a) a mean C_{max} for Compound 1 of about 40 ng/mL; (b) a T_{max} for Compound 1 of from about 3.0 to about 6.0 hours, or a median T_{max} for Compound 1 of about 4.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 12.5 hours; or combinations thereof, after a single 15 mg dose.

[00761] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject QD (once daily) under fasting conditions, the composition alternately or additionally provides (a) a mean $C_{max,ss}$ for Compound 1 of about 32 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of about 279 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of about 1.5 to about

4.0 hours, or a median $T_{max,ss}$ for Compound 1 of about 2.5 hours; (d) a mean $C_{min,ss}$ for Compound 1 of about 3.0 ng/mL or about 3.1 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of about 9.5 hours or about 10.3 hours; or combinations thereof. In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject QD (once daily) under non-fasting conditions, the composition alternately or additionally provides (a) a mean $C_{max,ss}$ for Compound 1 of about 36 ng/mL or about 37 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of about 317 ng-hours/mL or about 322 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of about 2.0 to about 6.0 hours or a median $T_{max,ss}$ for Compound 1 of about 4.0; (d) a mean $C_{min,ss}$ for Compound 1 of about 2.8 ng/mL or about 3.0 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of about 9.4 hours or about 9.5 hours or about 10.3 hours; or combinations thereof.

[00762] In one embodiment, the present disclosure is directed to pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) and, upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 25 to about 70 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 6.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to about 14.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 220 to about 450 ng-hours/mL; (e) a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 55 ng/mL; (f) a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 325 ng-hours/mL; (g) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (h) a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.2 ng/mL; (i) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.5 hours; or combinations thereof.

[00763] In one embodiment, the present disclosure is directed to pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% or about 20 w/w% or about 30 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) and, upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 25 to about 70 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 6.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 10.0 to about 14.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 220 to about 450 ng-hours/mL; or combinations thereof after a single 15 mg dose.

[00764] In one embodiment, the present disclosure is directed to pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% or about 20 w/w% or about 30 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release dosage form (e.g., tablet or capsule) and, upon oral administration of the pharmaceutical composition to an adult subject QD (once daily), the composition provides (a) a mean $C_{max,ss}$ for Compound 1 of from about 27 to about 55 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of from about 240 to about 325 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of from about 2.8 to about 3.2 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 9.4 to about 10.5 hours; or combinations thereof.

30 mg Dosage Formulations

[00765] In certain embodiments, the methods of the present disclosure comprise administering to an adult subject (e.g., a human subject) 30 mg of Compound 1 (freebase), or a pharmaceutically acceptable salt thereof or a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject 30 mg of Compound 1 freebase equivalent. In one embodiment, the freebase or the hydrate is in a once daily extended release formulation.

[00766] Unless otherwise indicated, the following pharmacokinetic parameters are achieved after administration of a single 30 mg dose the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate (e.g., Freebase Hydrate Form C) to the adult subject, or after administration of a sufficient number of once-daily 30 mg doses to achieve a steady-state. By a single 30 mg dose, it is meant a single dosage unit containing an amount of freebase or pharmaceutically acceptable salt or crystalline hydrate sufficient to deliver to the subject 30 mg of Compound 1 freebase equivalent. In one embodiment, the single dosage unit is a once daily extended release formulation.

[00767] In certain embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{max} for Compound 1 of from about 55 to about 85 ng/mL after a single 30 mg dose. In certain embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{max} for Compound 1 of from about 55 to about 70 ng/mL, or from about 55 to about 67 ng/mL, or from about 55 to about 66 ng/mL, or from about 70 to about 85 ng/mL, or from about 72 to about 85 ng/mL, or from about 74 to about 85 ng/mL, after a single 30 mg dose.

[00768] In certain embodiments, when administered to the subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{max} for Compound 1 of from about 55 ng/mL to about 66 ng/mL, or about 55 ng/mL, or about 56 ng/mL, or about 57 ng/mL, or about 59 ng/mL, or about 61 ng/mL, or about 64 ng/mL, or about 66 ng/mL after a single 30 mg dose. In other embodiments, when administered to the subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{max} for Compound 1 of from about 74 ng/mL to about 85 ng/mL, or about 74 ng/mL, or about 76 ng/mL, or about 77 ng/mL, or about 79 ng/mL, about 82 ng/mL, or about 84 ng/mL after a single 30 mg dose.

[00769] In certain embodiments, when the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is administered to the subject, the difference in the C_{max} for Compound 1 after a 30 mg dose in the fed versus the fasted state is about 55% or less, or about 53% or less, or about 30% or less, or about 20% or less, or about 10% or less. In one embodiment, the difference in the C_{max} for Compound 1 after a 30 mg dose in the fed versus the fasted state is from about 3% to about 40%, or from about 15% to about 55%.

[00770] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 from about 1.0 to about 8.0 hours after a single 30 mg dose. When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 from about 2.0 to about 6.0 hours, or from about 1.0 to about 4.0 hours, or from about 1.5 to about 4.0 hours, or from about 1.5 to about 8.0 hours, or from about 2.0 to about 4.0 hours, or from about 2.0 to about 3.0 hours, after a single 30 mg dose.

[00771] In other embodiments, when administered to the adult subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 of from about 1.0 to about 4.0 hours, or from about 1.5 to about 4.0 hours, or a median T_{max} for Compound 1 of about 2.0 hours, or about 2.5 hours, or about 3.0 hours after a single 30 mg dose. In other embodiments, when administered to the adult subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a T_{max} for Compound 1 of from about 1.5 to about 8.0 hours, or about 2.0 to about 6.0 hours, or a median T_{max} for Compound 1 of about 4.0 hours after a single 30 mg dose.

[00772] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 12.0 hours after a single 30 mg dose. When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 11.0 hours, or from about 9.0 to about 10.0 hours, or from about 10.0 to about 12.0 hours, or from about 10.0 to about 11.5 hours, after a single 30 mg dose.

[00773] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2}$ for Compound 1 of about 9.0 hours, or about 9.5 hours, or about 10.0 hours, or about 10.5 hours, or about 11.0 hours, or about 11.5 hours, or about 12.0 hours, after a single 30 mg dose.

[00774] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 453 to about 660 ng·hours/mL after a single 30 mg dose. When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 483 to about 660 ng·hours/mL, from about 483 to about 550 ng·hours/mL, or from about 484 to about 515 ng·hours/mL, or from about 484 to about 513 ng·hours/mL, or from about 560 to about 660 ng·hours/mL, or from about 570 to about 660 ng·hours/mL, or from about 577 to about 657 ng·hours/mL, after a single 30 mg dose.

[00775] When administered to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 484 to about 550 ng·hours/mL, or about 484 ng·hours/mL, or about 491 ng·hours/mL, or about 495 ng·hours/mL, or about 499 ng·hours/mL, or about 513 ng·hours/mL after a single 30 mg dose. When administered to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_t for Compound 1 of about 473 ng·hours/mL, or about 477 ng·hours/mL, about 481 ng·hours/mL, or about 487 ng·hours/mL, or about 495 ng·hours/mL, or a mean AUC_{24} of about 454 ng·hours/mL, after a single 30 mg dose. When administered to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a

pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{inf} for Compound 1 of from about 560 to about 660 ng•hours/mL, or about 577 ng•hours/mL, or about 609 ng•hours/mL, or about 622 ng•hours/mL, or about 657 ng•hours/mL, after a single 30 mg dose. When administered to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean AUC_{24} for Compound 1 of about 517 ng•hours/mL or about 563 ng•hours/mL, or a mean AUC_t of about 564 ng•hours/mL, or about 605 ng•hours/mL, or about 615 ng•hours/mL, or about 648 ng•hours/mL, after a single 30 mg dose.

[00776] In certain embodiments, when the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is administered to the subject, the difference in the AUC_{inf} for Compound 1 after a 30 mg dose in the fed versus the fasted state is about 30% or less, or about 20% or less, or about 10% or less.

[00777] When administered to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{24} for Compound 1 of from about 2.3 to about 4.5 ng/mL after a single 30 mg dose. When administered to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{24} for Compound 1 of about 2.7 ng/mL, or about 3.2 ng/mL, or about 2.8 ng/mL, or about 3.5 ng/mL, or about 3.7 ng/mL, or about 3.9 ng/mL, after a single 30 mg dose. When administered to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{24} for Compound 1 of about 2.4 ng/mL, or about 2.6 ng/mL, or about 2.8 ng/mL, or about 2.9 ng/mL, or about 4.3 ng/mL, after a single 30 mg dose.

[00778] When administered QD (once daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of from about 65 to about 86 ng/mL. When administered QD (once daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of from about 65 to about 70 ng/mL, or from about 67 to about 68 ng/mL, or from about 78 to about 86 ng/mL, or from about 80 to about 84 ng/mL.

[00779] When administered QD (once daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of about 67 ng/mL or

about 68 ng/mL. When administered QD (once daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{max,ss}$ for Compound 1 of about 80 ng/mL or about 84 ng/mL.

[00780] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ of from about 1.5 to about 6.0 hours. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ of from about 1.5 to about 4.0 hours, or from about 2.0 to about 4.0 hours, or from about 3.0 to about 4.0 hours, or from about 3.5 to about 4.0 hours.

[00781] When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ of from about 2.0 to about 4.0 hours, or a median $T_{max,ss}$ for Compound 1 of about 3.0 hours. When administered QD (once-daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a $T_{max,ss}$ of from about 1.5 to about 6.0 hours, or a median $T_{max,ss}$ for Compound 1 of about 3.5 hours or about 4.0 hours.

[00782] When administered QD (once daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or the crystalline hydrate achieve a mean C_{trough} for Compound 1 of from about 2.8 to about 6.1 ng/mL. When administered QD (once daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or the crystalline hydrate achieve a mean C_{trough} for Compound 1 of about 4.9 ng/mL. When administered QD (once daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean C_{trough} for Compound 1 of from about 2.8 to about 6.1 ng/mL, or from about 4.6 to about 6.1 ng/mL, or about 3.0 ng/mL, or about 4.7 ng/mL or about 5.3 ng/mL or about 6.1 ng/mL.

[00783] When administered QD (once daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of from about 485 to about 658 ng·hours/mL. When administered QD (once daily) to the adult subject, in certain embodiments, the Compound

1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of from about 520 to about 640 ng·hours/mL, or from about 520 to about 630 ng·hours/mL, or from about 525 to about 620 ng·hours/mL, or from about 525 to about 585 ng·hours/mL,or from about 580 to about 630 ng·hours/mL, or from about 582 to about 620 ng·hours/mL.

[00784] When administered to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of about 525 ng·hours/mL. When administered to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $AUC_{24,ss}$ for Compound 1 of about 582 ng·hours/mL or about 620 ng·hours/mL.

[00785] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{min,ss}$ for Compound 1 of from about 3.5 to about 5.3 ng/mL. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{min,ss}$ for Compound 1 of from about 3.6 to about 5.2 ng/mL, or from about 3.8 to about 5.2 ng/mL, or from about 4.6 to about 5.2 ng/mL.

[00786] When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{min,ss}$ for Compound 1 of about 3.8 ng/mL. When administered QD (once-daily) to the adult subject under non-fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{min,ss}$ for Compound 1 of about 4.6 ng/mL or about 5.2 ng/mL.

[00787] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{24,ss}$ for Compound 1 of from about 4.0 to about 5.3 hours. When administered QD (once-daily) to the adult subject under fasting conditions, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{24,ss}$ for Compound 1 of about 4.3 ng/mL or about 4.4 ng/mL. When administered QD (once-daily) to the adult subject under non-fasting conditions, in

certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a mean $C_{24,ss}$ for Compound 1 of about 5.3 ng/mL.

[00788] When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 10.0 to about 14.5 hours. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or the crystalline hydrate achieve a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 10.1 to about 14.4 hours, or from about 10.1 to about 10.4 hours, or from about 10.4 hours to about 14.4 hours. When administered QD (once-daily) to the adult subject, in certain embodiments, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate achieve a harmonic mean $t_{1/2,ss}$ for Compound 1 of about 14.4 hours or about 10.1 hours or about 10.4 hours.

[00789] In certain embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean C_{max} for Compound 1 of from about 55 to about 85 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 8.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 483 to about 660 ng-hours/mL; (e) a mean $C_{max,ss}$ for Compound 1 of from about 65 to about 85 ng/mL; (f) a mean $AUC_{24,ss}$ for Compound 1 of from about 485 to about 658 ng-hours/mL; (g) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (h) a mean $C_{min,ss}$ for Compound 1 of from about 3.5 to about 5.3 ng/mL; (i) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 10.0 to about 14.5 hours; or combinations thereof.

[00790] In certain embodiments, when administered to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean C_{max} for Compound 1 of from about 55 to about 85 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 8.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 483 to about 660 ng-hours/mL; or combinations thereof, after a single 30 mg dose.

[00791] In certain embodiments, when administered QD (once-daily) to the adult subject, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean $C_{max,ss}$ for Compound 1 of from about 65 to about 85 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of from about 485 to about 658 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of from

about 3.5 to about 5.3 ng/mL; (e) a harmonic mean $t_{1/2, ss}$ for Compound 1 of from about 10.0 to about 14.5 hours; or combinations thereof.

[00792] In certain embodiments, when administered to the adult subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides: (a) a mean C_{max} for Compound 1 of from about 55 ng/mL to about 66 ng/mL, or about 55 ng/mL, or about 56 ng/mL, or about 57 ng/mL, or about 59 ng/mL, or about 61 ng/mL, or about 64 ng/mL or about 66 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 4.0 hours, or about 1.5 hours to about 4.0 hours, or a median T_{max} for Compound 1 of about 2.0 hours, or about 2.5 hours, or about 3.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 9.0 hours, or about 9.5 hours, or about 10.0 hours, or about 10.5 hours, or about 11.0 hours, or about 11.5 hours, or about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of about 484 to about 550 ng•hours/mL, or about 484 ng•hours/mL, or about 491 ng•hours/mL, or about 495 ng•hours/mL, or about 499 ng•hours/mL, or about 513 ng•hours/mL; or combinations thereof, after a single 30 mg dose.

[00793] In certain embodiments, when administered to the adult subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate provides (a) a mean C_{max} for Compound 1 of from about 76 ng/mL to about 85 ng/mL, or about 76 ng/mL, or about 77 ng/mL, or about 79 ng/mL, about 82 ng/mL, or about 84 ng/mL; (b) a T_{max} for Compound 1 of from about 1.5 hours to about 8.0 hours, or from about 2.0 hours to about 6.0 hours, or a median T_{max} for Compound 1 of about 4.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 9.0 hours, or about 9.5 hours, or about 10.0 hours, or about 10.5 hours, or about 11.0 hours, or about 11.5 hours, or about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of about 577 ng•hours/mL, or about 609 ng•hours/mL, or about 622 ng•hours/mL, or about 657 ng•hours/mL; or combinations thereof, after a single 30 mg dose.

[00794] In one embodiment, when administered QD (once daily) to the adult subject under fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate alternately or additionally provides (a) a mean $C_{max,ss}$ for Compound 1 of about 67 ng/mL or about 68 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of about 525 ng•hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 2.0 to about 4.0 hours, or a median $T_{max,ss}$ for Compound 1 of about 3.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of about 3.8 ng/mL; (e) a harmonic mean $t_{1/2, ss}$ for Compound 1 of about 10.1 hours or or about 10.4 hours or about 14.4 hours; or combinations thereof.

[00795] In one embodiment, when administered QD (once daily) to the adult subject under non-fasting conditions, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate alternately or additionally provides (a) a mean $C_{max,ss}$ for Compound 1 of about 80 ng/mL or about 84 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of about 582 ng·hours/mL or about 620 ng·hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours or a median $T_{max,ss}$ for Compound 1 of about 3.5 hours or about 4.0 hours; (d) a $C_{min,ss}$ for Compound 1 of about 4.6 ng/mL or about 5.2 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of about 10.1 hours or about 10.4 hours or about 14.4 hours; or combinations thereof.

[00796] In certain embodiments, the present disclosure is directed to pharmaceutical compositions comprising a crystalline hydrate of Compound 1 in an amount sufficient to deliver to the subject 30 mg of Compound 1 freebase equivalent. In certain embodiments, the crystalline hydrate is Freebase Hydrate Form C. In one embodiment, the crystalline hydrate is in a once daily extended release formulation. In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 55 to about 85 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 8.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 483 to about 660 ng-hours/mL; (e) a mean $C_{max,ss}$ for Compound 1 of from about 65 to about 85 ng/mL; (f) a mean $AUC_{24,ss}$ for Compound 1 of from about 485 to about 658 ng-hours/mL; (g) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (h) a mean $C_{min,ss}$ for Compound 1 of from about 3.5 to about 5.3 ng/mL; (i) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 10.0 to about 14.5 hours; or combinations thereof.

[00797] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 55 to about 85 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 8.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 483 to about 660 ng-hours/mL; or combinations thereof, after a single 30 mg dose.

[00798] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject QD (once daily), the composition provides (a) a mean $C_{max,ss}$ for Compound 1 of from about 65 to about 85 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of from about 485 to about 658 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (d) a

mean $C_{min,ss}$ for Compound 1 of from about 3.5 to about 5.3 ng/mL; (e) a harmonic mean $t_{1/2, ss}$ for Compound 1 of from about 10.0 to about 14.5 hours; or combinations thereof.

[00799] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject under fasting conditions, the composition provides (a) a mean C_{max} for Compound 1 of from about 55 ng/mL to about 66 ng/mL, or about 55 ng/mL, or about 56 ng/mL, or about 57 ng/mL, or about 59 ng/mL, or about 61 ng/mL, or about 64 ng/mL or about 66 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 4.0 hours, or from about 1.5 hours to about 4.0 hours, or a median T_{max} for Compound 1 of about 2.0 hours, or about 2.5 hours, or about 3.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 9.0 hours, or about 9.5 hours, or about 10.0 hours, or about 10.5 hours, or about 11.0 hours, or about 11.5 hours, or about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of about 484 to about 550 ng·hours/mL, or about 484 ng·hours/mL, or about 491 ng·hours/mL, or about 495 ng·hours/mL, or about 499 ng·hours/mL, or about 513 ng·hours/mL; or combinations thereof, after a single 30 mg dose.

[00800] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject under non-fasting conditions, the composition provides (a) a mean C_{max} for Compound 1 of from about 76 ng/mL to about 85 ng/mL, or about 76 ng/mL, or about 77 ng/mL, or about 79 ng/mL, about 82 ng/mL, or about 84 ng/mL; (b) a T_{max} for Compound 1 of from about 1.5 hours to about 8.0 hours, or from about 2.0 hours to about 6.0 hours, or a median T_{max} for Compound 1 of about 4.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of about 9.0 hours, or about 9.5 hours, or about 10.0 hours, or about 10.5 hours, or about 11.0 hours, or about 11.5 hours, or about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of about 577 ng·hours/mL, or about 609 ng·hours/mL, or about 622 ng·hours/mL, or about 657 ng·hours/mL; or combinations thereof, after a single 30 mg dose.

[00801] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject QD (once daily) under fasting conditions, the composition alternately or additionally provides (a) a mean $C_{max,ss}$ for Compound 1 of about 67 ng/mL or about 68 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of about 525 ng·hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 2.0 to about 4.0 hours, or a median $T_{max,ss}$ for Compound 1 of about 3.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of about 3.8 ng/mL; (e) a harmonic mean $t_{1/2, ss}$ for Compound 1 of about 10.1 hours or about 10.4 hours or about 14.4 hours; or combinations thereof.

[00802] In one embodiment, upon oral administration of the pharmaceutical composition to an adult subject QD (once daily) under non-fasting conditions, the composition alternately or additionally provides (a) a mean $C_{max,ss}$ for Compound 1 of about 80 ng/mL or about 84 ng/mL;

(b) a mean $AUC_{24,ss}$ for Compound 1 of about 582 ng·hours/mL or about 620 ng·hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours or a median $T_{max,ss}$ for Compound 1 of about 3.5 hours or about 4.0 hours; (d) a $C_{min,ss}$ for Compound 1 of about 4.6 ng/mL or about 5.2 ng/mL; (e) a harmonic mean $t_{1/2,\ ss}$ for Compound 1 of about 10.1 hours or about 10.4 hours or about 14.4 hours; or combinations thereof; or combinations thereof.

[00803] In one embodiment, the present disclosure is directed to pharmaceutical compositions comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily daily extended release formulation, and wherein upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 55 to about 85 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 8.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 483 to about 660 ng-hours/mL; (e) a mean $C_{max,ss}$ for Compound 1 of from about 65 to about 85 ng/mL; (f) a mean $AUC_{24,ss}$ for Compound 1 of from about 485 to about 658 ng-hours/mL; (g) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (h) a mean $C_{min,ss}$ for Compound 1 of from about 3.5 to about 5.3 ng/mL; (i) a harmonic mean $t_{1/2,\ ss}$ for Compound 1 of from about 10.0 to about 14.5 hours; or combinations thereof.

[00804] In one embodiment, the present disclosure is directed to pharmaceutical compositions comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% or about 20 w/w% or about 30 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily daily extended release formulation, and wherein upon oral administration of the pharmaceutical composition to an adult subject, the composition provides (a) a mean C_{max} for Compound 1 of from about 55 to about 85 ng/mL; (b) a T_{max} for Compound 1 of from about 1.0 hours to about 8.0 hours; (c) a harmonic mean $t_{1/2}$ for Compound 1 of from about 9.0 to about 12.0 hours; (d) a mean AUC_{inf} for Compound 1 of from about 483 to about 660 ng-hours/mL; or combinations thereof after a single 30 mg dose.

[00805] In one embodiment, the present disclosure is directed to pharmaceutical compositions comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% or about 20 w/w.% or about 30 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily daily extended release formulation, and wherein upon oral administration of the pharmaceutical composition to an adult subject QD (once daily), the composition provides (a) a mean $C_{max,ss}$ for Compound 1 of from about 65 to

about 85 ng/mL; (b) a mean $AUC_{24,ss}$ for Compound 1 of from about 485 to about 658 ng-hours/mL; (c) a $T_{max,ss}$ for Compound 1 of from about 1.5 to about 6.0 hours; (d) a mean $C_{min,ss}$ for Compound 1 of from about 3.5 to about 5.3 ng/mL; (e) a harmonic mean $t_{1/2,ss}$ for Compound 1 of from about 10.0 to about 14.5 hours; or combinations thereof.

VIII. Extended Release Tablets

[00806] In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate used in the methods of the present disclosure is in a once daily extended release formulation. In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is in a once daily extended release formulation, and the formulation delivers about 7.5 mg or about 15 mg or about 30 mg or about 45 mg per unit dosage form (e.g., per tablet or capsule) of Compound 1 (freebase equivalent) orally QD (once daily). In one particular embodiment, the crystalline hydrate is Freebase Hydrate Form C.

[00807] In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is in a once daily extended release formulation, and the formulation delivers 7.5 mg of Compound 1 (freebase equivalent) orally QD (once daily). In some such embodiments, the once daily extended release formulation will have a relative bioavailability approximately equivalent to that of an immediate release capsule comprising Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form thereof that delivers 3 mg of Compound 1 (freebase equivalent) and that is administered two times per day (BID). In one embodiment, the immediate release capsule comprises a crystalline hydrate of Compound 1. In one embodiment, the immediate release capsule comprises Freebase Hydrate Form C. In one embodiment, the immediate release capsule comprises Tartrate Hydrate.

[00808] In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is in a once daily extended release formulation, and the formulation delivers 15 mg of Compound 1 (freebase equivalent) orally QD (once daily). In some such embodiments, the once daily extended release formulation will have a relative bioavailability approximately equivalent to that of an immediate release capsule comprising Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form thereof that delivers 6 mg of Compound 1 (freebase equivalent) and that is administered two times per day (BID). In one embodiment, the immediate release capsule comprises a crystalline hydrate of Compound 1. In one embodiment, the immediate release capsule

comprises Freebase Hydrate Form C. In one embodiment, the immediate release capsule comprises Tartrate Hydrate.

[00809] In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is in a once daily extended release formulation, and the formulation delivers 30 mg of Compound 1 (freebase equivalent) orally QD (once daily). In some such embodiments, the once daily extended release formulation will have a relative bioavailability approximately equivalent to that of an immediate release capsule comprising Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form thereof that delivers 12 mg of Compound 1 (freebase equivalent) and that is administered two times per day (BID). In one embodiment, the immediate release capsule comprises a crystalline hydrate of Compound 1. In one embodiment, the immediate release capsule comprises Freebase Hydrate Form C. In one embodiment, the immediate release capsule comprises Tartrate Hydrate.

[00810] In one embodiment, the Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or the crystalline hydrate is in a once daily extended release formulation, and the formulation delivers 45 mg of Compound 1 (freebase equivalent) orally QD (once daily). In some such embodiments, the once daily extended release formulation will have a relative bioavailability approximately equivalent to that of an immediate release capsule comprising Compound 1 (freebase) or a pharmaceutically acceptable salt thereof or a solid state form thereof that delivers 18 mg of Compound 1 (freebase equivalent) and that is administered two times per day (BID). In one embodiment, the immediate release capsule comprises a crystalline hydrate of Compound 1. In one embodiment, the immediate release capsule comprises Freebase Hydrate Form C. In one embodiment, the immediate release capsule comprises Tartrate Hydrate.

[00811] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, and a pharmaceutically acceptable carrier, wherein pharmaceutical composition is a once daily extended release formulation, and the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D.

[00812] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, a pharmaceutically acceptable carrier, and a

pH modifier, wherein the pharmaceutical composition is a once daily extended release formulation, and the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In one embodiment, the pharmaceutical composition comprises from about 10 wt% to about 30 wt. % of the pH modifier. In one embodiment, the pH modifier is tartaric acid.

[00813] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of a solid state form of Compound 1, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release formulation, and the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D.

[00814] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form B, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00815] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Amorphous Freebase, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00816] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Anhydrate Form D, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00817] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00818] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release formulation.

[00819] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 20 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release formulation.

[00820] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 15 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 30 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release formulation.

[00821] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, and a pharmaceutically acceptable carrier, wherein pharmaceutical composition is a once daily extended release formulation, and the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D.

[00822] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Compound 1 freebase or a pharmaceutically acceptable salt thereof or a solid state form of Compound 1, a pharmaceutically acceptable carrier, and a pH modifier, wherein the pharmaceutical composition is a once daily extended release formulation, and the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D. In one embodiment, the pharmaceutical composition comprises from about 10 wt% to about 30 wt. % of the pH modifier. In one embodiment, the pH modifier is tartaric acid.

[00823] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of a solid state form of Compound 1, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid, wherein the pharmaceutical composition is a once daily extended release formulation, and the solid state form of Compound 1 is selected from the group consisting of Amorphous Freebase, Freebase Hydrate Form B, Freebase Hydrate Form C, and Freebase Anhydrate Form D.

[00824] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form B, a pharmaceutically

acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00825] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Amorphous Freebase, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00826] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Anhydrate Form D, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00827] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and from about 10 w/w% to about 35 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00828] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 10 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00829] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 20 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

[00830] In one embodiment, the present disclosure is directed to a pharmaceutical composition comprising about 30 mg of Freebase Hydrate Form C, a pharmaceutically acceptable carrier, and about 30 w/w% of tartaric acid wherein the pharmaceutical composition is a once daily extended release formulation.

IX. Kits

[00831] The present disclosure also relates to kits comprising one or more solid pharmaceutical dosage units (such as tablets or capsules) comprising a solid state form of the present disclosure. The kit optionally can comprise one or more additional therapeutic agents and/or instructions, for example, instructions for using the kit. In one aspect, the kit comprises

one or more solid pharmaceutical dosage units (such as tablets or capsules) comprising a solid state form of the present disclosure and instructions for administering the one or more dosage forms to a subject.

[00832] In one embodiment, the kit comprises a first dosage unit and a second dosage unit, wherein the first dosage unit is a solid pharmaceutical dosage unit comprising a solid state form of the present disclosure, and the second dosage unit comprises a second therapeutic agent. In one aspect, the second therapeutic agent is one of the therapeutic agents identified in the previous discussion relating to combination therapies. In another aspect, the second therapeutic agent is an imunosuppressant. In another aspect, the second therapeutic agent is a therapeutic agent for treating systemic lupus erythematosus. In another aspect, the second therapeutic agent is acetaminophen. In another aspect, the second therapeutic agent is methotrexate. In another aspect, the second therapeutic agent is a TNF antagonist, such as a humanized or human anti-TNF antibody (*e.g.*, adalimumab, infliximab, golimumab, certolizumab pegol, tocilizumab, or enteracept).

X. Methods of Preparation

[00833] The present disclosure also relates to methods for preparing a solid state form of Compound 1. In one aspect, the solid state form prepared is the Amorphous Freebase. In another aspect, the solid state form prepared is the Freebase Hydrate Form B. In another aspect, the solid state form prepared is the Freebase Hydrate Form C. In another aspect, the solid state form prepared is the Tartrate Hydrate. In another aspect, the solid state form prepared is the Freebase Anhydrate Form D.

A. Preparation of Amorphous Freebase

[00834] The present disclosure relates to methods for preparing the Amorphous Freebase. In one embodiment, the method comprises dehydrating the Freebase Hydrate Form B to provide the Amorphous Freebase. In another embodiment, the method comprises desolvating the Freebase Solvate Form A to provide the Amorphous Freebase. A wide range of process conditions can be employed for the dehydration/desolvation. The dehydration can be conducted, for example, under ambient conditions or in a vacuum oven. Figure 1A schematically illustrates one method of preparing the Amorphous Freebase by dehydration of the Freebase Hydrate Form B.

[00835] In another embodiment, the method comprises dissolving Compound 1 in a solvent or mixture of solvents; and adjusting the pH of the solvent or mixture of solvents to a pH

greater than about 8 to initiate precipitation of the Amorphous Freebase. In one aspect, the solvent or mixture of solvents comprises water. In another aspect, the pH is adjusted to a pH greater than about 9. In another aspect, the pH is adjusted to a pH greater than about 10. In another aspect, the pH is adjusted to a pH greater than about 11. In another aspect, the pH is adjusted to a pH of at least about 9.

[00836] In still other embodiments, the method comprises preparing the Amorphous Freebase using a method selected from the group consisting of impinging jet, spray drying, and hot-melt extrusion.

B. Preparation of Crystalline Freebase Solvate Form A and Crystalline Freebase Hydrate Form B

[00837] The present disclosure additionally relates to methods for preparing the Freebase Solvate Form A and Freebase Hydrate Form B. In one embodiment, the method comprises dissolving Compound 1 in a solvent or mixture of solvents comprising an anti-solvent; and maintaining the solvent or mixture of solvents at a temperature less than about 15°C for an amount of time sufficient to initiate crystallization of the Freebase Solvate Form A or the Freebase Hydrate Form B. The anti-solvent can comprise, for example, water. The solvent or mixture of solvents can comprise a polar solvent such as a solvent is selected from the group consisting of methanol, ethanol, n-butylamine, acetone, acetonitrile, ethyl formate, methyl acetate, ethyl acetate, methyl ethyl ketone, methyl isobutyl ketone, methyl isobutyl ketone, methyl tert-butyl ether, and isopropyl acetate. The Freebase Solvate Form A and Freebase Hydrate Form B exhibit similar PXRD patterns, and are therefore isostructural. The method generally is conducted at sub-ambient temperatures, for example, less than about 10°C, less than about 5°C, or less than about 0°C. In certain aspects, the process further comprises seeding the solvent or mixture of solvents with crystals of the Freebase Solvate Form A or the Freebase Hydrate Form B.

C. Preparation of Crystalline Freebase Hydrate Form C

[00838] The present disclosure additionally relates to methods for preparing the Freebase Hydrate Form C. In one embodiment, the method comprises dissolving Compound 1 in a solvent or mixture of solvents; and initiating crystallization to provide the Freebase Hydrate Form C. The solvent or mixture of solvents generally will comprise an anti-solvent (such as water) which can be present in the solvent or mixture of solvents before, or added to the solvent or mixture of solvents after, the Compound 1 is dissolved in the solvent or mixture of solvents.

The solvent or mixture of solvents can comprise, for example, one or more polar solvents (such as polar solvent selected from the group consisting of ethanol and ethyl acetate); one or more nonpolar solvents (such as a nonpolar solvent is selected from the group consisting of hexane and heptane); or at least one polar solvent and at least one nonpolar solvent. In one aspect, the solvent or mixture of solvents is a ternary solvent mixture comprising ethyl acetate, heptane, and water. The method generally is conducted at temperatures less than about 30°C, less than about 20°C, or less than about 10°C. In certain aspects, the initiating crystallization step comprises mixing the solvent or mixture of solvents to provide sufficient agitation to initiate crystallization. In certain aspects, the initiating crystallization step comprises seeding the solvent or mixture of solvents with crystals of the Freebase Hydrate Form C. In certain aspects, the initiating crystallization step comprises both mixing the solvent or mixture of solvents and seeding the solvent or mixture of solvents with crystals of the Freebase Hydrate Form C.

[00839] In one embodiment, Compound 1 is first prepared according to any of the methods set forth herein, a reaction mixture comprising Compound 1 is filtered, and the resulting solution is suspended in a solvent or mixture of solvents. The solvent or mixture of solvents can comprise, for example, one or more polar solvents (such as polar solvent selected from the group consisting of ethanol and ethyl acetate); one or more nonpolar solvents (such as a nonpolar solvent is selected from the group consisting of hexane and heptane); or at least one polar solvent and at least one nonpolar solvent. In one particular embodiment, the solvent is ethyl acetate, or a mixture of ethyl acetate and water. In certain aspects, the initiating crystallization step comprises seeding the solvent or mixture of solvents with crystals of the Freebase Hydrate Form C. In one particular aspect, the crystallization occurs in a wet mill.

[00840] Figure 1B schematically illustrates one method of preparing the Freebase Hydrate Form C.

D. Preparation of Crystalline Freebase Anhydrate Form D

[00841] The present disclosure additionally relates to methods for preparing the Freebase Anhydrate Form D. In one embodiment, the method comprises dissolving Compound 1 in a solvent or mixture of solvents; and initiating crystallization to provide the Freebase Anhydrate Form D. The solvent or mixture of solvents will be water-free, or close to water-free. In embodiments, the solvent or mixture of solvents will have a water content of less than about 0.15 wt%, or less than about 0.10 wt.%, or less than about 0.05 wt.%, or about 0 wt.% at 23°C. In one embodiment, the solvent or mixture of solvents will have a water activity of about 2.4% or less, or about 2.2% or less, or about 2.0% or less, or about 1.5% or less. The solvent or

mixture of solvents can comprise, for example, ethyl acetate (EtOAc), heptane, and combinations thereof. In one embodiment, the solvent system comprises a mixture of heptane in ethyl acetate. In some embodiments, the solvent system comprises about 10 wt.%, or about 20 wt.%, or about 30 wt.%, or about 40 wt.% heptane in ethyl acetate. The method generally is conducted at temperatures of at least about 7°C, at least about 23°C, at least about 25°C or less, or at least about 30°C. In one embodiment, the method is conducted at about 23°C. In certain aspects, the initiating crystallization step comprises mixing the solvent or mixture of solvents to provide sufficient agitation to initiate crystallization. In certain aspects, the initiating crystallization step comprises seeding the solvent or mixture of solvents with crystals of the Freebase Anhydrate Form D. In certain aspects, the initiating crystallization step comprises both mixing the solvent or mixture of solvents and seeding the solvent or mixture of solvents with crystals of the Freebase Anhydrate Form D.

E. Preparation of Crystalline Tartrate Hydrate

[00842] The present disclosure additionally relates to methods for preparing the Tartrate Hydrate. In one embodiment, the method comprises dissolving Compound 1 and L-tartaric acid in a solvent or mixture of solvents to form a crystallization solution; and crystallizing the Tartrate Hydrate from the crystallization solution. The solvent or mixture of solvents can comprise, for example, water and/or, for example, one or more polar solvents (such as isopropyl acetate). The solvent or mixture of solvents also can comprise an anti-solvent (such as isopropyl acetate). In certain aspects, the process further comprises seeding the solvent or mixture of solvents with crystals of the Tartrate Hydrate.

[00843] The crystallization generally is conducted at a temperature less than about 40°C. When an anti-solvent is used, a moderate rate of addition is employed for the anti-solvent as a faster rate of addition typically results in the precipitation of an amorphous tartrate and a slower rate of addition allows the resulting slurry to thicken. Proper control of filtration, washing, and drying may be needed to avoid potential issues associated with consolidation of the filter cake, including solvent entrapment, solid properties (*e.g.*, hard, chunky solids) and handing, and damage to equipment. Depending upon the properties of the dried Tartrate Hydrate material, milling may require a mechanical impact-type of mills rather than a shear-based mill (such as a co-mill).

[00844] Figure 1C schematically illustrates one method of preparing the Tartrate Hydrate.

XI. Product-By-Process

[00845] The present disclosure also relates to a solid state form of Compound 1 prepared in accordance with any of the methods described in the disclosure.

[00846] In one embodiment, the solid state form prepared is the Amorphous Freebase.

[00847] In one embodiment, the solid state form prepared is the Freebase Hydrate Form B.

[00848] In one embodiment, the solid state form prepared is the Freebase Hydrate Form C.

[00849] In one embodiment, the solid state form prepared is the Tartrate Hydrate.

[00850] In one embodiment, the solid state form prepared is Freebase Anhydrate Form D.

XII. Additional Embodiments

[00851] In some aspects, the disclosure is directed to the following additional embodiments:

[00852] Embodiment A: A crystalline hydrate of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00853] Embodiment A1: The crystalline hydrate of Embodiment A, wherein the hydrate is a hemihydrate.

[00854] Embodiment A2: The crystalline hydrate of Embodiment A or Embodiment A1 having an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00855] Embodiment A3: The crystalline hydrate of Embodiment A2, wherein the X-ray powder diffraction pattern is further characterized by a peak at 15.5 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00856] Embodiment A4: The crystalline hydrate of Embodiment A3, wherein the X-ray powder diffraction pattern is further characterized by a peak at 17.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00857] Embodiment A5: The crystalline hydrate of Embodiment A4, wherein the X-ray powder diffraction pattern is further characterized by a peak at 20.9 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00858] Embodiment A6: The crystalline hydrate of any one of Embodiments A to A5, wherein the crystalline hydrate has an X-ray powder diffraction pattern substantially as shown in Figure 3C.

[00859] Embodiment A7: The crystalline hydrate of any one of Embodiments A to A6, wherein the crystalline hydrate has a thermogravimetric analysis profile substantially as shown in Figure 4E.

[00860] Embodiment A8: The crystalline hydrate of any one of Embodiments A to A7, wherein the crystalline hydrate has a differential scanning calorimetry profile substantially as shown in Figure 5C.

[00861] Embodiment A9: The crystalline hydrate of any one of Embodiments A to A8, wherein the crystalline hydrate has a moisture sorption isotherm profile substantially as shown in Figure 6B.

[00862] Embodiment A10: The crystalline hydrate of any one of Embodiments A to A9, wherein the crystalline hydrate has a thermogravimetric analysis profile showing a weight loss of about 2.3% to about 2.6% between about 120°C and 160°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 120°C and about 170°C when heated at a rate of 10°C/minute.

[00863] Embodiment A11: The crystalline hydrate of any one of Embodiments A to A10, wherein the crystalline hydrate has an orthorhombic lattice type.

[00864] Embodiment A12: The crystalline hydrate of Embodiment A11, wherein the crystalline hydrate has a $P2_12_12_1$ space group.

[00865] Embodiment A13: The crystalline hydrate of Embodiment A11 or A12, wherein the crystalline hydrate has unit cell a, b and c values of about 12.7Å, about 13.1Å, and about 22.6Å, respectively

[00866] Embodiment A14: The crystalline hydrate of Embodiment A having an X-ray powder diffraction pattern characterized by peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00867] Embodiment A15: The crystalline hydrate of Embodiment A14, wherein the X-ray powder diffraction pattern is further characterized by a peak at 20.8 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00868] Embodiment A16: The crystalline hydrate of Embodiment A15, wherein the X-ray powder diffraction pattern is further characterized by a peak at 25.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00869] Embodiment A17: The crystalline hydrate of any one of Embodiments A or A14 to A16, wherein the crystalline hydrate has an X-ray powder diffraction pattern substantially as shown in Figure 3B.

[00870] Embodiment A18: The crystalline hydrate of any one of Embodiments A or A14 to A17, wherein the crystalline hydrate has a thermogravimetric analysis profile substantially as shown in Figure 4D.

[00871] Embodiment A19: The crystalline hydrate of any one of Embodiments A or A14 to A18, wherein the crystalline hydrate has a differential scanning calorimetry profile substantially as shown in Figure 5B.

[00872] Embodiment A20: A pharmaceutical composition comprising a crystalline hydrate of any one of Embodiments A to A19, and a pharmaceutically acceptable carrier.

[00873] Embodiment A21: The pharmaceutical composition of Embodiment A20, wherein greater than about 90% by weight of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide in the composition is a crystalline hydrate of (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)-pyrrolidine-1-carboxamide having an X-ray powder diffraction pattern characterized by peaks at 13.4 ± 0.2, 15.1 ± 0.2, and 21.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00874] Embodiment A22: The pharmaceutical composition of Embodiment A20, wherein greater than about 90% by weight of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide in the composition is a crystalline hydrate of (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)-pyrrolidine-1-carboxamide having an X-ray powder diffraction pattern comprising peaks at 3.1 ± 0.2, 9.3 ± 0.2, and 12.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00875] . Embodiment B: Amorphous freebase (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00876] Embodiment B1: The amorphous freebase (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of Embodiment B comprising less than about 12% by weight water.

[00877] Embodiment B2: The amorphous freebase (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of Embodiment B or B1 having a glass transition temperature onset at about 119°C.

[00878] Embodiment B3: The amorphous freebase (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any of Embodiments B to B2 having a glass transition temperature midpoint at about 122°C.

[00879] Embodiment B4: A pharmaceutical composition comprising the amorphous freebase (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments B to B3, and a pharmaceutically acceptable carrier.

[00880] Embodiment B5: The pharmaceutical composition of Embodiment B4, wherein greater than about 90% by weight of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide in the composition is amorphous freebase (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00881] Embodiment C: A crystalline anhydrate of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00882] Embodiment C1: The crystalline anhydrate of Embodiment C having an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00883] Embodiment C2: The crystalline anhydrate of Embodiment C1, wherein the X-ray powder diffraction pattern is further characterized by a peak at 4.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00884] Embodiment C3: The crystalline anhydrate of Embodiment C2, wherein the X-ray powder diffraction pattern is further characterized by a peak at 19.0 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00885] Embodiment C4: The crystalline anhydrate of Embodiment C3, wherein the X-ray powder diffraction pattern is further characterized by peaks at 18.4 ± 0.2, 23.0 ± 0.2, and 24.7 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00886] Embodiment C5: The crystalline anhydrate of any one of Embodiments C to C4, wherein the crystalline anhydrate has an X-ray powder diffraction pattern substantially as shown in Figure 3J.

[00887] Embodiment C6: The crystalline anhydrate of any one of Embodiments C to C5, wherein the crystalline anhydrate has a thermogravimetric analysis profile substantially as shown in Figure 4I.

[00888] Embodiment C7: The crystalline anhydrate of any one of Embodiments C to C6, wherein the crystalline anhydrate has a differential scanning calorimetry profile substantially as shown in Figure 5E.

[00889] Embodiment C8: The crystalline anhydrate of any one of Embodiments C to C7, wherein the crystalline anhydrate has a moisture sorption isotherm profile substantially as shown in Figure 6D.

[00890] Embodiment C9: The crystalline anhydrate of any one of Embodiments C to C8, wherein the crystalline anhydrate has an orthorhombic lattice type.

[00891] Embodiment C10: The crystalline anhydrate of any one of Embodiments C to C9, wherein the crystalline anhydrate has a $P2_12_12$ space group.

[00892] Embodiment C11: The crystalline anhydrate of any one of Embodiments C to C10, wherein the crystalline anhydrate has unit cell a, b and c values of about 43.8Å, about 8.6Å, and about 9.2Å, respectively.

[00893] Embodiment C12: The crystalline anhydrate of any one of Embodiments C to C11, wherein the crystalline anhydrate has a thermogravimetric analysis profile showing a weight loss of about 0.5% to about 0.8% between about 43°C and 188°C when heated at a rate of 10°C/minute; and a differential scanning calorimetry profile comprising an endotherm between about 180°C and about 220°C when heated at a rate of 10°C/minute.

[00894] Embodiment C13: The crystalline anhydrate of any one of Embodiments C to C12, wherein the crystalline anhydrate has an onset melting point of about 199.6°C.

[00895] Embodiment C14: A pharmaceutical composition comprising a crystalline anhydrate of any one of embodiments C to C13, and a pharmaceutically acceptable carrier.

[00896] Embodiment C15: The pharmaceutical composition of Embodiment C14, wherein greater than about 90% by weight of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide in the composition is a crystalline anhydrate of (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)-pyrrolidine-1-carboxamide having an X-ray powder diffraction pattern characterized by peaks at 8.0 ± 0.2, 9.7 ± 0.2, 14.2 ± 0.2, 14.5 ± 0.2, and 20.3 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00897] Embodiment D: A pharmaceutical composition comprising (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide tartrate, from about 10 w/w% to about 35 w/w% of an organic acid selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and combinations thereof, and a pharmaceutically acceptable carrier.

[00898] Embodiment D1: The pharmaceutical composition of Embodiment D, wherein the tartrate is crystalline (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide tartrate tetrahydrate.

[00899] Embodiment D2: The pharmaceutical composition of Embodiment D or Embodiment D1, wherein the tartrate has an X-ray powder diffraction pattern characterized by peaks at 3.9 ± 0.2, 6.8 ± 0.2, and 14.1 ± 0.2 degrees two theta when measured at about 25°C with monochromatic Kα1 radiation.

[00900] Embodiment D3: The pharmaceutical composition of any one of Embodiments D to D2, wherein the tartrate has an X-ray powder diffraction pattern substantially as shown in Figure 3D.

[00901] Embodiment D4: The pharmaceutical composition of any one of Embodiments D to D3, wherein the tartrate has a thermogravimetric analysis profile substantially as shown in Figure 4F.

[00902] Embodiment D5: The pharmaceutical composition of any one of Embodiments D to D4, wherein the tartrate has a differential scanning calorimetry profile substantially as shown in Figure 5D.

[00903] Embodiment D6: The pharmaceutical composition of any one of Embodiments D to D5, wherein the tartrate has a moisture sorption isotherm profile substantially as shown in Figure 6C.

[00904] Embodiment D7: The pharmaceutical composition of any one of Embodiments D to D6, wherein greater than about 90% by weight of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide in the composition is crystalline (3S,4R)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide tartrate tetrahydrate.

[00905] Embodiment E: The pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, or D to D7, wherein the composition comprises a release control polymer.

[00906] Embodiment E1: The pharmaceutical composition of Embodiment E, wherein the release control polymer is a hydrophilic polymer.

[00907] Embodiment E2: The pharmaceutical composition of Embodiment E or E1, wherein the release control polymer is a cellulose derivative with a viscosity between 1000 and 150,000 mPa-s.

[00908] Embodiment E3: The pharmaceutical composition of any one of Embodiments E to E2, wherein the release control polymer is selected from the group consisting of hydroxypropylmethyl cellulose, hydroyethyl cellulose, and copolymers of acrylic acid crosslinked with a polyalkenyl polyether, and combinations thereof.

[00909] Embodiment E4: The pharmaceutical composition of any one of Embodiments E to E3, wherein the release control polymer is selected from the group consisting of hydroxypropylmethyl cellulose, hydroyethyl cellulose, and combinations thereof.

[00910] Embodiment E5: The pharmaceutical composition of any one of Embodiments E to E4, wherein the release control polymer is hydroxypropylmethyl cellulose.

[00911] Embodiment E6: The pharmaceutical composition of Embodiment E5, wherein the hydroxypropylmethyl cellulose is grade E, F, or K.

[00912] Embodiment E6: The pharmaceutical composition of Embodiment E5, wherein the hydroxypropylmethyl cellulose is Hypromellose 2208.

[00913] Embodiment E7: The pharmaceutical composition of any one of Embodiments E to E6, wherein the composition comprises a filler.

[00914] Embodiment E8: The pharmaceutical composition of Embodiment E7, wherein the filler is selected from the group consisting of microcrystalline cellulose, mannitol, and combinations thereof.

[00915] Embodiment E9: The pharmaceutical composition of any one of Embodiments E to E8, wherein the composition comprises a lubricant.

[00916] Embodiment E10: The pharmaceutical composition of any one of Embodiments E to E9, wherein the composition comprises a glidant.

[00917] Embodiment E11: The pharmaceutical composition of any one of Embodiments E to E10, wherein the composition comprises a pH modifier.

[00918] Embodiment E12: The pharmaceutical composition of Embodiment E11, wherein the pH modifier is selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, malic acid, and combinations thereof.

[00919] Embodiment E13: The pharmaceutical composition of Embodiments E11 or E12, wherein the pH modifier is selected from the group consisting of tartaric acid, fumaric acid, citric acid, succinic acid, and combinations thereof.

[00920] Embodiment E14: The pharmaceutical composition of any one of Embodiments E11 to E13, wherein the pH modifier is selected from the group consisting of tartaric acid, fumaric acid, and combinations thereof.

[00921] Embodiment E15: The pharmaceutical composition of any one of Embodiments E11 to E14, wherein the pH modifier is tartaric acid.

[00922] Embodiment E16: The pharmaceutical composition of any one of Embodiments E11 to E14, wherein the pH modifier is fumaric acid or citric acid.

[00923] Embodiment E17: The pharmaceutical composition of any one of Embodiments E11 to E16, wherein the pH modifier is present in an amount from about 10 to about 35 w/w%.

[00924] Embodiment E18: The pharmaceutical composition of any one of Embodiments E11 to E17, wherein the pH modifier is present in an amount from about 20 to about 35 w/w%.

[00925] Embodiment E19: The pharmaceutical composition of any one of Embodiments E11 to E18, wherein the pH modifier is present in an amount from about 20 to about 30 w/w%.

[00926] Embodiment E20: The pharmaceutical composition of any one of Embodiments E11 to E19, wherein the pH modifier is present in an amount from about 20 to about 25 w/w%.

[00927] Embodiment E21: The pharmaceutical composition of any one of Embodiments E11 to E20, wherein the pH modifier is present in an amount of about 10 w/w%.

[00928] Embodiment E22: The pharmaceutical composition of any one of Embodiments E11 to E20, wherein the pH modifier is present in an amount of about 20 w/w%.

[00929] Embodiment E23: The pharmaceutical composition of any one of Embodiments E11 to E20, wherein the pH modifier is present in an amount of about 30 w/w%.

[00930] Embodiment F: A method of treating a JAK-1 associated condition, the method comprising administering a therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 to a subject suffering from or susceptible to the condition.

[00931] Embodiment F1: The method of embodiment F, wherein the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is selected from the group consisting of 7.5 mg once daily, 15 mg once daily, 30 mg once daily, and 45 mg once daily.

[00932] Embodiment F2: A method of treating a JAK-1 associated condition, the method comprising administering the pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 to a subject suffering from or susceptible to the condition.

[00933] Embodiment F2a: The method of any one of Embodiments F to F2, wherein the condition is selected from the group consisting of immunomodulation, inflammation, and proliferative disorders.

[00934] Embodiment F2b: The method of any one of Embodiments F to F2a, wherein the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is the Freebase Hydrate Form C.

[00935] Embodiment F3: A (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 for use in treating a JAK-1 associated condition. In certain aspects of Embodiment E3, the use comprising administering a therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 to a subject suffering from or susceptible to the condition. In one embodiment, the condition is selected from the group consisting of immunomodulation, inflammation, and proliferative disorders. In certain aspects, in Embodiment F3, the (3S,4R)-3-ethyl-4-(3H-

imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide may be the Freebase Hydrate Form C. In some aspects, in Embodiment F3, the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is selected from the group consisting of 7.5 mg once daily, 15 mg once daily, 30 mg once daily, and 45 mg once daily.

[00936] Embodiment F4: A pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 for use in treating a JAK-1 associated condition. In certain aspects of Embodiment F4, the use comprises administering the pharmaceutical composition to a subject suffering from or susceptible to the condition. In one embodiment, the condition is selected from the group consisting of immunomodulation, inflammation, and proliferative disorders. In certain aspects, in Embodiment F4, the composition comprises the Freebase Hydrate Form C.

[00937] Embodiment G: A method of treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus, the method comprising administering a therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 to a subject suffering from or susceptible to the condition.

[00938] Embodiment G1: The method of embodiment G, wherein the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is selected from the group consisting of 7.5 mg once daily, 15 mg once daily, 30 mg once daily, and 45 mg once daily.

[00939] Embodiment G2: A method of treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus, the method comprising administering the pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 to a subject suffering from or susceptible to the condition.

[00940] Embodiment G3: The method of any one of Embodiments G to G2, wherein the condition is rheumatoid arthritis.

[00941] Embodiment G3a: The method of any one of Embodiments G to G3, wherein the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is the Freebase Hydrate Form C.

[00942] Embodiment G4: A (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 for use in treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus. In certain aspects of Embodiment G4, the use comprises administering a therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 to a subject suffering from or susceptible to the condition. In one embodiment, the condition is rheumatoid arthritis. In some instances, in Embodiment G4, the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide may be selected from the group consisting of 7.5 mg once daily, 15 mg once daily, 30 mg once daily, and 45 mg once daily. In certain aspects, in Embodiment G4, the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide may be the Freebase Hydrate Form C.

[00943] Embodiment G5: A pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 for use in treating a condition selected from the group consisting of rheumatoid arthritis, juvenile idiopathic arthritis, Crohn's disease, ulcerative colitis, psoriasis, plaque psoriasis, nail psoriasis, psoriatic arthritis, ankylosing spondylitis, alopecia areata, hidradenitis suppurativa, atopic dermatitis, and systemic lupus erythematosus. In certain aspects of Embodiment G5, the use comprises administering the pharmaceutical composition to a subject suffering from or susceptible to the condition. In one embodiment, the condition is rheumatoid arthritis. In certain aspects, in Embodiment G5, the composition comprises Freebase Hydrate Form C.

[00944] Embodiment H: A method of treating moderate to severe active rheumatoid arthritis, the method comprising administering a therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-

carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 to a subject suffering from or susceptible to the condition.

[00945] Embodiment H1: The method of Embodiment H wherein the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is about 7.5 mg once daily.

[00946] Embodiment H2: The method of Embodiment H wherein the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is about 15 mg once daily.

[00947] Embodiment H3: The method of Embodiment H wherein the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is about 30 mg once daily.

[00948] Embodiment H4: The method of Embodiment H wherein the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is about 45 mg once daily.

[00949] Embodiment H5: A method of treating moderate to severe active rheumatoid arthritis, the method comprising administering the pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 to a subject suffering from or susceptible to the condition.

[00950] Embodiment H6: The method of any one of Embodiments H to H5, wherein the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is the Freebase Hydrate Form C.

[00951] Embodiment H7: The method of any one of Embodiments H to H6, wherein the subject has had an inadequate response to methotrexate.

[00952] Embodiment H8: The method of any one of Embodiments H to H7, wherein the subject has had an inadequate response to biologics medicines approved for rheumatoid arthritis.

[00953] Embodiment H9: The method of any one of Embodiments H to H8, wherein the subject has not previously been administered biologics medicines approved for rheumatoid arthritis.

[00954] Embodiment H10: A (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 for use in treating moderate to severe active rheumatoid arthritis.

In certain aspects of Embodiment H10, the use comprises administering a therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 to a subject suffering from or susceptible to the condition. In one aspect, in Embodiment H10, the therapeutically effective amount of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide is about 7.5 mg or about 15 mg or about 30 mg or about 45 mg once daily.

[00955] Embodiment H11: A pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 for use in treating moderate to severe active rheumatoid arthritis. In certain aspects of Embodiment H11, the use comprises administering the pharmaceutical composition to a subject suffering from or susceptible to the condition.

[00956] Embodiment I: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, per unit dosage form of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide orally once daily.

[00957] Embodiment I1: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 7.5 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00958] Embodiment I1a: A (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 for use in treating a subject having rheumatoid arthritis. In certain aspects of Embodiment E1a, the use comprises administering to the subject about 7.5 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00959] Embodiment I2: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject orally once daily the pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23, wherein the composition comprises about 7.5 mg, per unit dosage form of the (3S,4R)-3-ethyl-

4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00960] Embodiment I3: A pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 for use in treating a subject having rheumatoid arthritis. In certain aspects of Embodiment I3, the use comprises administering to the subject orally once daily the pharmaceutical composition, wherein the composition comprises about 7.5 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00961] Embodiment I4: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 15 mg, per unit dosage form of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide orally once daily.

[00962] Embodiment I5: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 15 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00963] Embodiment I6: A (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 for use in treating a subject having rheumatoid arthritis. In certain aspects of Embodiment I6, the use comprises administering to the subject about 15 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00964] Embodiment I7: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject orally once daily the pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23, wherein the composition comprises about 15 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00965] Embodiment I8: A pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 for use in treating a subject having rheumatoid

arthritis. In certain aspects of Embodiment I8, the use comprises administering to the subject orally once daily the pharmaceutical composition, wherein the composition comprises about 15 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00966] Embodiment I9: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 30 mg, per unit dosage form of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide orally once daily.

[00967] Embodiment I10: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 30 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00968] Embodiment I11: A (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 for use in treating a subject having rheumatoid arthritis. In certain aspects of Embodiment I11, the use comprises administering to the subject about 30 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00969] Embodiment I12: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject orally once daily the pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23, wherein the composition comprises about 30 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00970] Embodiment I13: A pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 for use in treating a subject having rheumatoid arthritis. In certain aspects of Embodiment I13, the use comprises administering to the subject orally once daily the pharmaceutical composition, wherein the composition comprises about 30 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00971] Embodiment I14: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 45 mg, per unit dosage form of (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide orally once daily.

[00972] Embodiment I15: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject about 45 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00973] Embodiment I16: A (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 for use in treating a subject having rheumatoid arthritis. In certain aspects of Embodiment I16, the use comprises administering to the subject about 45 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide of any one of Embodiments A to A19, B to B3, or C to C13 orally once daily.

[00974] Embodiment I17: A method of treating a subject having rheumatoid arthritis, the method comprising administering to the subject orally once daily the pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23, wherein the composition comprises about 45 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00975] Embodiment I18: A pharmaceutical composition of any one of Embodiments A20 to A22, B4, B5, C14, C15, D to D7, or E to E23 for use in treating a subject having rheumatoid arthritis. In certain aspects of Embodiment I18, the use comprises administering to the subject orally once daily the pharmaceutical composition, wherein the composition comprises about 45 mg, per unit dosage form of the (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

[00976] Embodiment J: A method for the preparation of the crystalline hydrate of Embodiment A1 or A2, the method comprising:

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __2 __

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

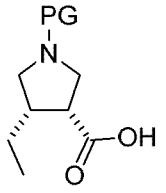
THIS IS VOLUME __1___ OF __2___

NOTE: For additional volumes please contact the Canadian Patent Office.

We Claim:

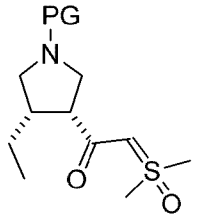
1. A process for preparing (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or a pharmaceutically acceptable salt thereof, the process comprising:

(a) reacting a compound of formula (I)



(I)

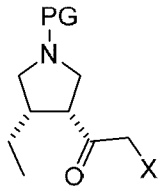
or a pharmaceutically acceptable salt thereof with trimethylsulfoxonium chloride to form a compound of formula (II)



(II)

wherein PG is a protecting group;

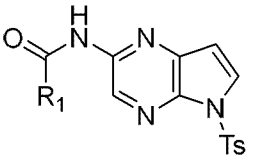
(b) contacting the compound of formula (II) with LiX and a sulfonic acid to form a compound of formula (III)



(III)

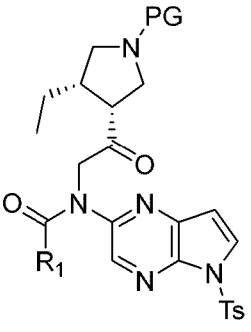
wherein X is Br or Cl;

(c) reacting the compound of formula (III) with a compound of formula (IV)



(IV)

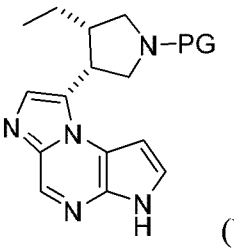
to produce a compound of formula (V)



(V)

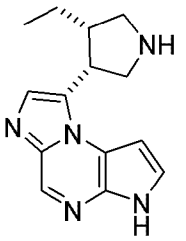
wherein R_1 is selected from the group consisting of alkyl, aryl, and $-OR_2$; R_2 is alkyl; and Ts is tosyl;

(d) contacting the compound of formula (V) with a perfluoro acid anhydride and an organic base to form a compound of formula (VI)



(VI)

(e) deprotecting the compound of formula (VI) and forming a pharmaceutically acceptable salt of the compound of formula (VII):

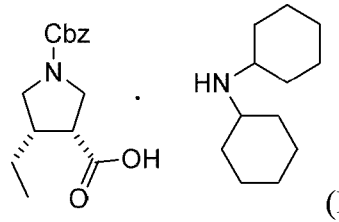


(VII)

(f) reacting the pharmaceutically acceptable salt of the compound of formula (VII) with 2,2,2-trifluoroethylamine to produce (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide.

2. The process of claim 1, wherein step e) comprises contacting the compound of formula (VII) with an acid to form the pharmaceutically acceptable salt of the compound of formula (VII).

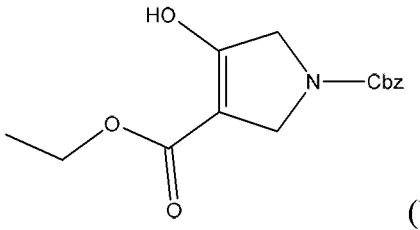
3. The process of claim 1 or claim 2, wherein the pharmaceutically acceptable salt of the compound of formula (I) is the compound of formula (Ib):



(Ib),

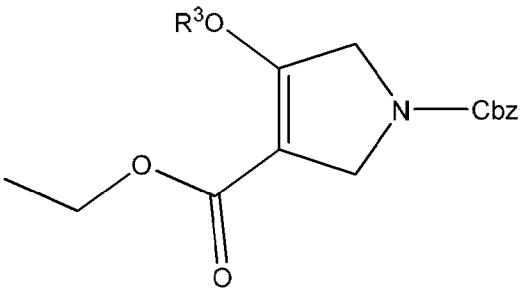
wherein the compound of formula (Ib) is prepared by:

(i) reacting carboxybenzyl-glycine ethyl ester with ethyl acrylate to form a compound of formula (VIII):



(VIII)

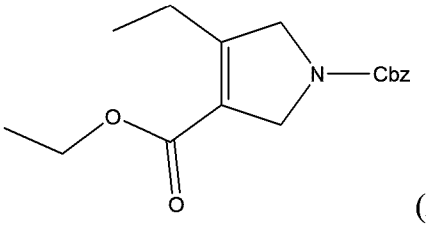
(ii) protecting the compound of formula (VIII) to form a compound of formula (IX):



(IX)

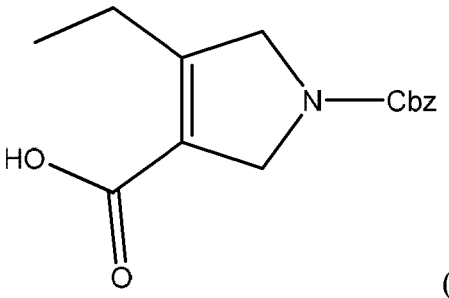
wherein R^3 is selected from the group consisting of CF_3SO_2-; CH_3SO_2-; and tosyl;

(iii) contacting the compound of formula (IX) with one of ethyl boronic acid, ethyl magnesium bromide, or ethyl zinc chloride in the presence of a catalyst to form a compound of formula (X):



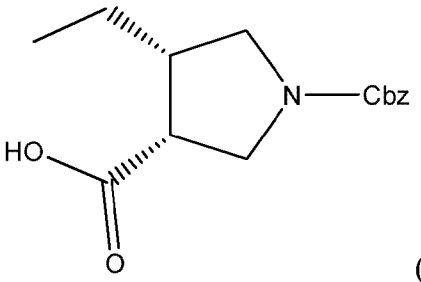
(X)

(iv) hydrolyzing the compound of formula (X) to produce the compound of formula (XI):



(XI)

(v) converting the compound of formula (XI) to the compound of formula (XII):



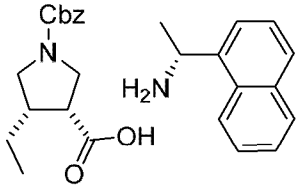
(XII)

(vi) contacting the compound of formula (XII) with dicyclohexylamine to form the compound of formula (Ib);

wherein Cbz is carboxybenzyl.

Date Reçue/Date Received 2020-08-19

4. The process of claim 1 or claim 2, wherein the pharmaceutically acceptable salt of the compound of formula (I) is the compound of formula (Ia):

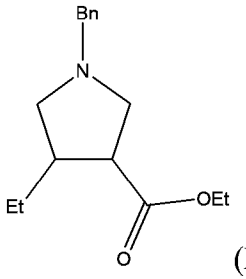


(Ia),

wherein the compound of formula (Ia) is prepared by:

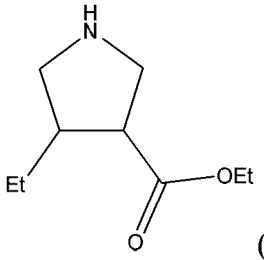
(i) hydrogenating ethyl pent-2-ynoate with a Lindlar catalyst to form (Z)-ethyl pent-2-enoate;

(ii) reacting (Z)-ethyl pent-2-enoate with N-(methoxymethyl)-N-(trimethylsilyl methyl)benzylamine to form a compound of formula (XIII)



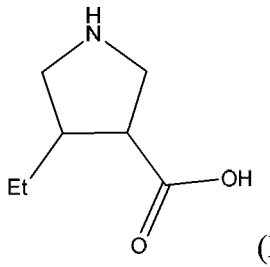
(XIII)

(iii) deprotecting the compound of formula (XIII) to form a compound of formula (XIV)



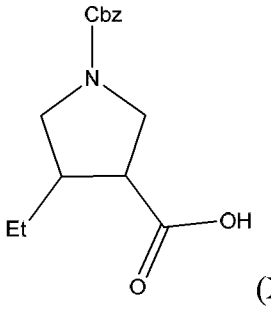
(XIV)

(iv) hydrolyzing the compound of formula (XIV) to form a compound of formula (XV)



(XV)

(v) reacting the compound of formula (XV) with N-benzyloxycarbonyloxy succinimide to form a compound of formula (XVI)

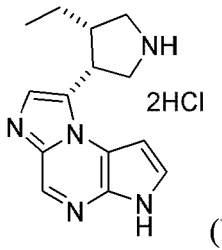


(XVI)

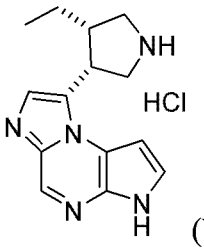
(vi) contacting the compound of formula (XVI) with (R)-1-(naphthalene-1-yl)ethanamine to form the compound of formula (Ia);

wherein Cbz is carboxybenzyl; Bn is benzyl; and Et is ethyl.

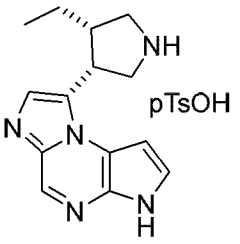
5. The process of any one of claims 1 to 4, wherein the pharmaceutically acceptable salt of the compound of formula (VII) is selected from the group consisting of:



(VIIa),



(VIIb), and



(VIIc).

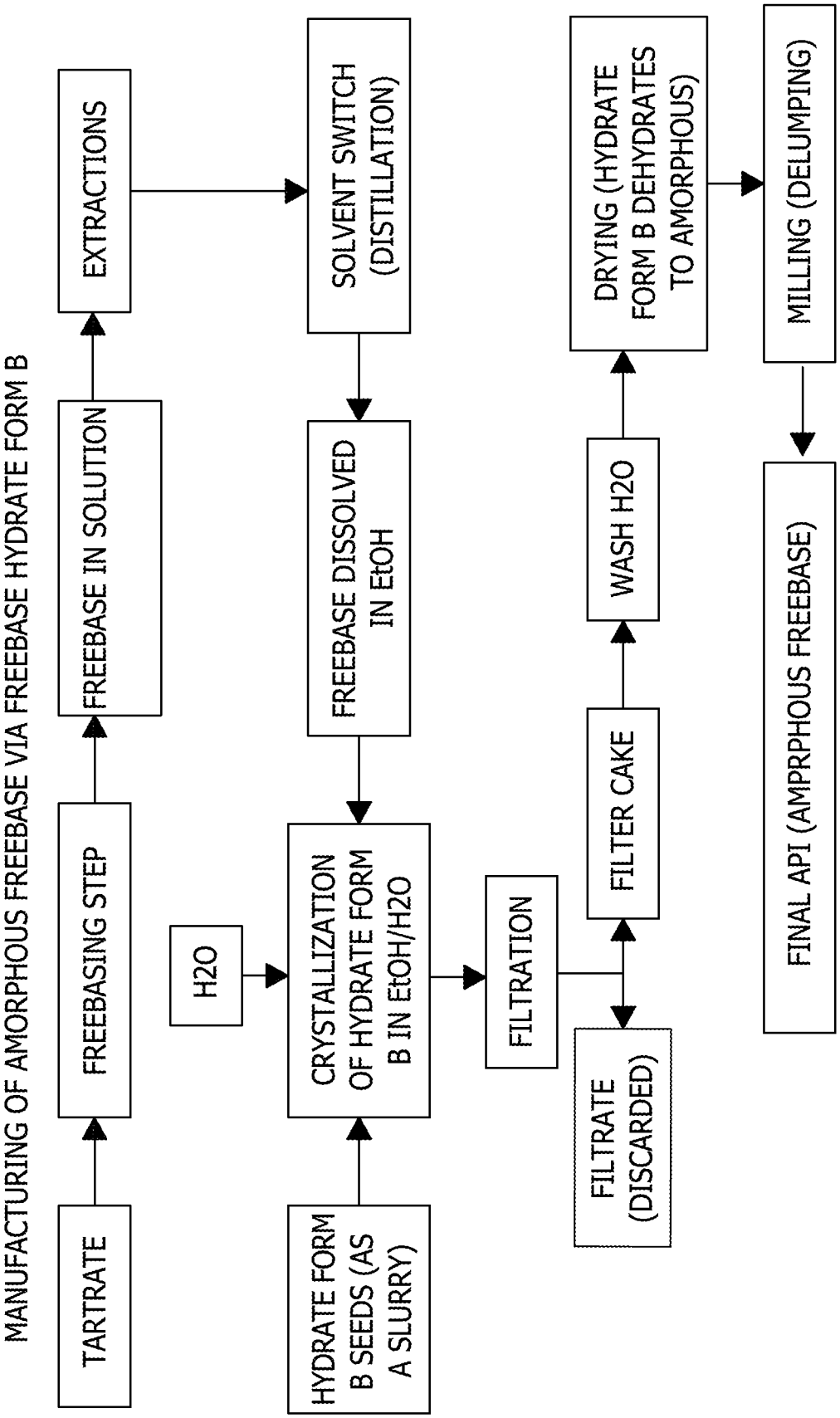

MANUFACTURING OF AMORPHOUS FREEBASE VIA FREEBASE HYDRATE FORM B
TARTRATE
FREEBASING STEP
FREEBASE IN SOLUTION
EXTRACTIONS
SOLVENT SWITCH (DISTILLATION)
FREEBASE DISSOLVED IN EtOH
H2O
HYDRATE FORM B SEEDS (AS A SLURRY)
CRYSTALLIZATION OF HYDRATE FORM B IN EtOH/H2O
FILTRATION
FILTRATE (DISCARDED)
FILTER CAKE
WASH H2O
DRYING (HYDRATE FORM B DEHYDRATES TO AMORPHOUS)
MILLING (DELUMPING)
FINAL API (AMPRPHOUS FREEBASE)

FIG. 1A

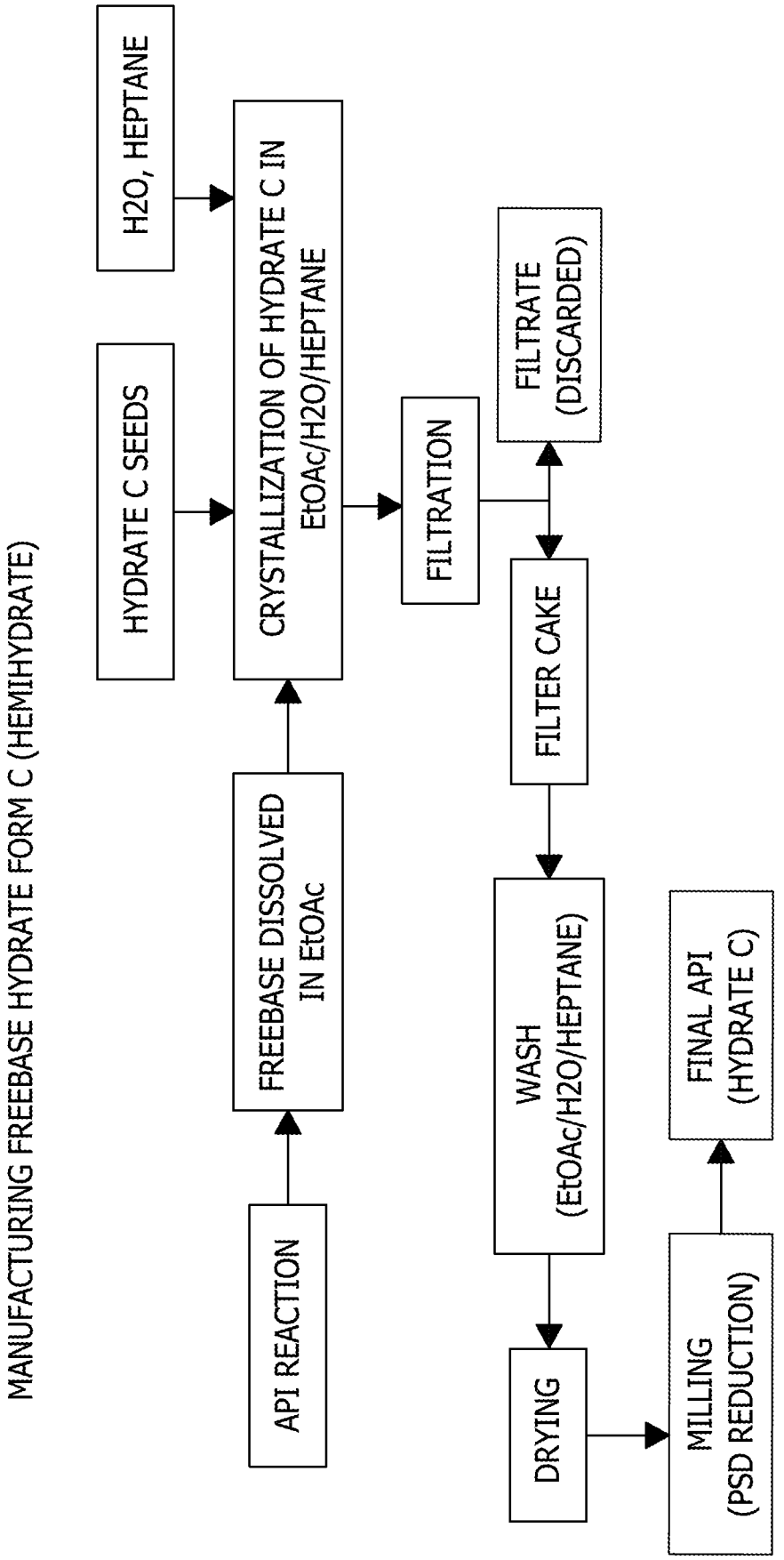

MANUFACTURING FREEBASE HYDRATE FORM C (HEMIHYDRATE)
API REACTION
FREEBASE DISSOLVED IN EtOAc
HYDRATE C SEEDS
H2O, HEPTANE
CRYSTALLIZATION OF HYDRATE C IN EtOAc/H2O/HEPTANE
FILTRATION
FILTRATE (DISCARDED)
FILTER CAKE
WASH (EtOAc/H2O/HEPTANE)
DRYING
MILLING (PSD REDUCTION)
FINAL API (HYDRATE C)

FIG. 1B

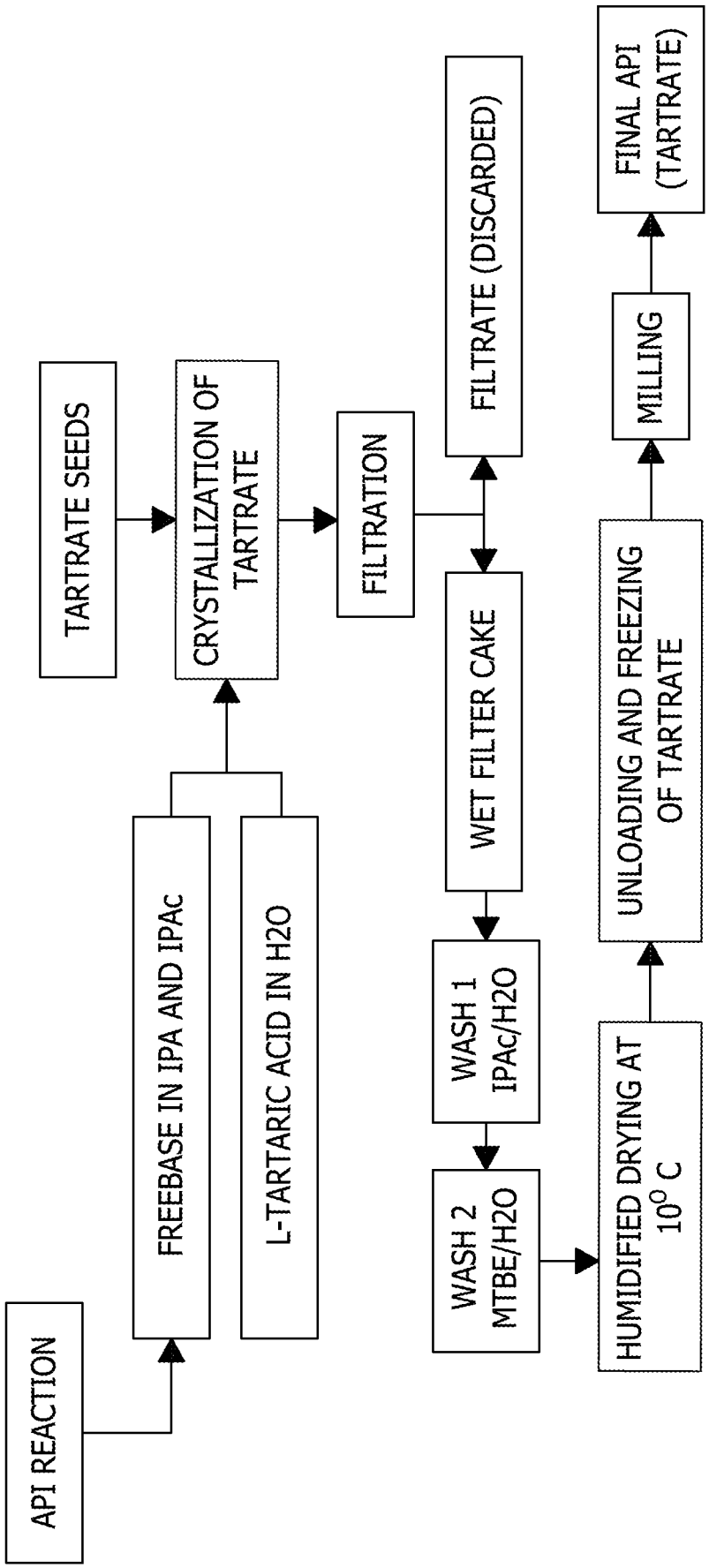

API REACTION
FREEBASE IN IPA AND IPAc
L-TARTARIC ACID IN H2O
TARTRATE SEEDS
CRYSTALLIZATION OF TARTRATE
FILTRATION
FILTRATE (DISCARDED)
WET FILTER CAKE
WASH 1 IPAc/H2O
WASH 2 MTBE/H2O
HUMIDIFIED DRYING AT 10° C
UNLOADING AND FREEZING OF TARTRATE
MILLING
FINAL API (TARTRATE)

FIG. 1C

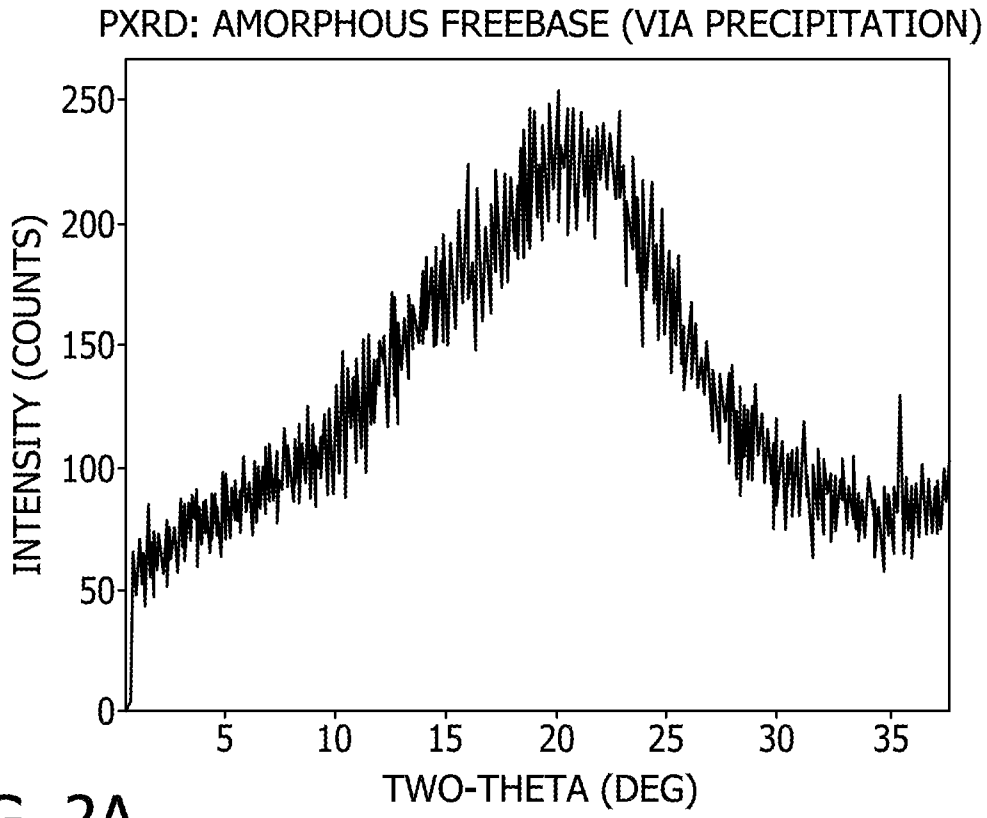

PXRD: AMORPHOUS FREEBASE (VIA PRECIPITATION)
INTENSITY (COUNTS)
0
50
100
150
200
250
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 2A

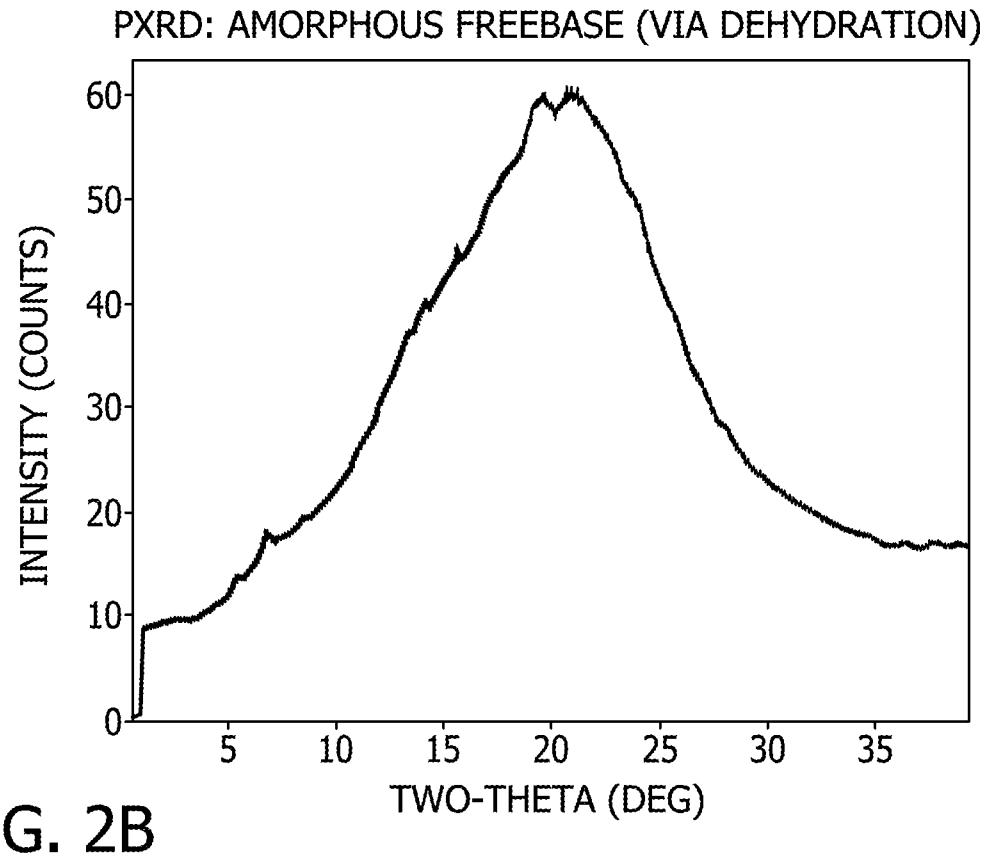

PXRD: AMORPHOUS FREEBASE (VIA DEHYDRATION)
INTENSITY (COUNTS)
0
10
20
30
40
50
60
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 2B

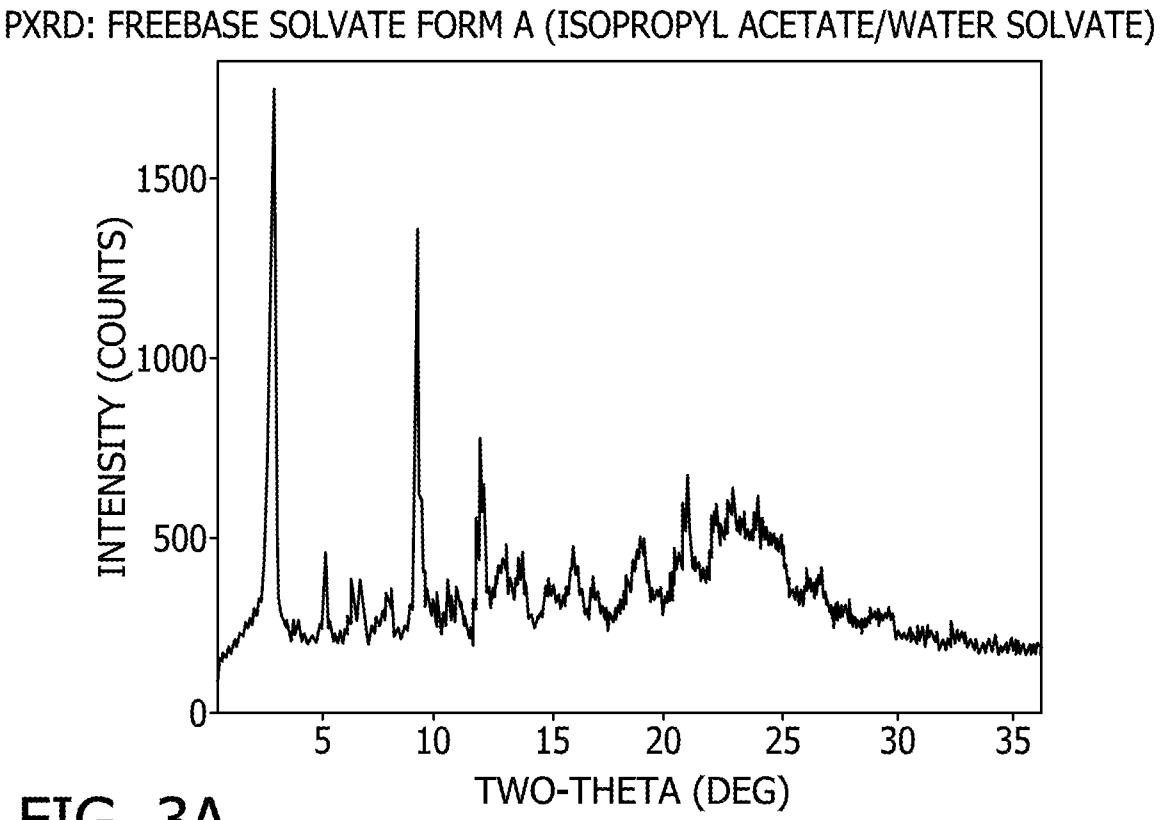

PXRD: FREEBASE SOLVATE FORM A (ISOPROPYL ACETATE/WATER SOLVATE)
INTENSITY (COUNTS)
0
500
1000
1500
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3A

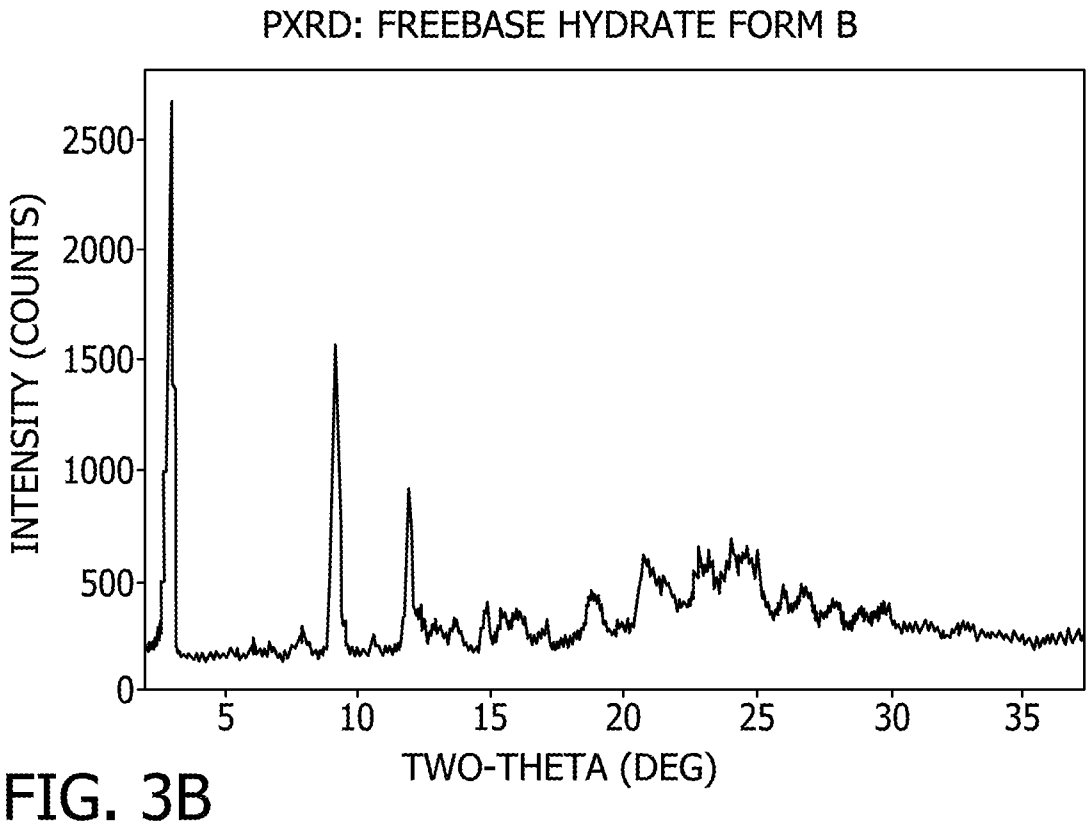

PXRD: FREEBASE HYDRATE FORM B
INTENSITY (COUNTS)
0
500
1000
1500
2000
2500
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3B

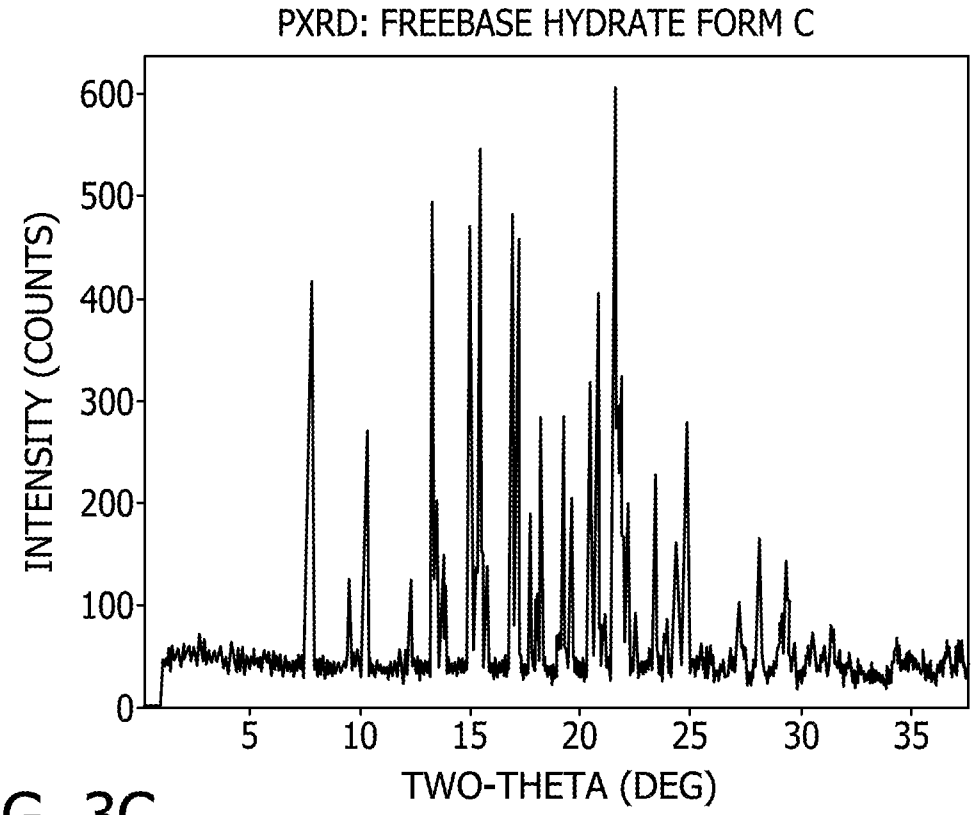

PXRD: FREEBASE HYDRATE FORM C
INTENSITY (COUNTS)
600
500
400
300
200
100
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3C

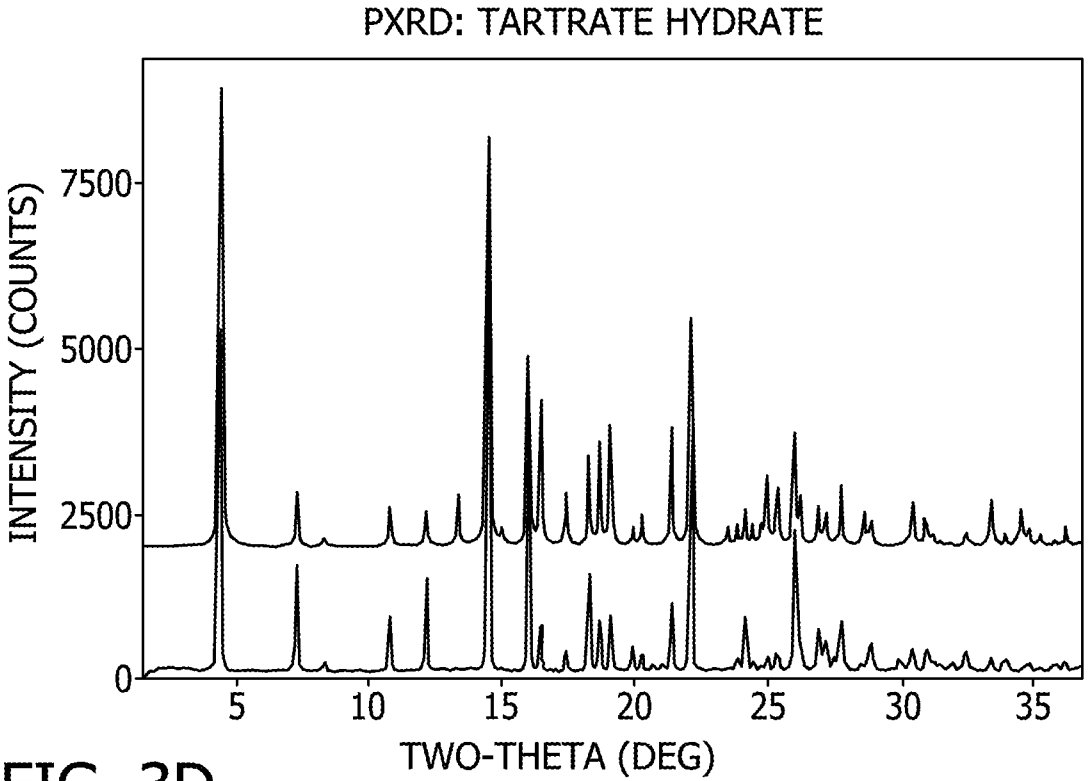

PXRD: TARTRATE HYDRATE
INTENSITY (COUNTS)
7500
5000
2500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3D

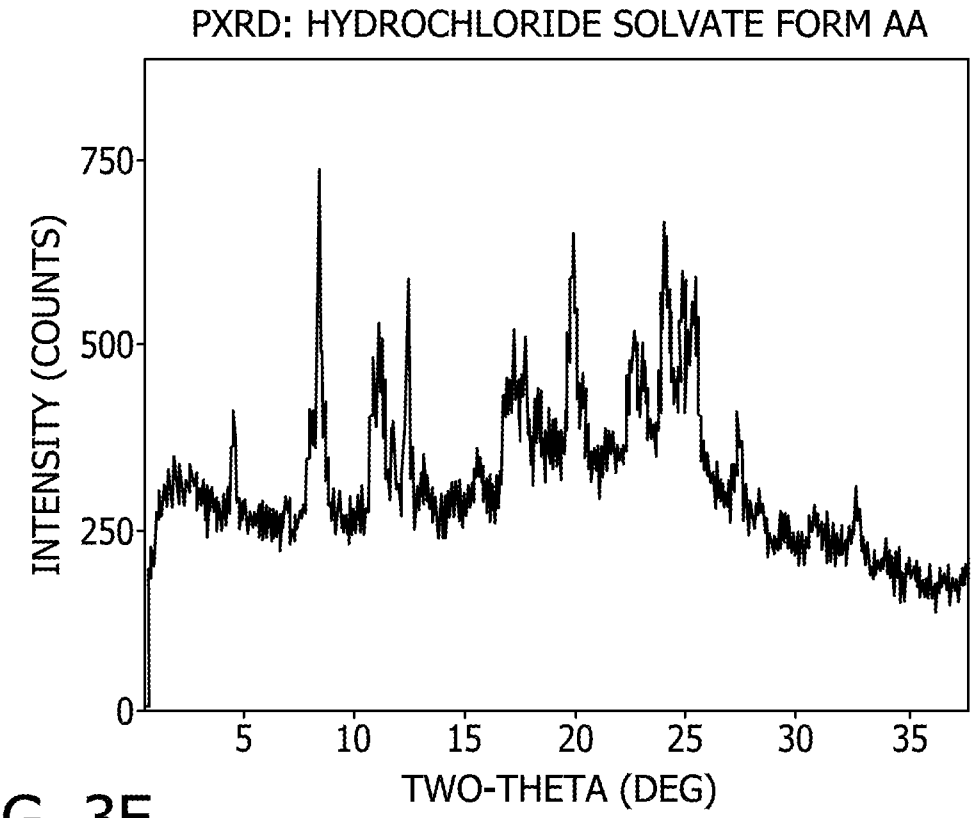

PXRD: HYDROCHLORIDE SOLVATE FORM AA
INTENSITY (COUNTS)
0
250
500
750
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3E

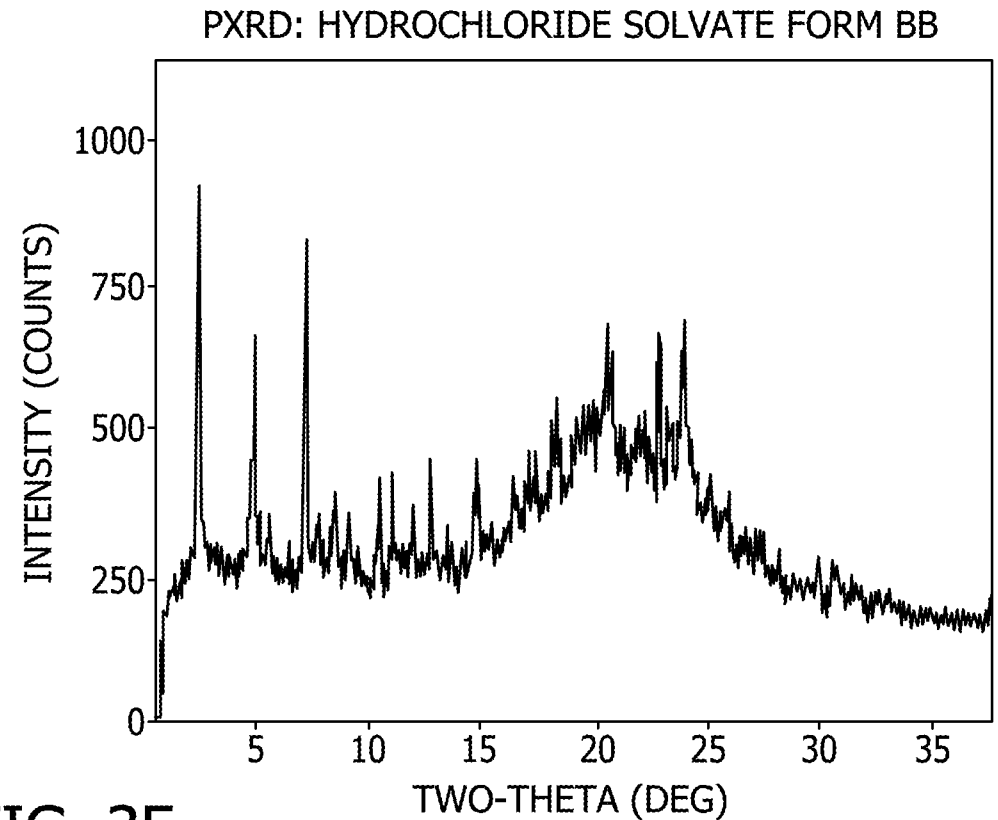

PXRD: HYDROCHLORIDE SOLVATE FORM BB
INTENSITY (COUNTS)
0
250
500
750
1000
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3F

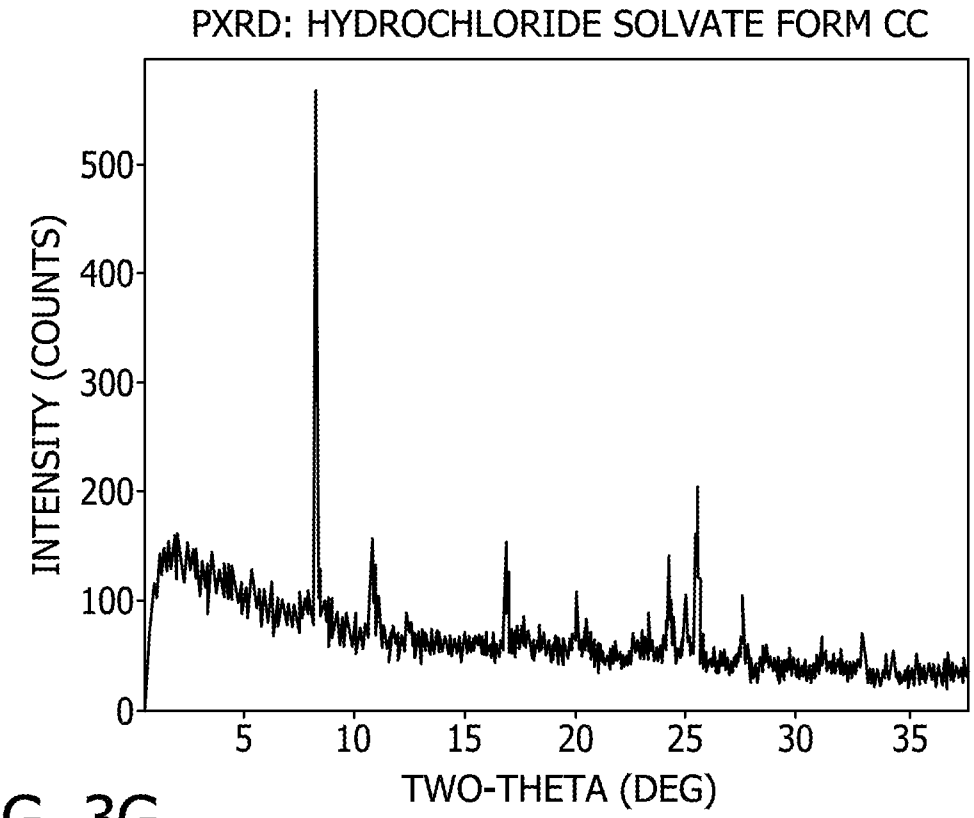

PXRD: HYDROCHLORIDE SOLVATE FORM CC
INTENSITY (COUNTS)
0
100
200
300
400
500
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3G

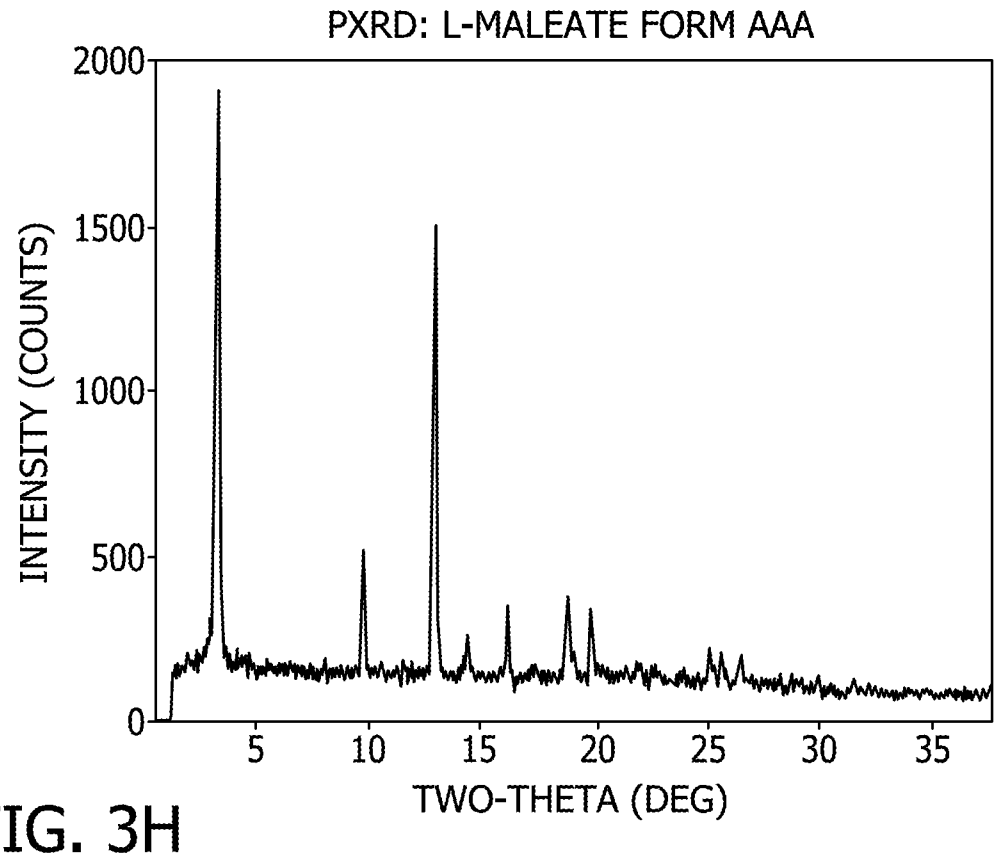

PXRD: L-MALEATE FORM AAA
INTENSITY (COUNTS)
0
500
1000
1500
2000
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3H

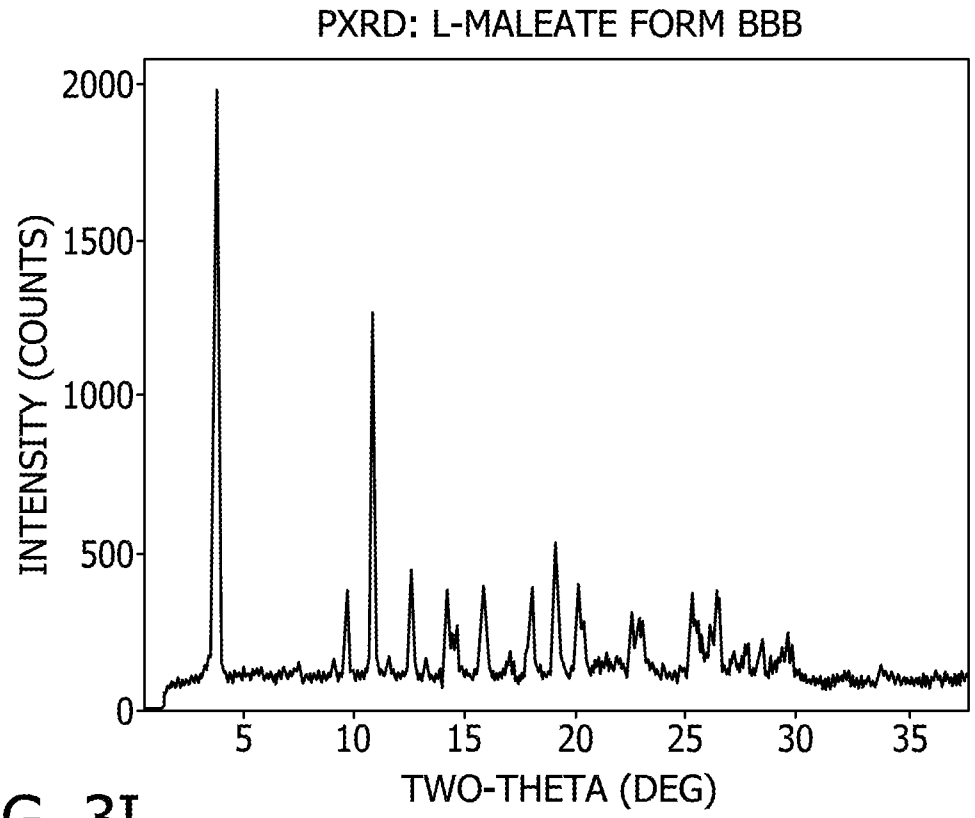

PXRD: L-MALEATE FORM BBB
INTENSITY (COUNTS)
2000
1500
1000
500
0
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3I

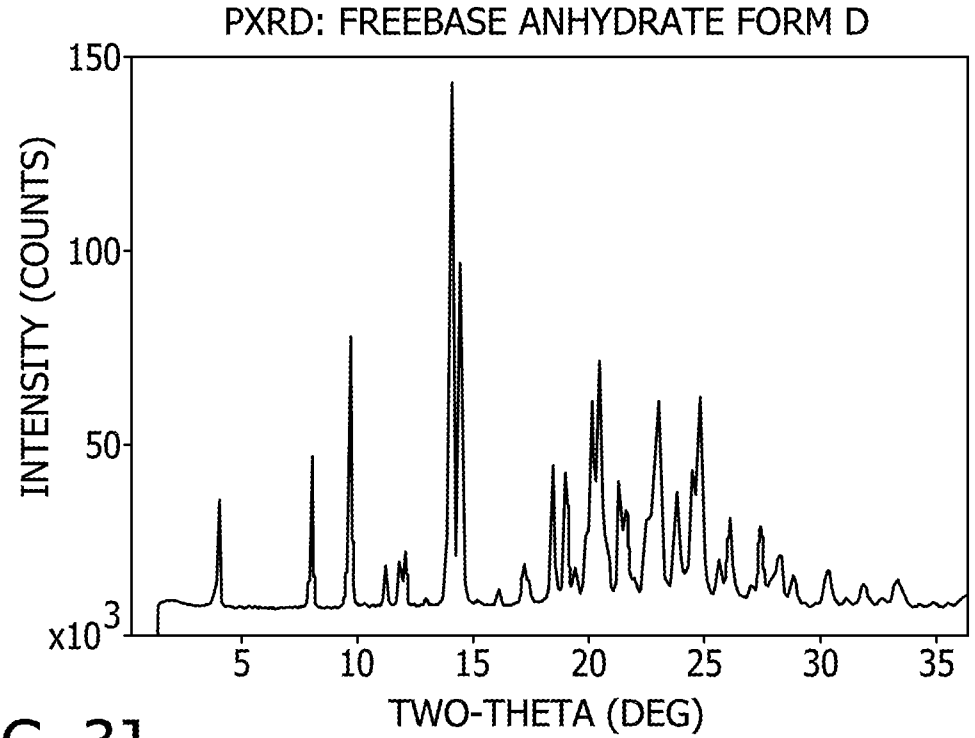

PXRD: FREEBASE ANHYDRATE FORM D
INTENSITY (COUNTS)
150
100
50
x10^3
5
10
15
20
25
30
35
TWO-THETA (DEG)

FIG. 3J

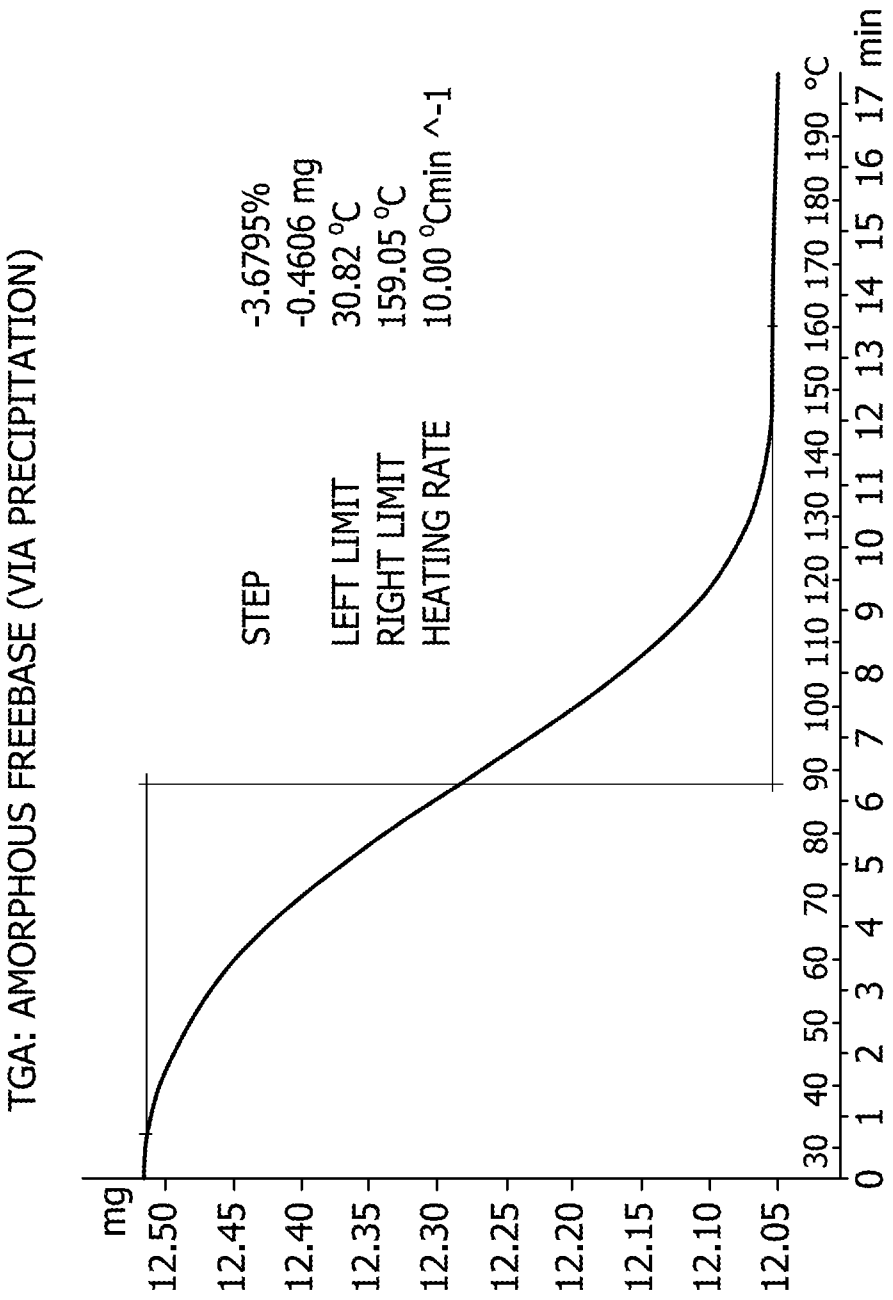

TGA: AMORPHOUS FREEBASE (VIA PRECIPITATION)
STEP -3.6795%
-0.4606 mg
LEFT LIMIT 30.82 °C
RIGHT LIMIT 159.05 °C
HEATING RATE 10.00 °Cmin ^-1
mg
12.50
12.45
12.40
12.35
12.30
12.25
12.20
12.15
12.10
12.05
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 min
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C

FIG. 4A

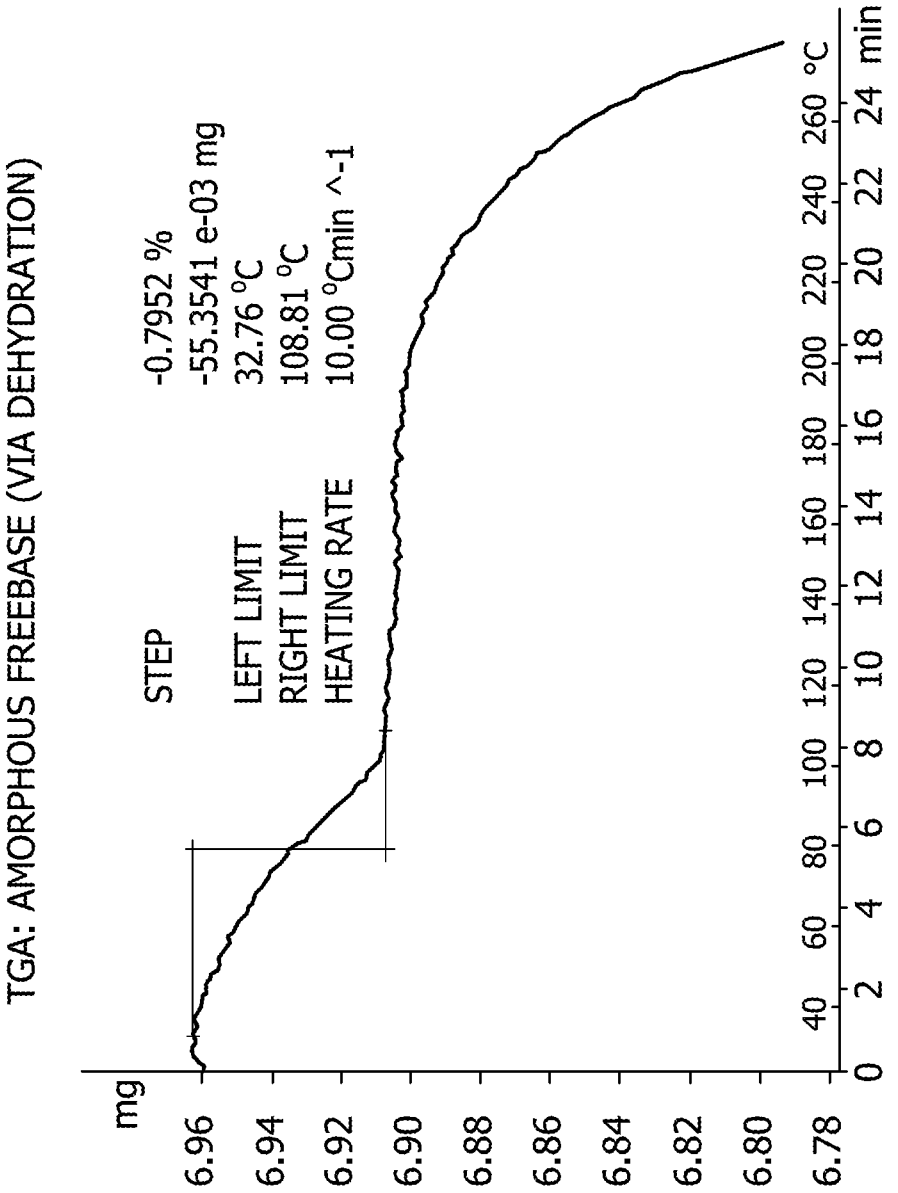

TGA: AMORPHOUS FREEBASE (VIA DEHYDRATION)
STEP
-0.7952 %
-55.3541 e-03 mg
LEFT LIMIT
32.76 °C
RIGHT LIMIT
108.81 °C
HEATING RATE
10.00 °Cmin ^-1
mg
6.96
6.94
6.92
6.90
6.88
6.86
6.84
6.82
6.80
6.78
0
2
4
6
8
10
12
14
16
18
20
22
24
min
40
60
80
100
120
140
160
180
200
220
240
260
°C

FIG. 4B

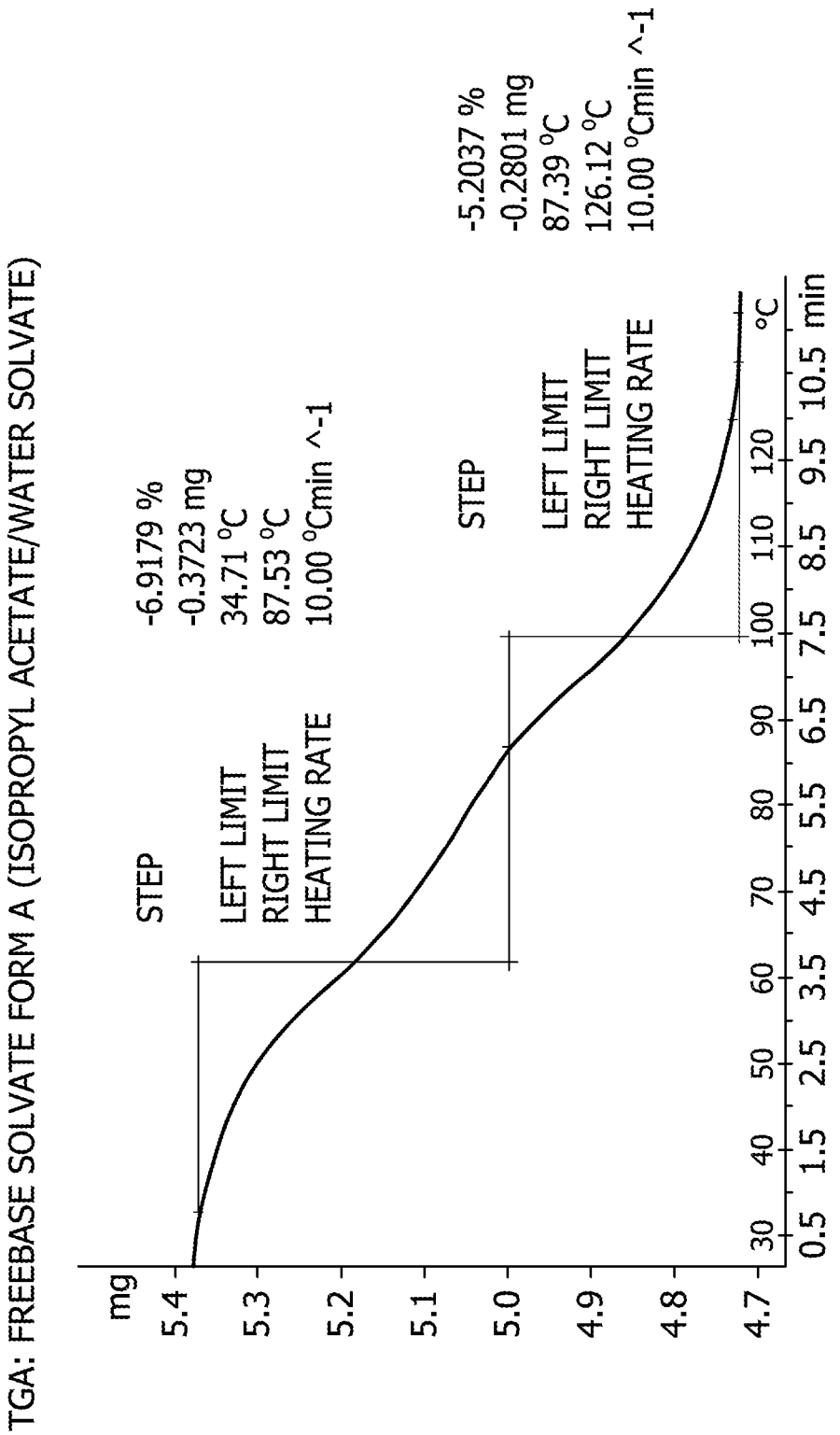

TGA: FREEBASE SOLVATE FORM A (ISOPROPYL ACETATE/WATER SOLVATE)
STEP
-6.9179 %
-0.3723 mg
LEFT LIMIT 34.71 °C
RIGHT LIMIT 87.53 °C
HEATING RATE 10.00 °Cmin ^-1
STEP
-5.2037 %
-0.2801 mg
LEFT LIMIT 87.39 °C
RIGHT LIMIT 126.12 °C
HEATING RATE 10.00 °Cmin ^-1
mg
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
0.5 1.5 2.5 3.5 4.5 5.5 6.5 7.5 8.5 9.5 10.5 min
30 40 50 60 70 80 90 100 110 120 °C

FIG. 4C

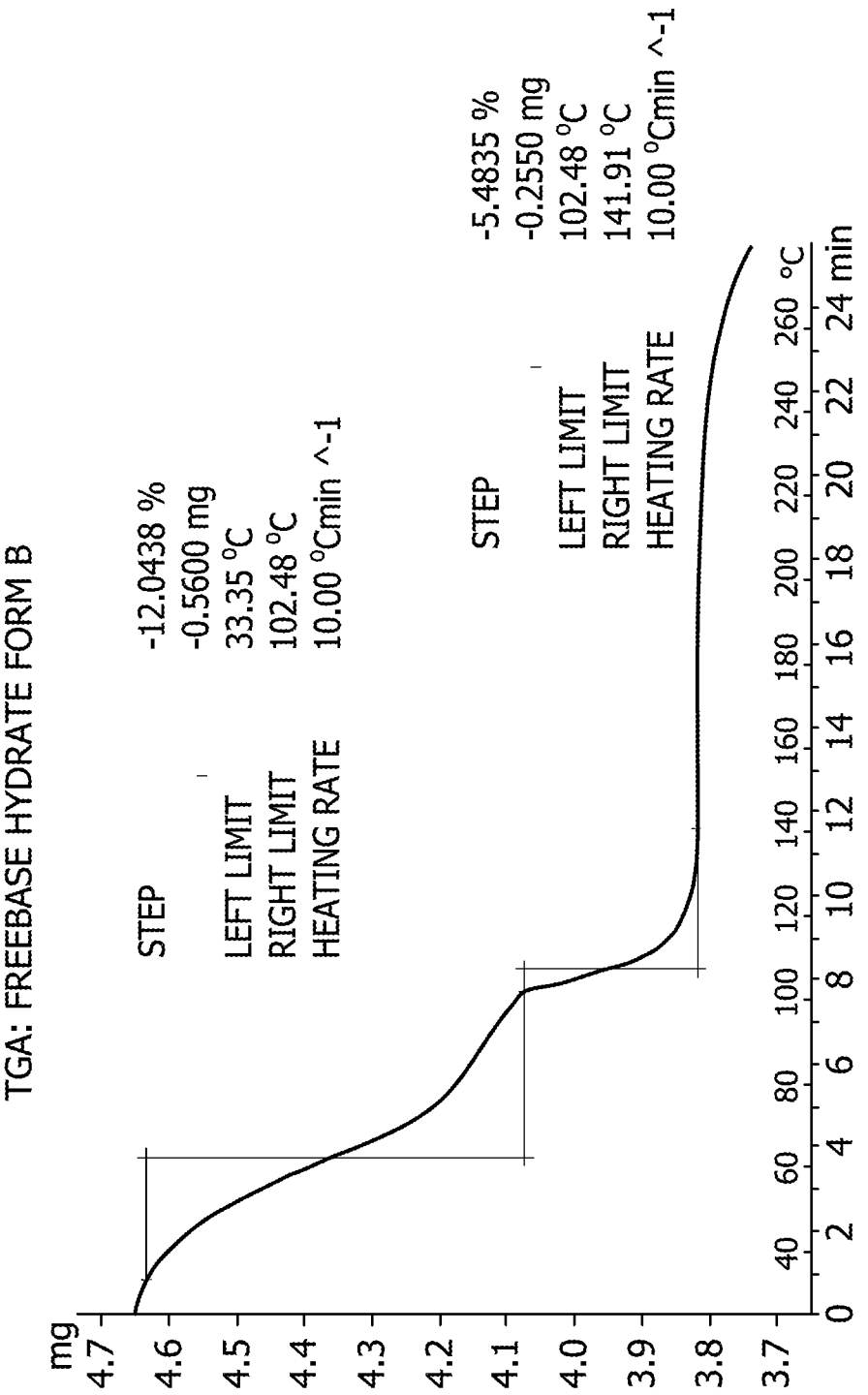

TGA: FREEBASE HYDRATE FORM B
STEP -12.0438 %
-0.5600 mg
LEFT LIMIT 33.35 °C
RIGHT LIMIT 102.48 °C
HEATING RATE 10.00 °Cmin ^-1
STEP -5.4835 %
-0.2550 mg
LEFT LIMIT 102.48 °C
RIGHT LIMIT 141.91 °C
HEATING RATE 10.00 °Cmin ^-1
mg
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
0 2 4 6 8 10 12 14 16 18 20 22 24 min
40 60 80 100 120 140 160 180 200 220 240 260 °C

FIG. 4D

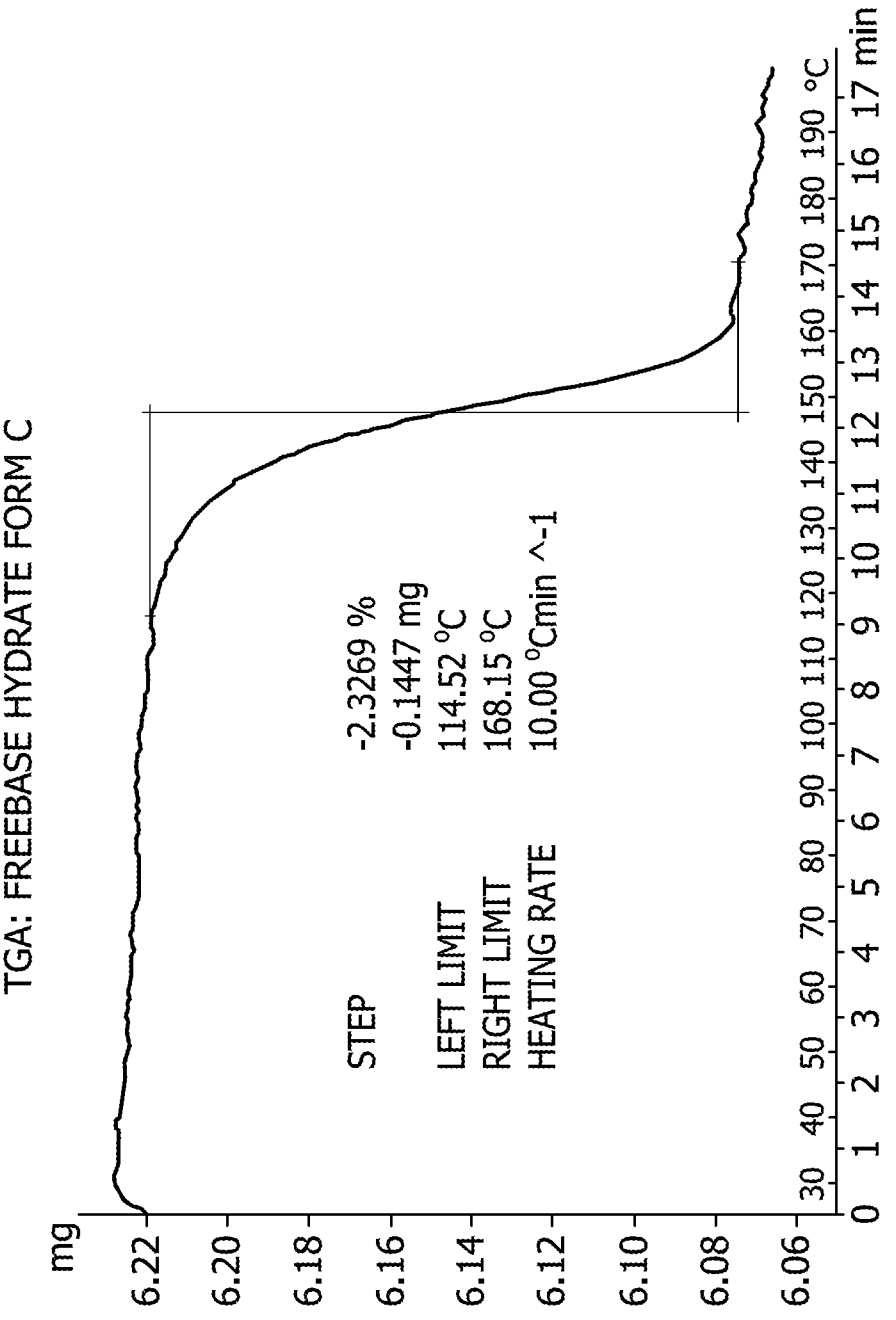

TGA: FREEBASE HYDRATE FORM C
mg
6.22
6.20
6.18
6.16
6.14
6.12
6.10
6.08
6.06
STEP
-2.3269 %
-0.1447 mg
LEFT LIMIT
114.52 °C
RIGHT LIMIT
168.15 °C
HEATING RATE
10.00 °Cmin ^-1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 min
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C

FIG. 4E

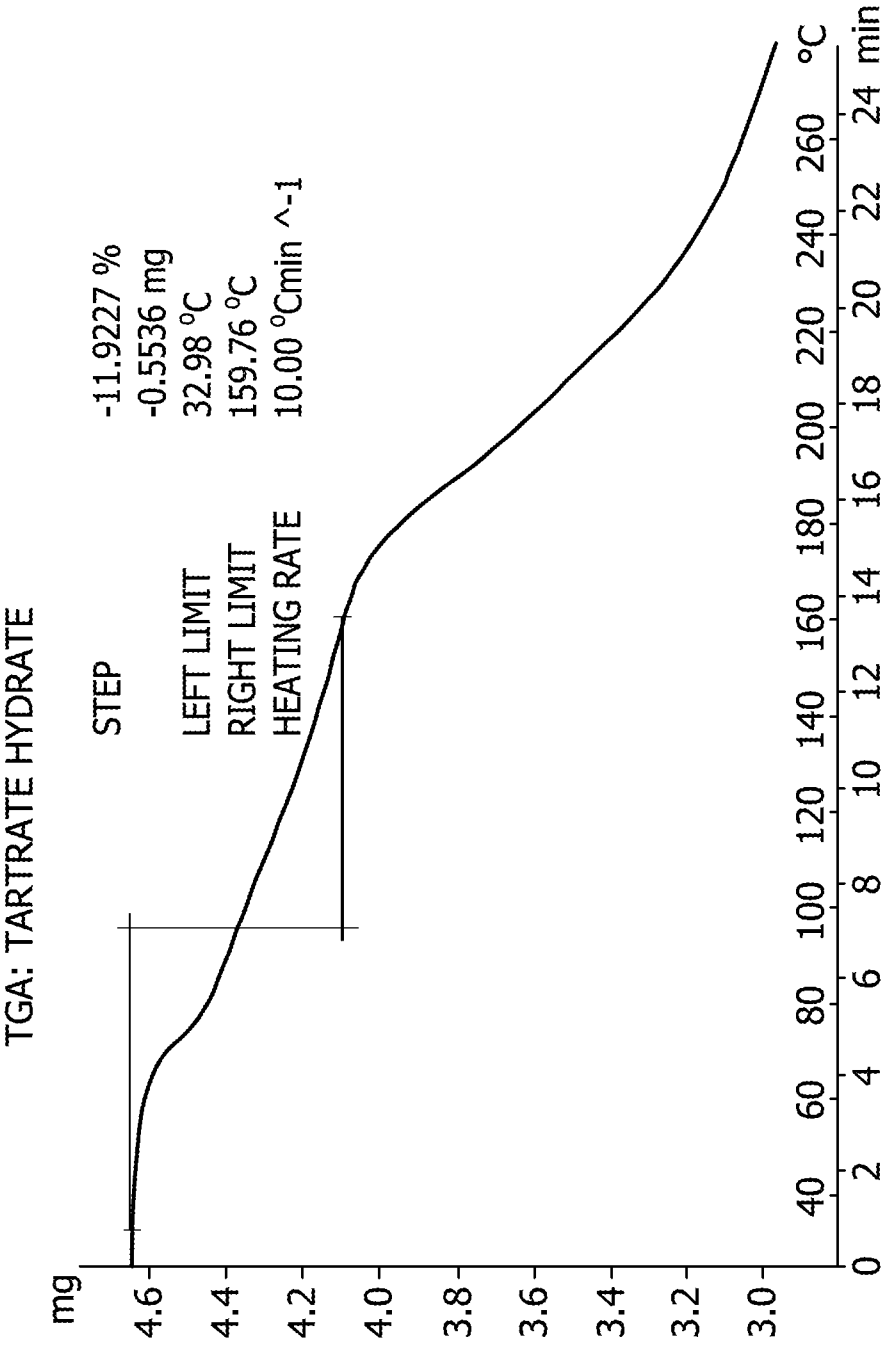

TGA: TARTRATE HYDRATE
STEP
LEFT LIMIT
RIGHT LIMIT
HEATING RATE
-11.9227 %
-0.5536 mg
32.98 °C
159.76 °C
10.00 °Cmin ^-1
mg
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
0
2
4
6
8
10
12
14
16
18
20
22
24 min
40
60
80
100
120
140
160
180
200
220
240
260
°C

FIG. 4F

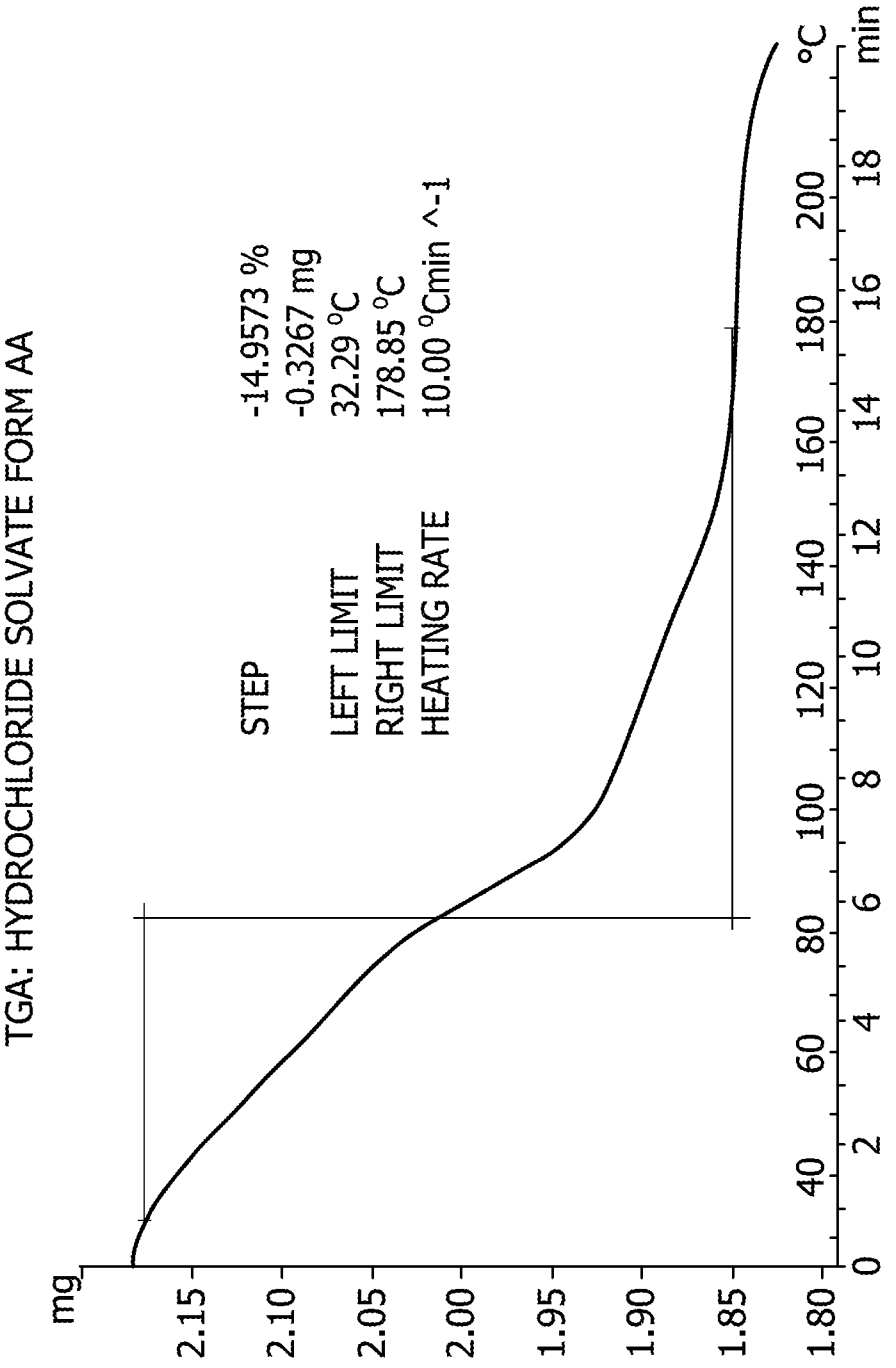

TGA: HYDROCHLORIDE SOLVATE FORM AA
STEP
LEFT LIMIT
RIGHT LIMIT
HEATING RATE
-14.9573 %
-0.3267 mg
32.29 °C
178.85 °C
10.00 °Cmin ^-1
mg
2.15
2.10
2.05
2.00
1.95
1.90
1.85
1.80
40
60
80
100
120
140
160
180
200
°C
0
2
4
6
8
10
12
14
16
18
min

FIG. 4G

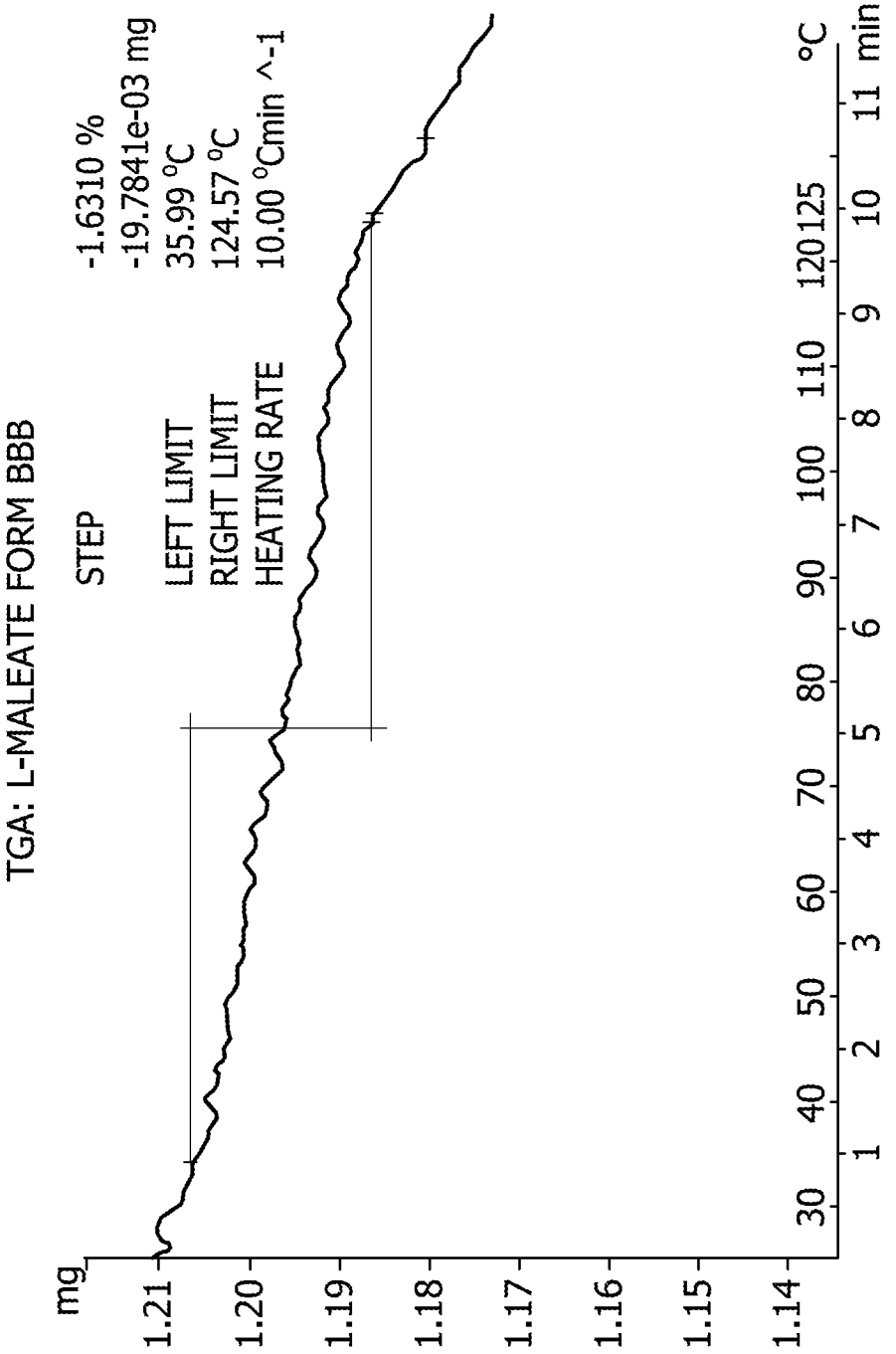

TGA: L-MALEATE FORM BBB
STEP
LEFT LIMIT
RIGHT LIMIT
HEATING RATE
-1.6310 %
-19.7841e-03 mg
35.99 °C
124.57 °C
10.00 °Cmin ^-1
mg
1.21
1.20
1.19
1.18
1.17
1.16
1.15
1.14
30
40
50
60
70
80
90
100
110
120
125
°C
1
2
3
4
5
6
7
8
9
10
11
min

FIG. 4H

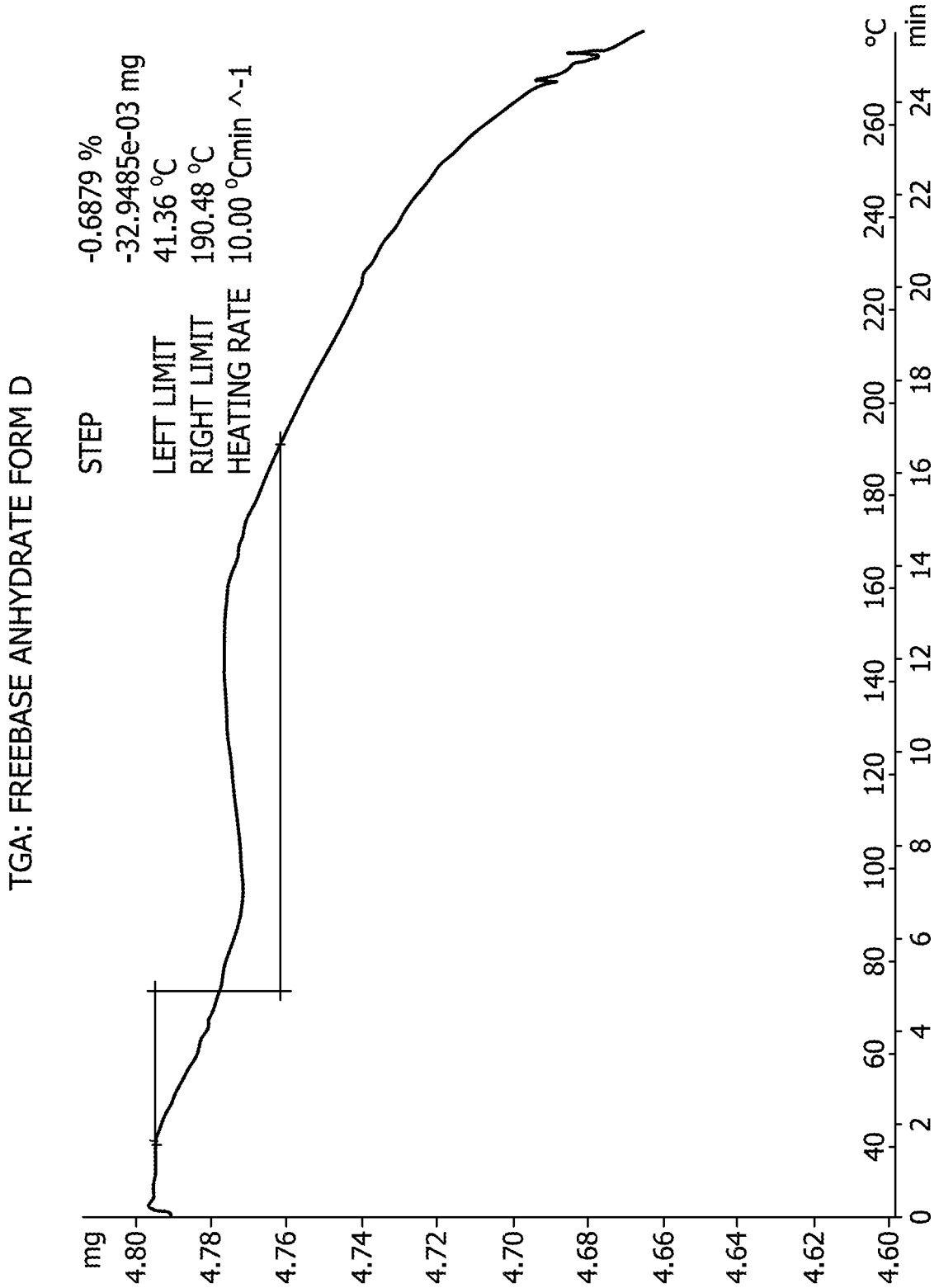

TGA: FREEBASE ANHYDRATE FORM D
STEP
-0.6879 %
-32.9485e-03 mg
LEFT LIMIT
41.36 °C
RIGHT LIMIT
190.48 °C
HEATING RATE
10.00 °Cmin ^-1
mg
4.80
4.78
4.76
4.74
4.72
4.70
4.68
4.66
4.64
4.62
4.60
0
40
2
60
4
80
6
100
8
120
10
140
12
160
14
180
16
200
18
220
20
240
22
260
24
°C
min

FIG. 4I

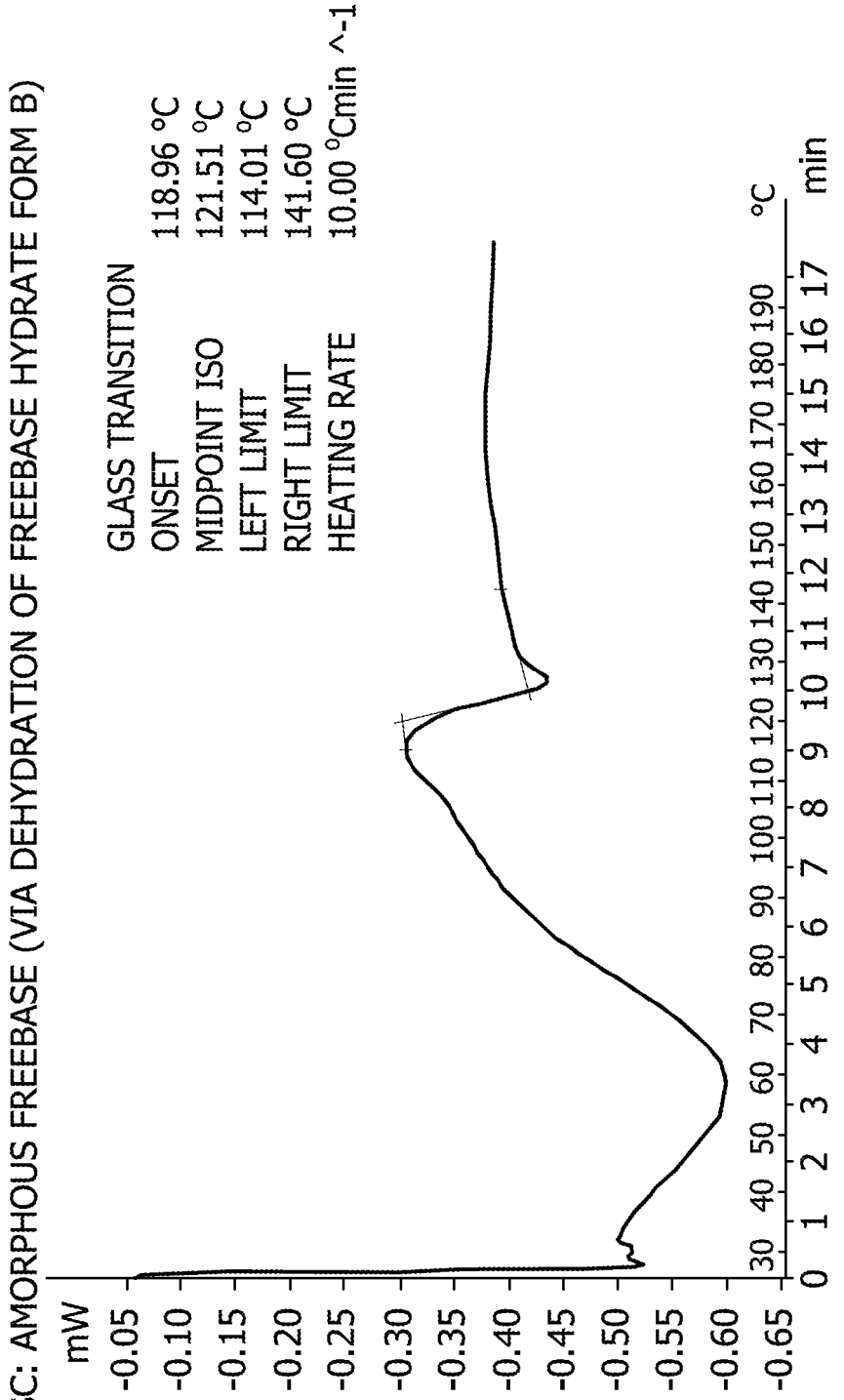

DSC: AMORPHOUS FREEBASE (VIA DEHYDRATION OF FREEBASE HYDRATE FORM B)
GLASS TRANSITION
ONSET 118.96 °C
MIDPOINT ISO 121.51 °C
LEFT LIMIT 114.01 °C
RIGHT LIMIT 141.60 °C
HEATING RATE 10.00 °Cmin ^-1
mW
-0.05
-0.10
-0.15
-0.20
-0.25
-0.30
-0.35
-0.40
-0.45
-0.50
-0.55
-0.60
-0.65
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 min

FIG. 5A

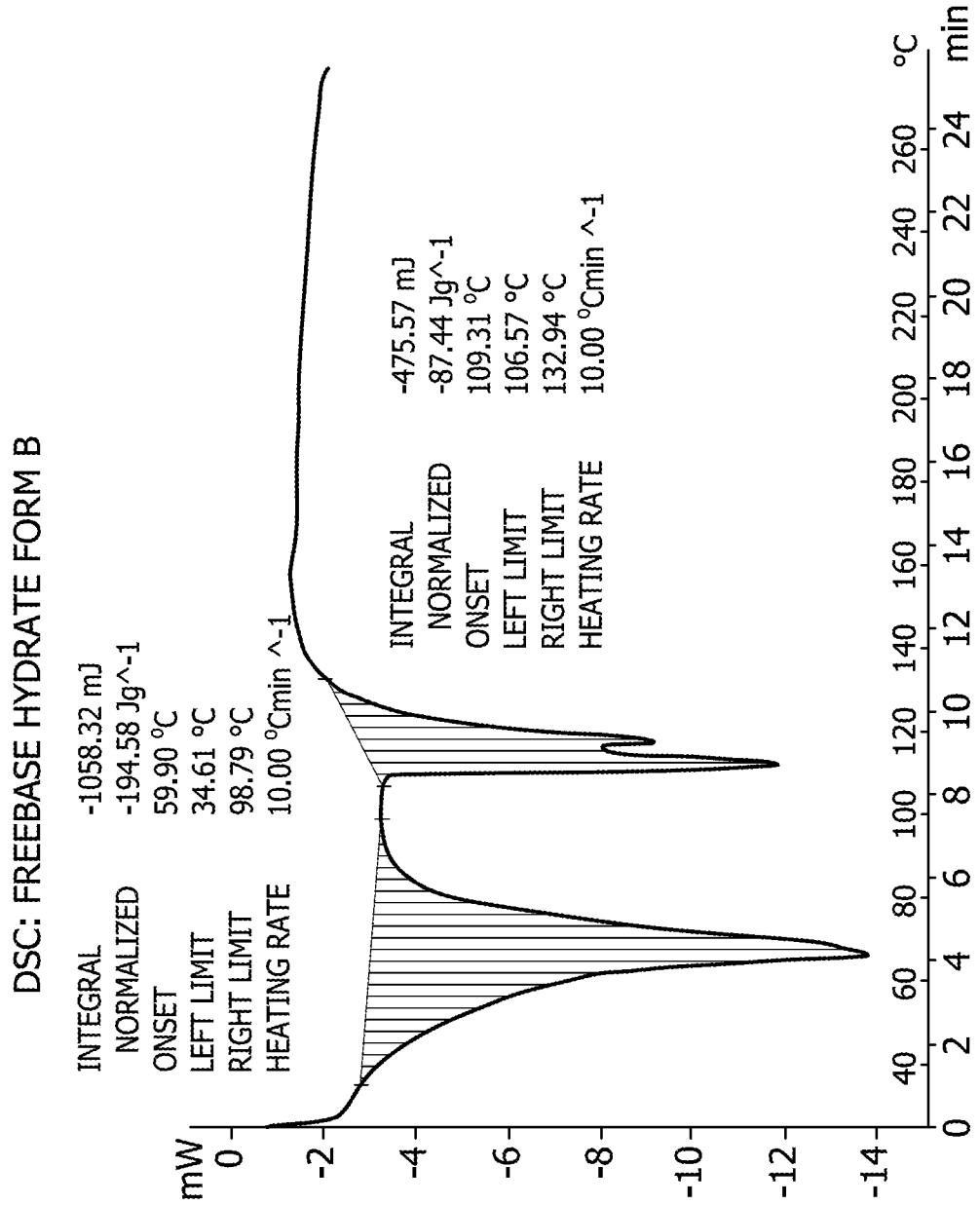

DSC: FREEBASE HYDRATE FORM B
INTEGRAL -1058.32 mJ
NORMALIZED -194.58 Jg^-1
ONSET 59.90 °C
LEFT LIMIT 34.61 °C
RIGHT LIMIT 98.79 °C
HEATING RATE 10.00 °Cmin ^-1
INTEGRAL -475.57 mJ
NORMALIZED -87.44 Jg^-1
ONSET 109.31 °C
LEFT LIMIT 106.57 °C
RIGHT LIMIT 132.94 °C
HEATING RATE 10.00 °Cmin ^-1
mW
0
-2
-4
-6
-8
-10
-12
-14
0 2 4 6 8 10 12 14 16 18 20 22 24 min
40 60 80 100 120 140 160 180 200 220 240 260 °C

FIG. 5B

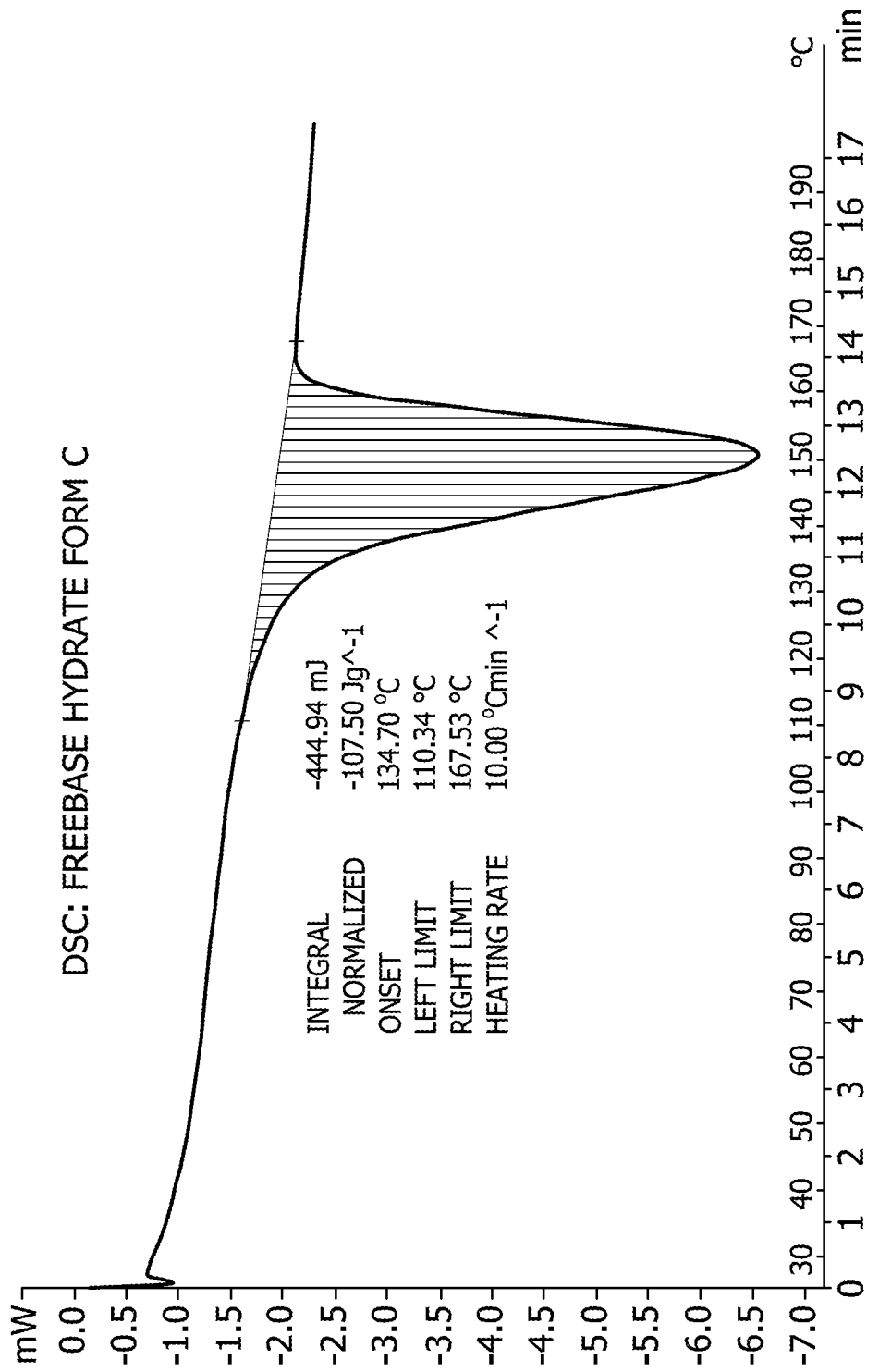

DSC: FREEBASE HYDRATE FORM C
INTEGRAL -444.94 mJ
NORMALIZED -107.50 Jg^-1
ONSET 134.70 °C
LEFT LIMIT 110.34 °C
RIGHT LIMIT 167.53 °C
HEATING RATE 10.00 °Cmin ^-1
mW
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
-7.0
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
°C
min

FIG. 5C

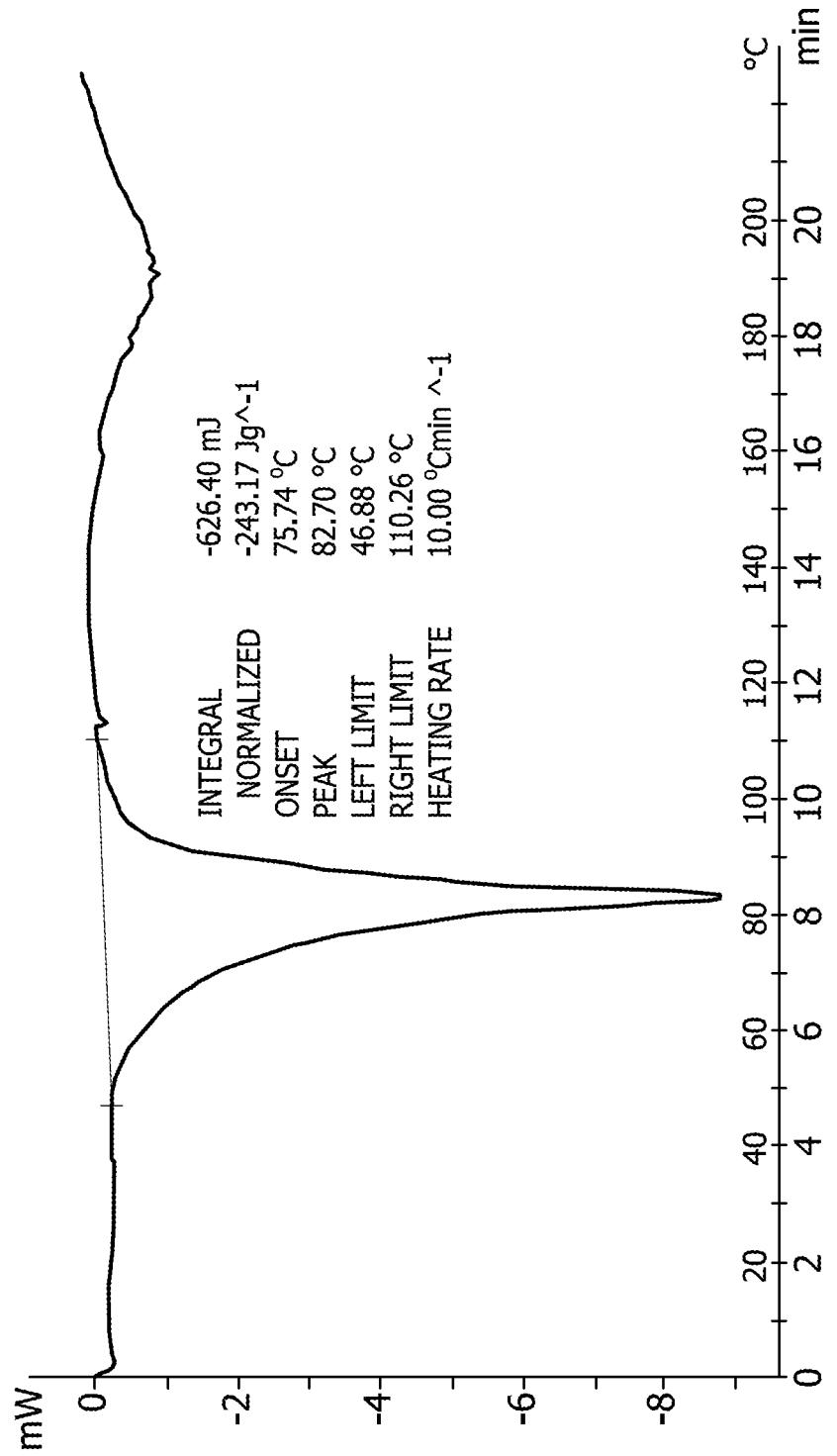

DSC: TARTRATE HYDRATE
INTEGRAL -626.40 mJ
NORMALIZED -243.17 Jg^-1
ONSET 75.74 °C
PEAK 82.70 °C
LEFT LIMIT 46.88 °C
RIGHT LIMIT 110.26 °C
HEATING RATE 10.00 °Cmin ^-1
mW
0
-2
-4
-6
-8
°C
min
0
20
40
60
80
100
120
140
160
180
200
2
4
6
8
10
12
14
16
18
20

FIG. 5D

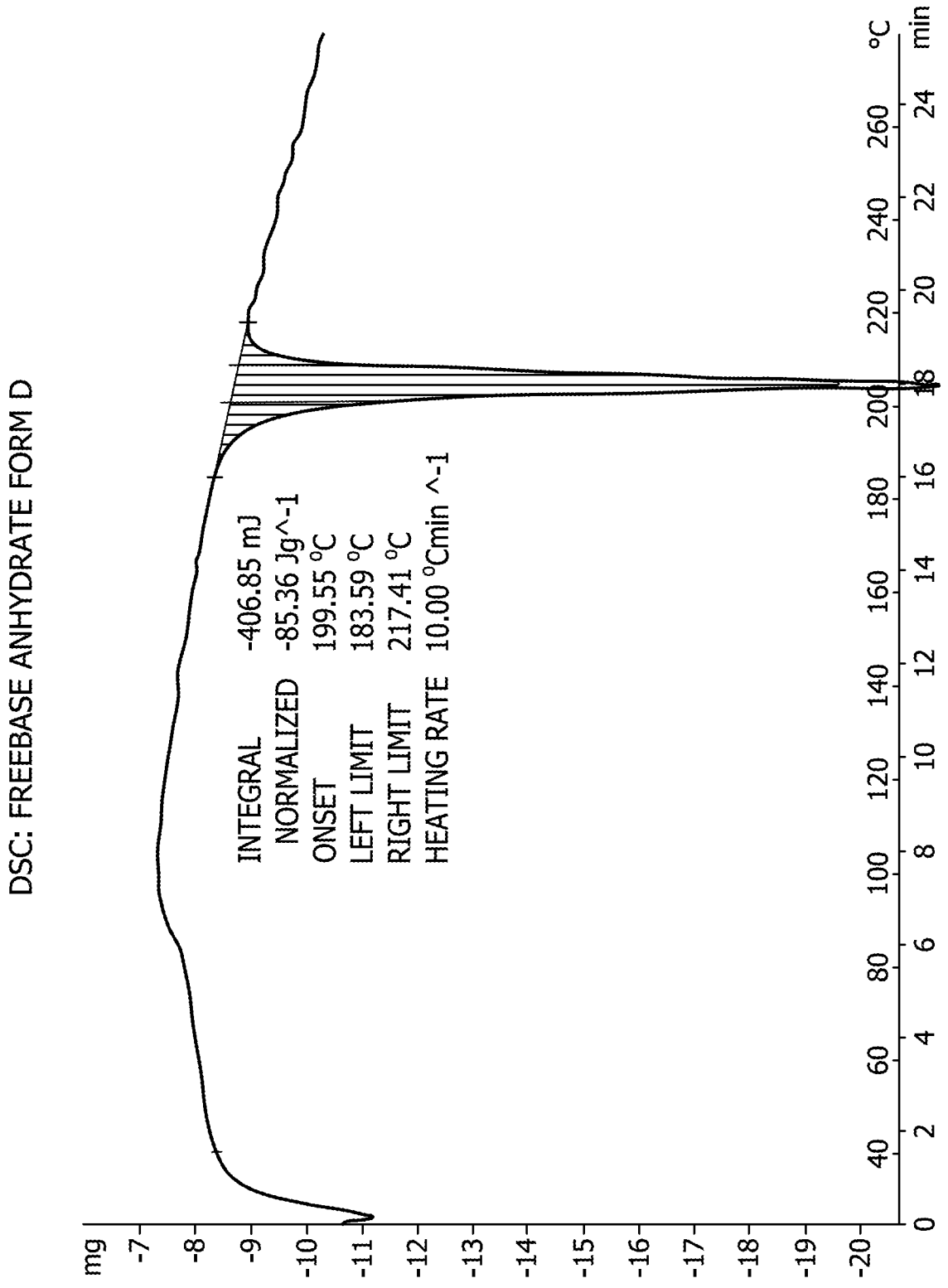

DSC: FREEBASE ANHYDRATE FORM D
INTEGRAL -406.85 mJ
NORMALIZED -85.36 Jg^-1
ONSET 199.55 °C
LEFT LIMIT 183.59 °C
RIGHT LIMIT 217.41 °C
HEATING RATE 10.00 °Cmin ^-1
mg
-7
-8
-9
-10
-11
-12
-13
-14
-15
-16
-17
-18
-19
-20
0
2
4
6
8
10
12
14
16
18
20
22
24
min
40
60
80
100
120
140
160
180
200
220
240
260
°C

FIG. 5E

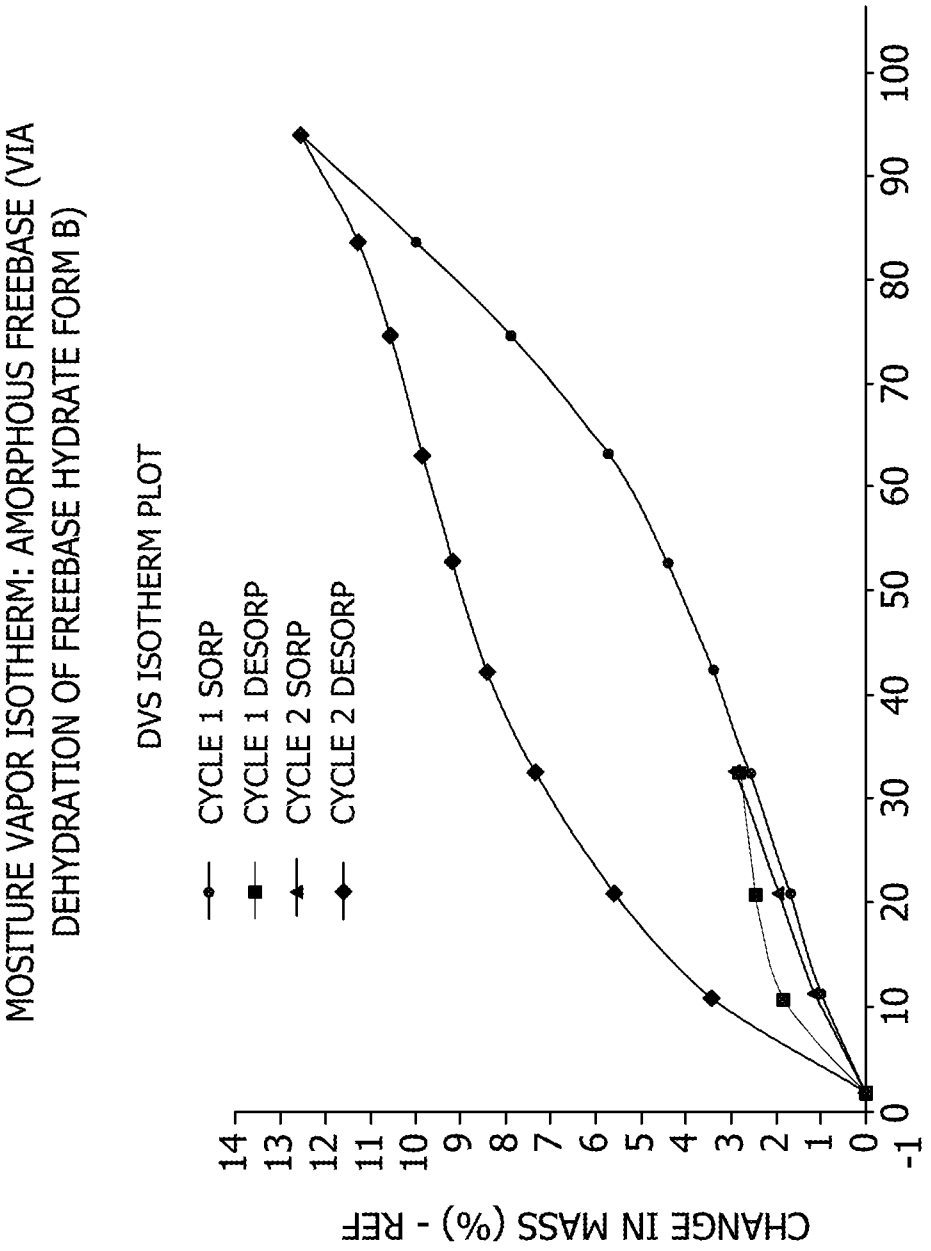

MOSITURE VAPOR ISOTHERM: AMORPHOUS FREEBASE (VIA DEHYDRATION OF FREEBASE HYDRATE FORM B)
DVS ISOTHERM PLOT
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
CHANGE IN MASS (%) - REF
SAMPLE % P/Po
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
0
10
20
30
40
50
60
70
80
90
100

FIG. 6A

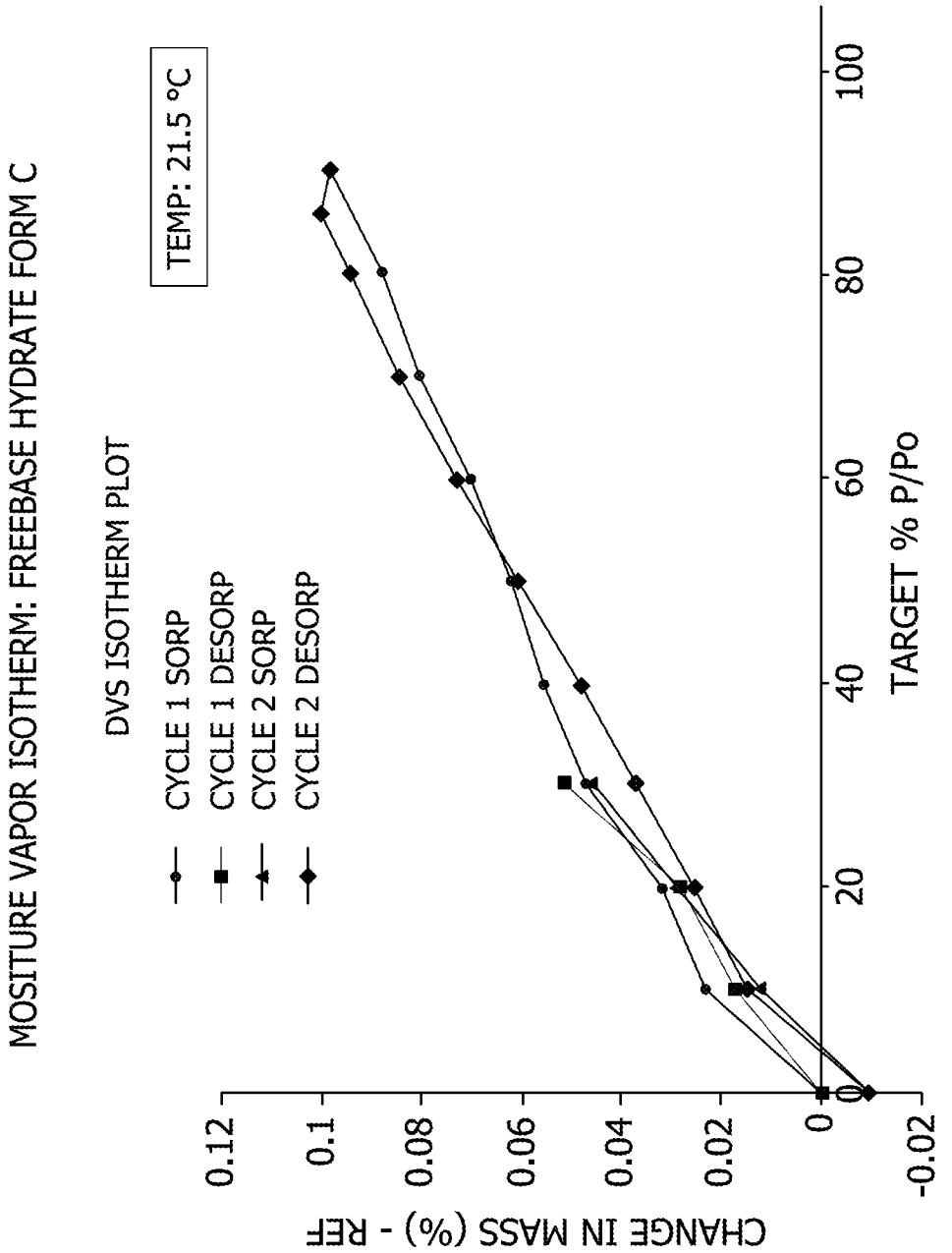

MOSITURE VAPOR ISOTHERM: FREEBASE HYDRATE FORM C
DVS ISOTHERM PLOT
TEMP: 21.5 °C
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
CHANGE IN MASS (%) - REF
0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
0
20
40
60
80
100
TARGET % P/Po

FIG. 6B

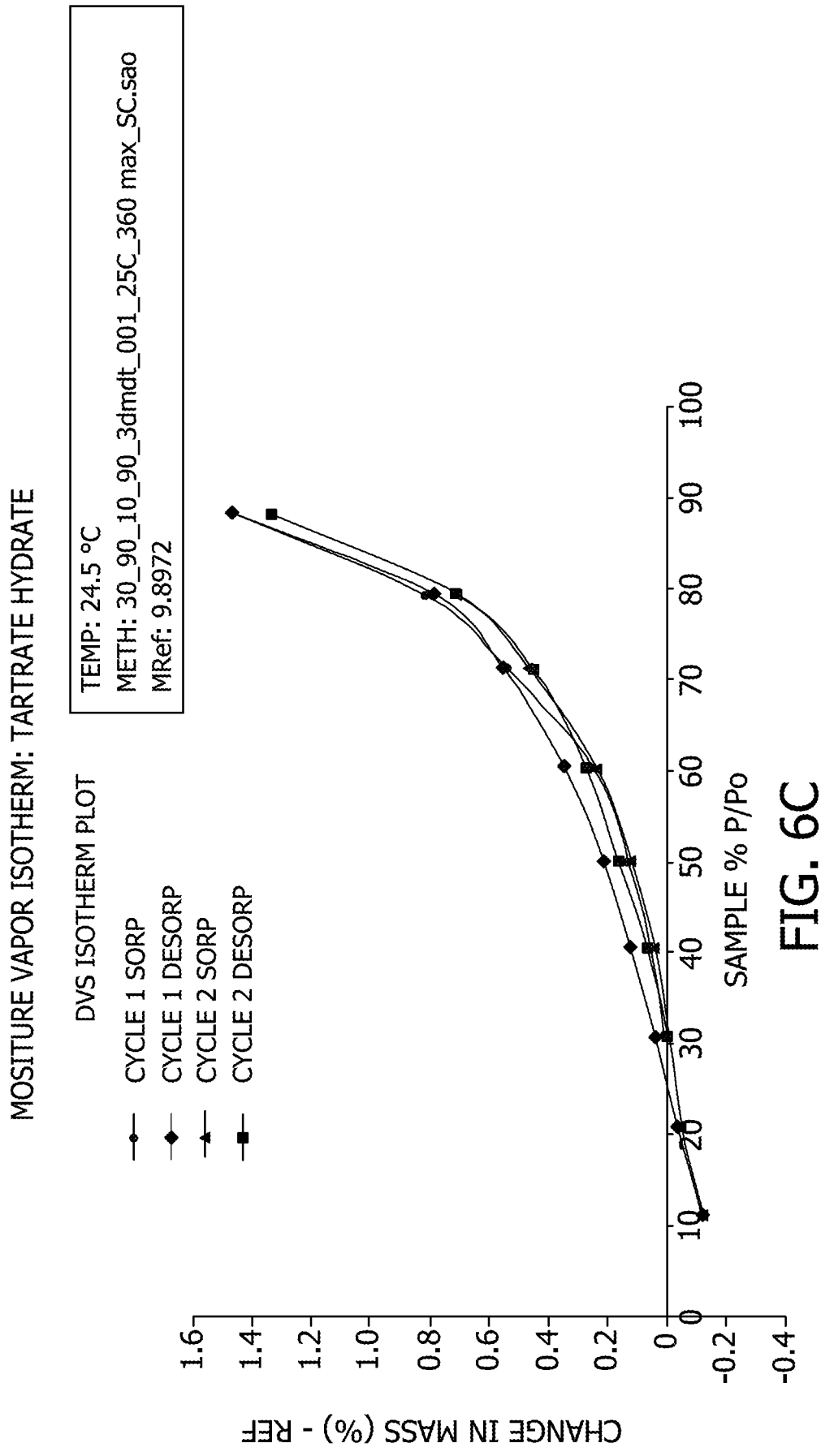

MOSITURE VAPOR ISOTHERM: TARTRATE HYDRATE
DVS ISOTHERM PLOT
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
TEMP: 24.5 °C
METH: 30_90_10_90_3dmdt_001_25C_360 max_SC.sao
MRef: 9.8972
CHANGE IN MASS (%) - REF
SAMPLE % P/Po
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0
10
20
30
40
50
60
70
80
90
100

FIG. 6C

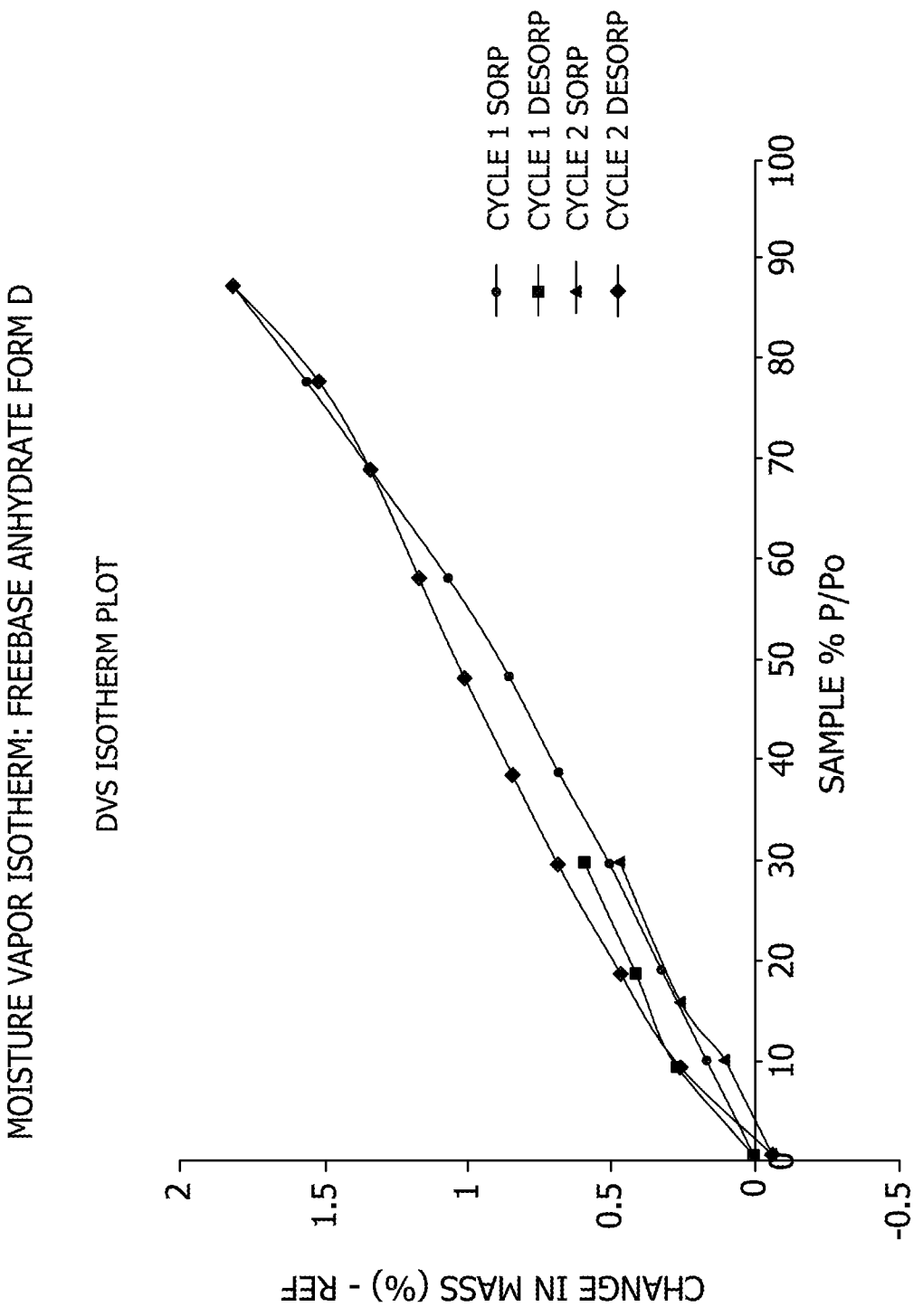

MOISTURE VAPOR ISOTHERM: FREEBASE ANHYDRATE FORM D
DVS ISOTHERM PLOT
CYCLE 1 SORP
CYCLE 1 DESORP
CYCLE 2 SORP
CYCLE 2 DESORP
CHANGE IN MASS (%) - REF
SAMPLE % P/Po
2
1.5
1
0.5
0
-0.5
0
10
20
30
40
50
60
70
80
90
100

FIG. 6D

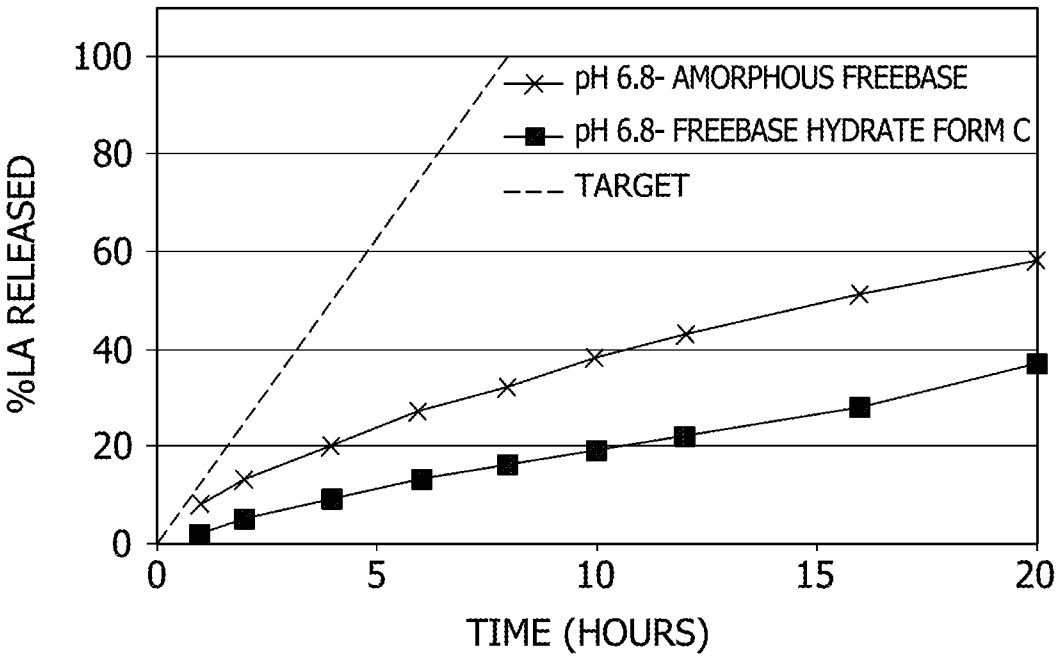

100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
TIME (HOURS)
pH 6.8- AMORPHOUS FREEBASE
pH 6.8- FREEBASE HYDRATE FORM C
TARGET

FIG. 7

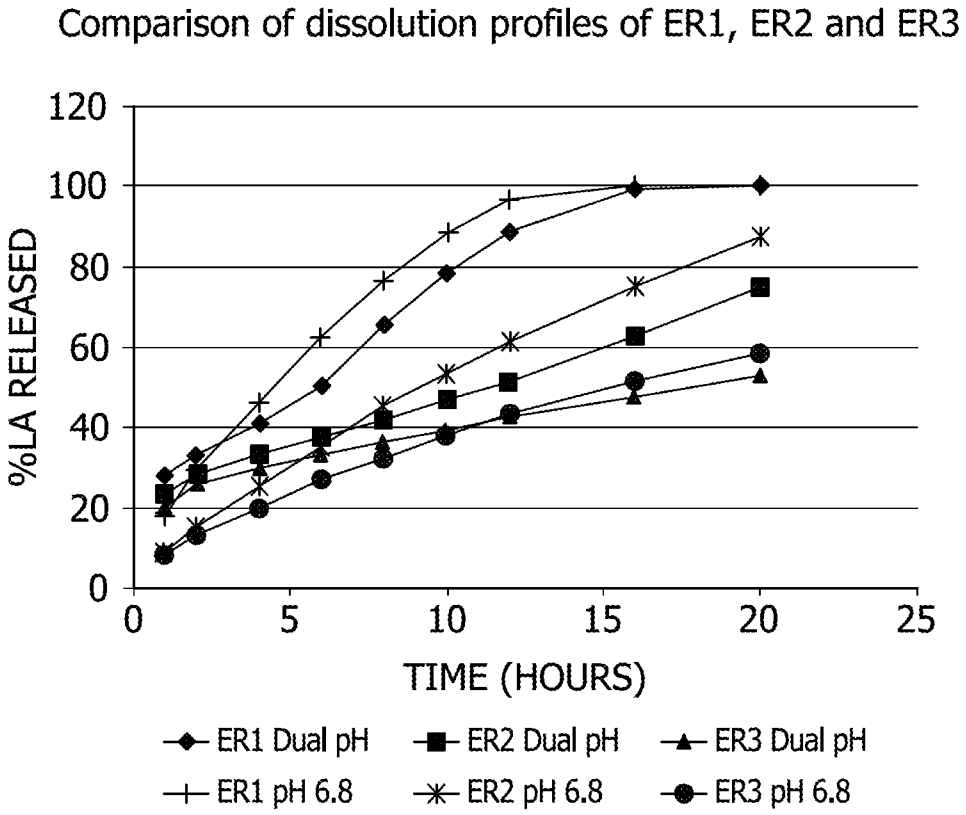

Comparison of dissolution profiles of ER1, ER2 and ER3
120
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
25
TIME (HOURS)
ER1 Dual pH
ER2 Dual pH
ER3 Dual pH
ER1 pH 6.8
ER2 pH 6.8
ER3 pH 6.8

FIG. 8

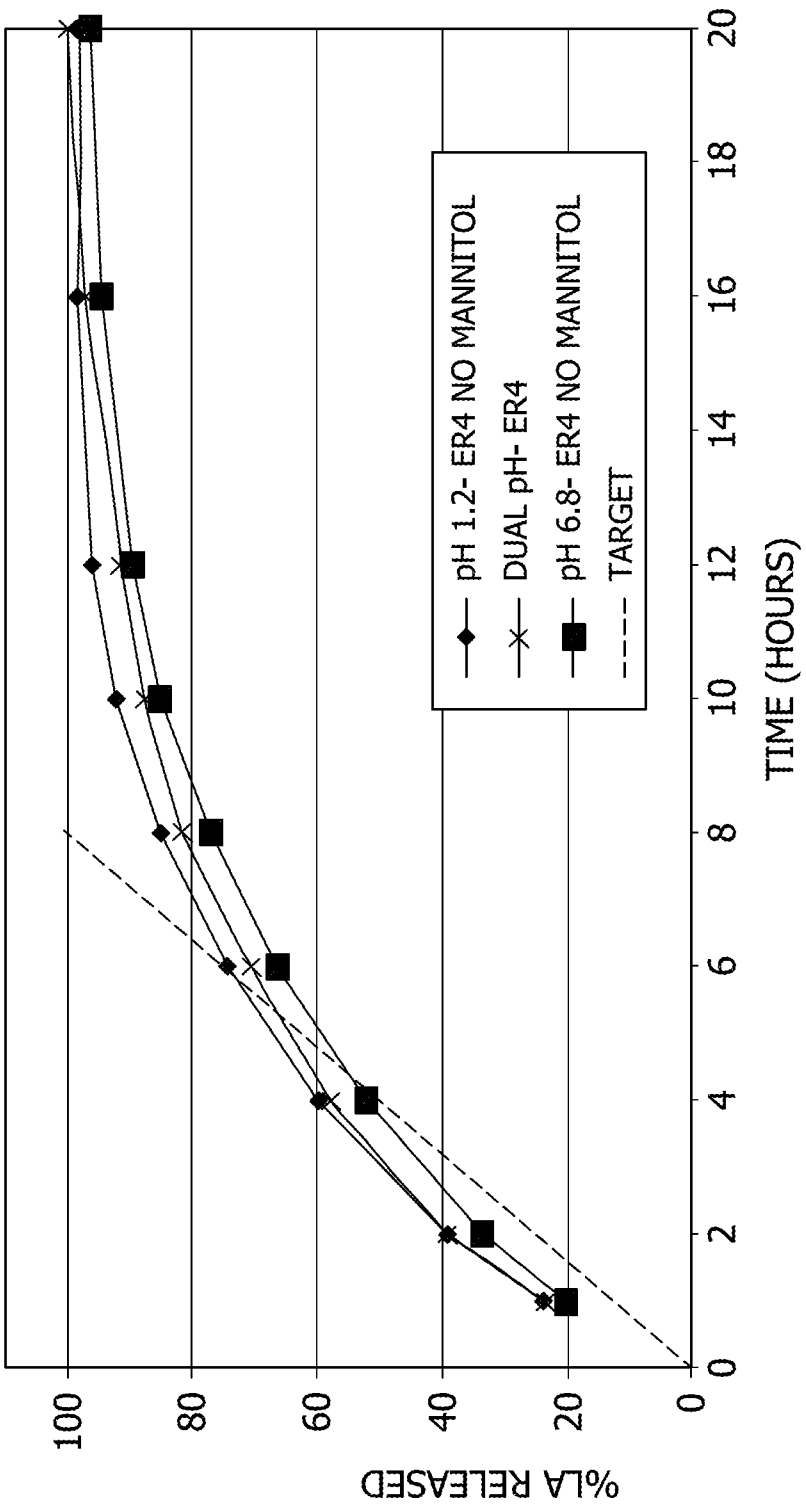

%LA RELEASED
0
20
40
60
80
100
TIME (HOURS)
0
2
4
6
8
10
12
14
16
18
20
pH 1.2- ER4 NO MANNITOL
DUAL pH- ER4
pH 6.8- ER4 NO MANNITOL
TARGET

FIG. 9

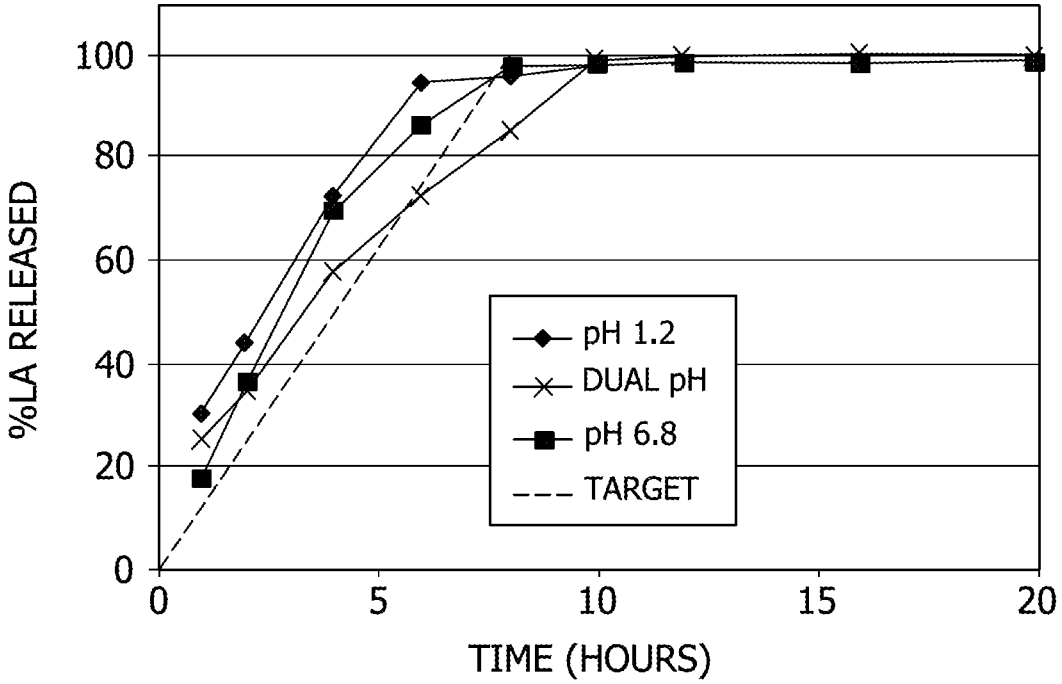

100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
TIME (HOURS)
pH 1.2
DUAL pH
pH 6.8
TARGET

FIG. 10

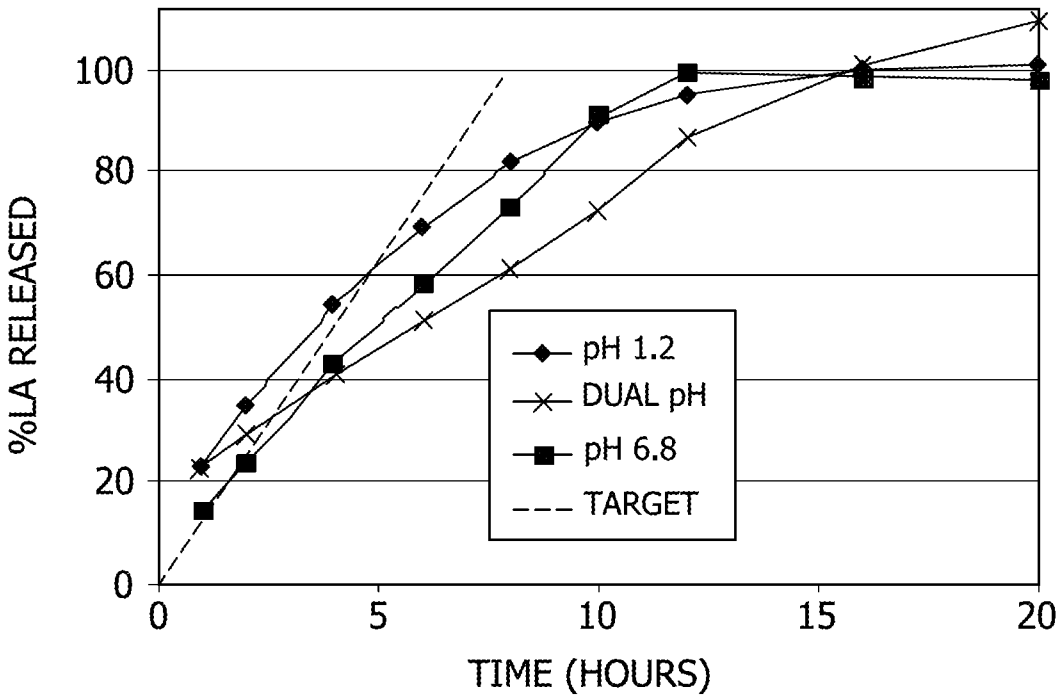

100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
TIME (HOURS)
pH 1.2
DUAL pH
pH 6.8
TARGET

FIG. 11

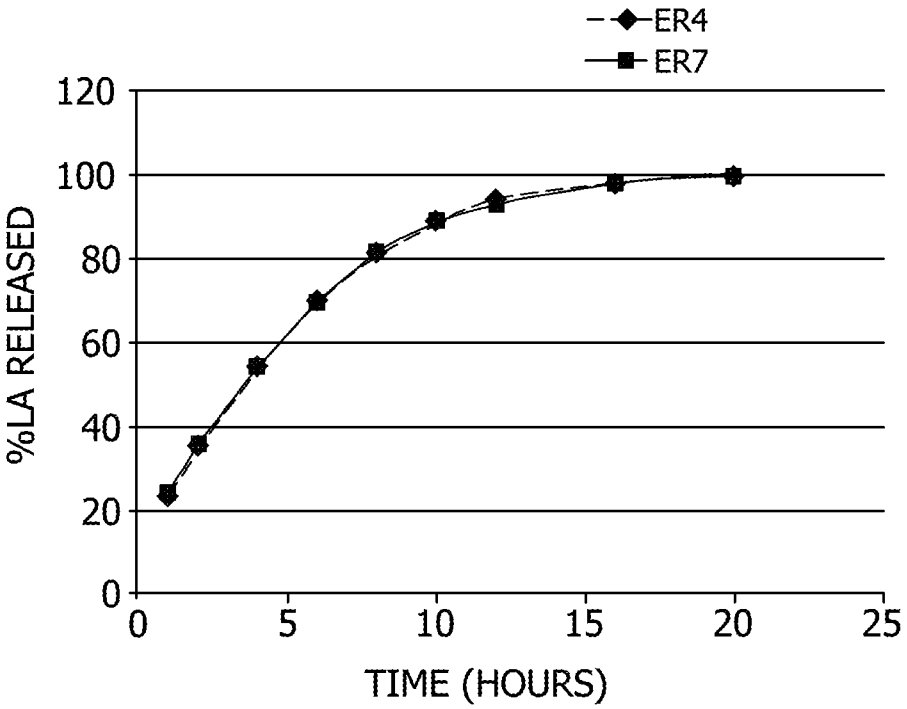

ER4
ER7
120
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
25
TIME (HOURS)

FIG. 12

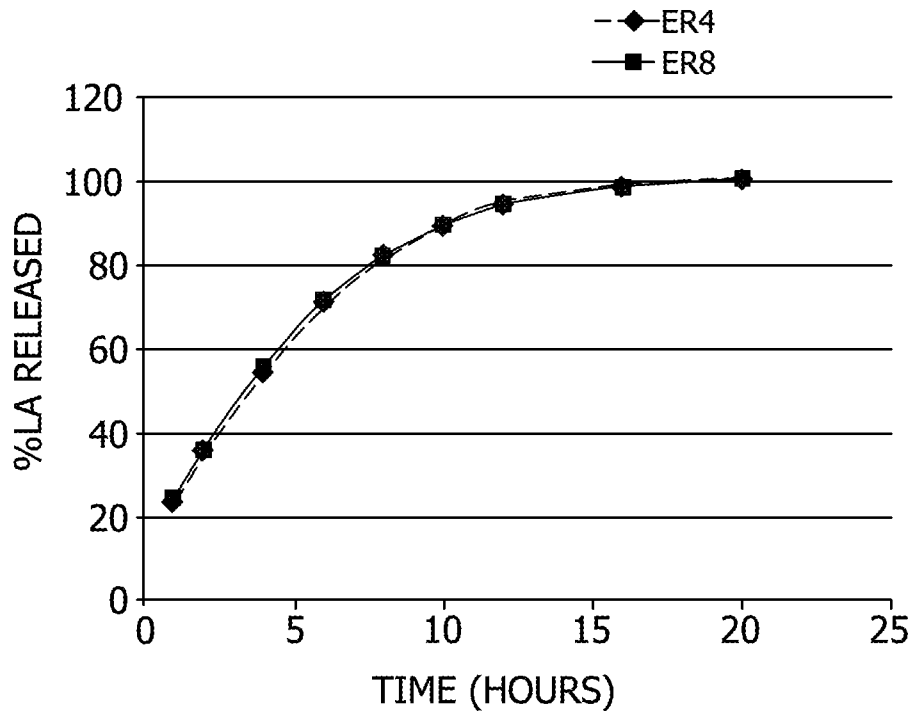

ER4
ER8
120
100
80
60
40
20
0
%LA RELEASED
0
5
10
15
20
25
TIME (HOURS)

FIG. 13

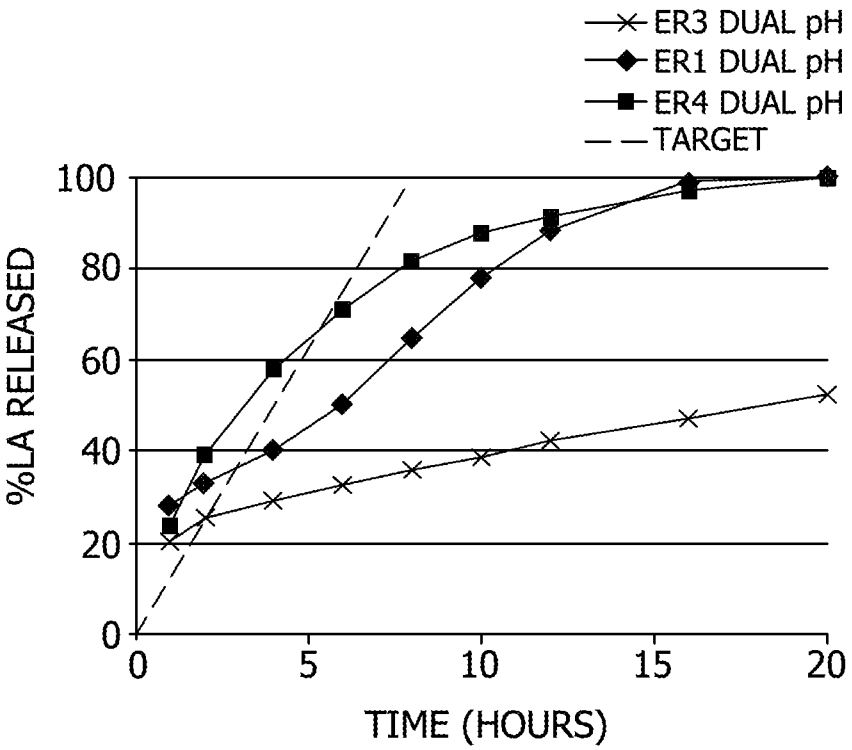

ER3 DUAL pH
ER1 DUAL pH
ER4 DUAL pH
TARGET
%LA RELEASED
100
80
60
40
20
0
0
5
10
15
20
TIME (HOURS)

FIG. 14

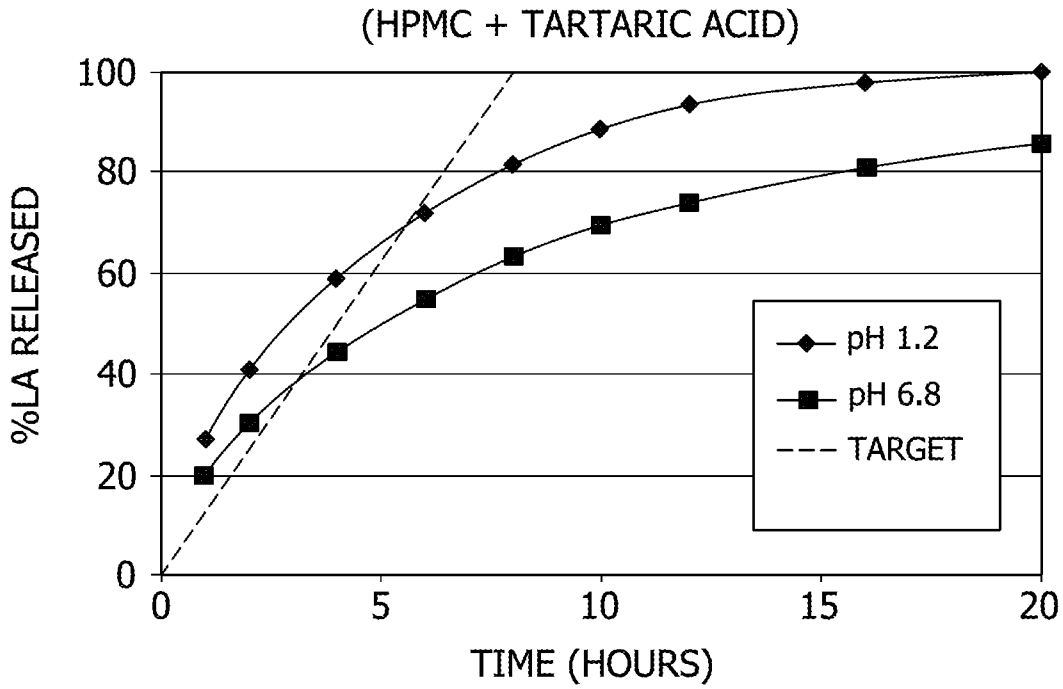


FIG. 15A

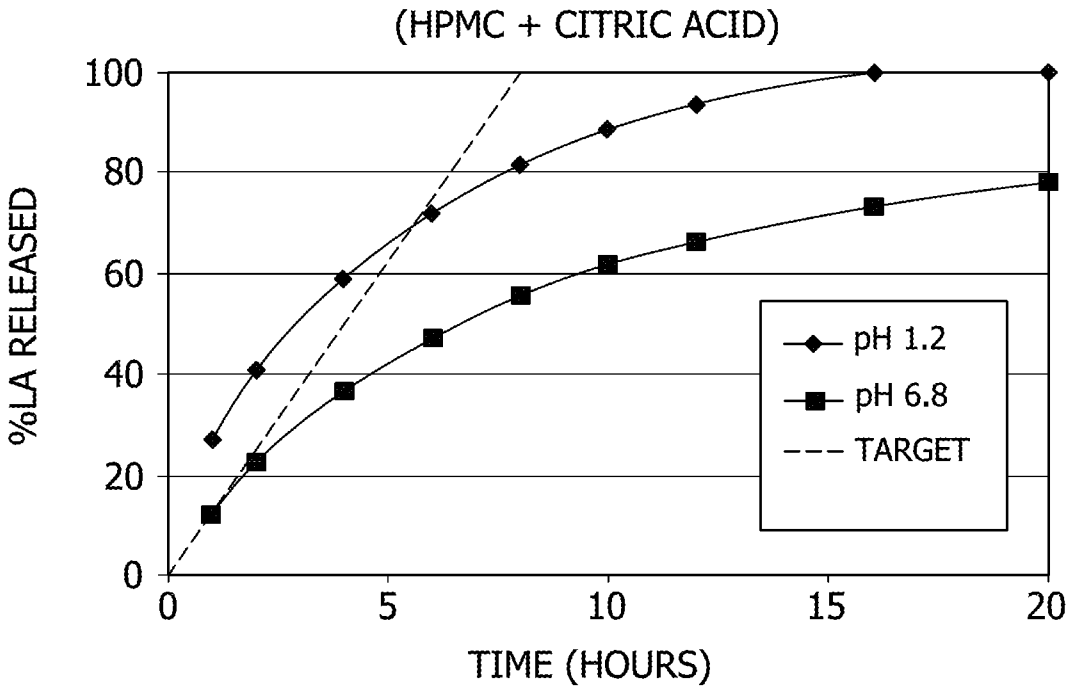


FIG. 15B

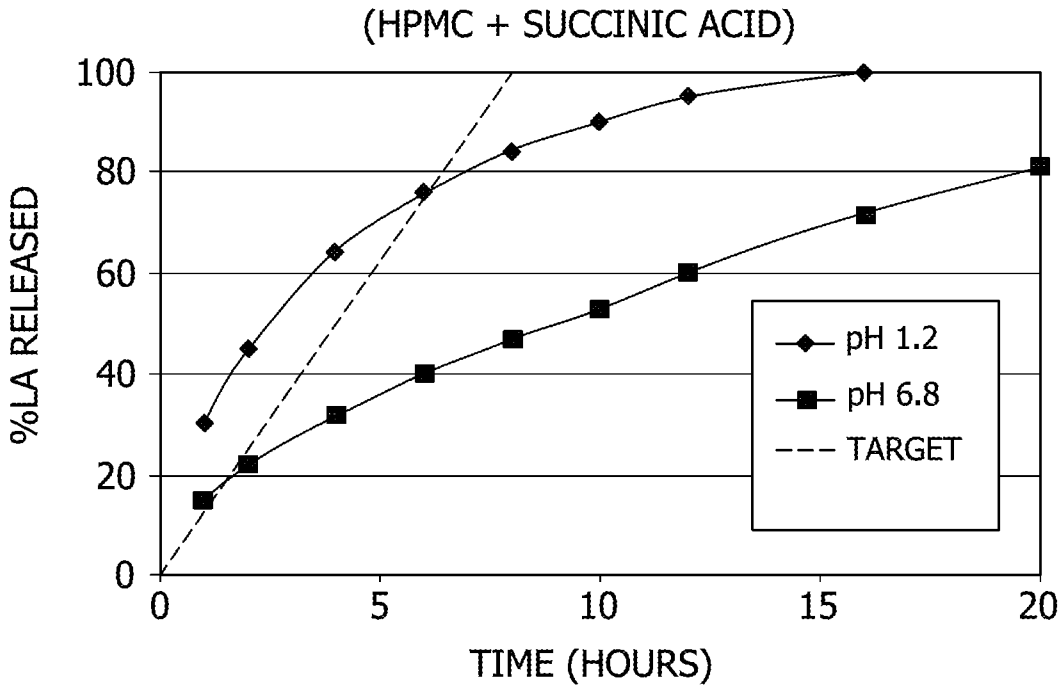


FIG. 15C

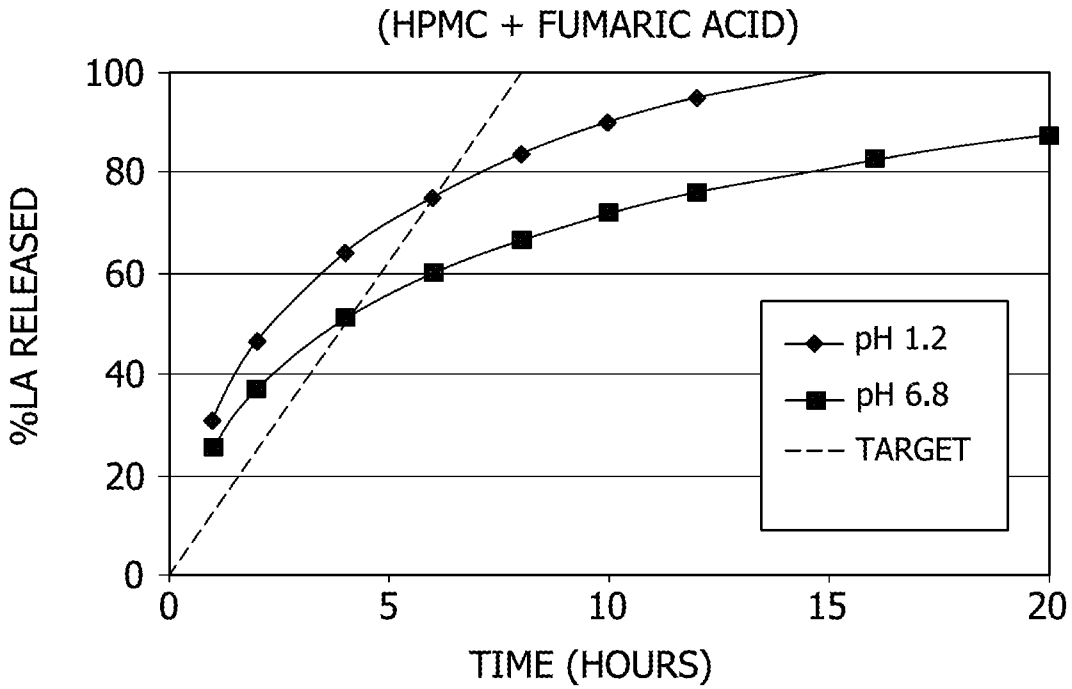


FIG. 15D

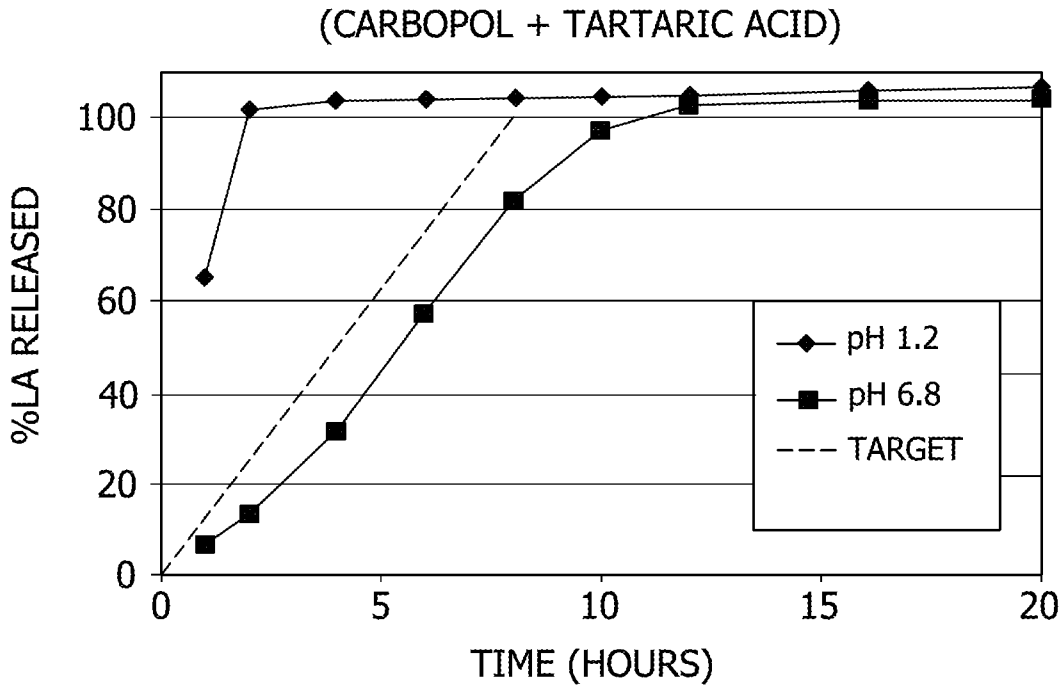


FIG. 15E

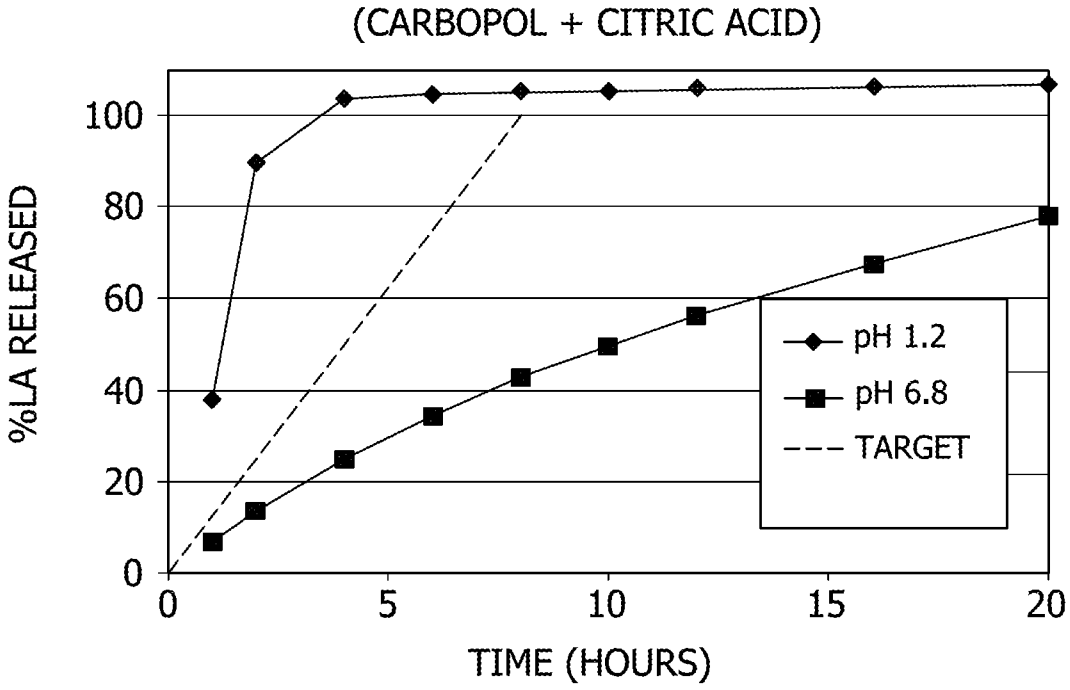


FIG. 15F

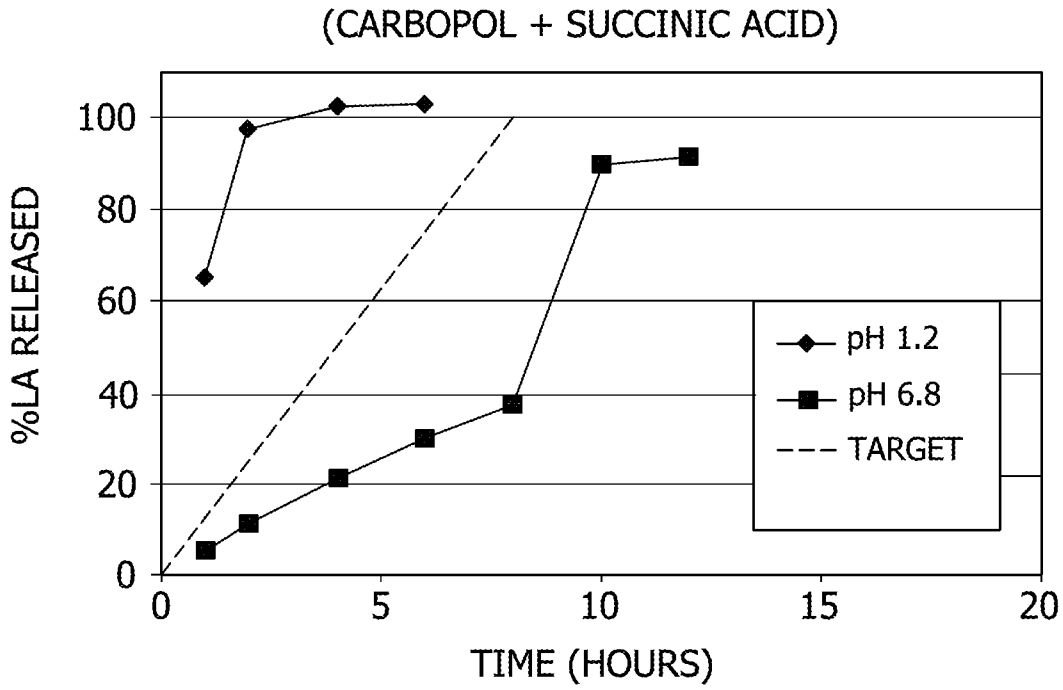


FIG. 15G

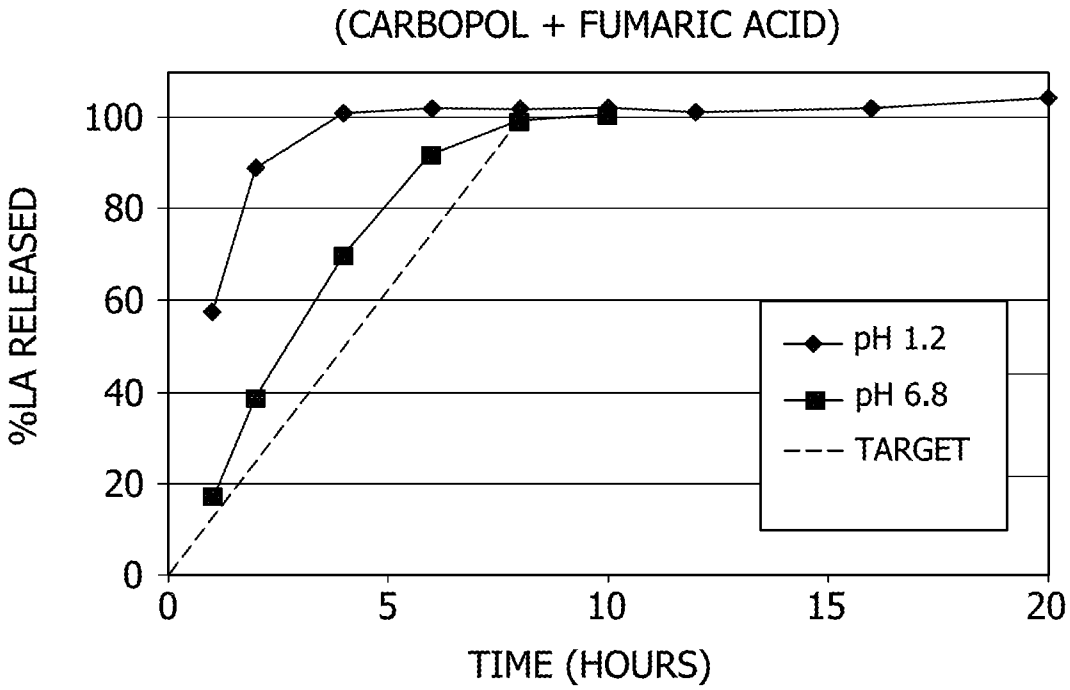


FIG. 15H

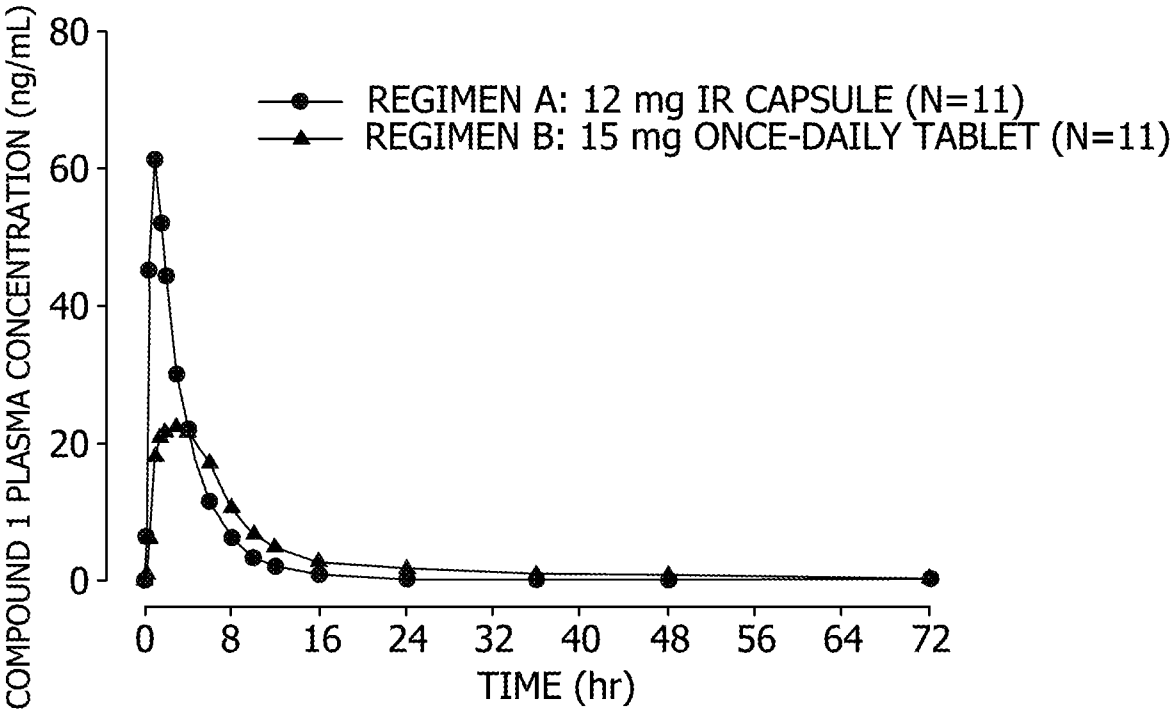


FIG. 16A

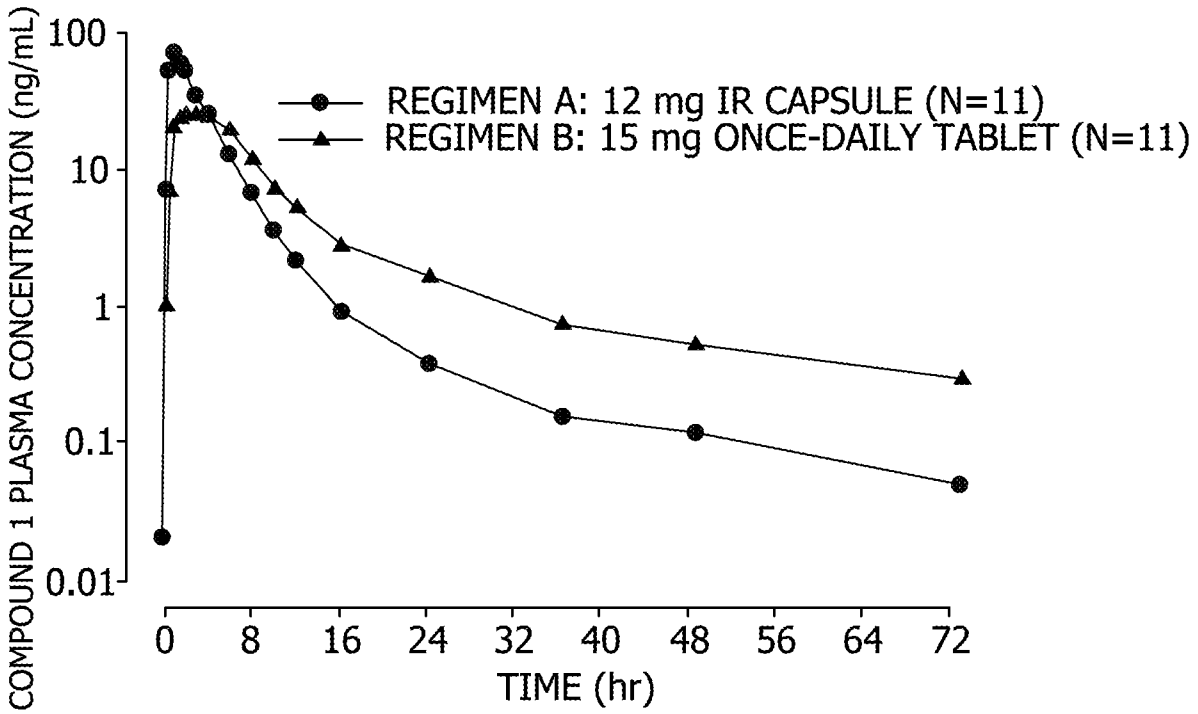


FIG. 16B

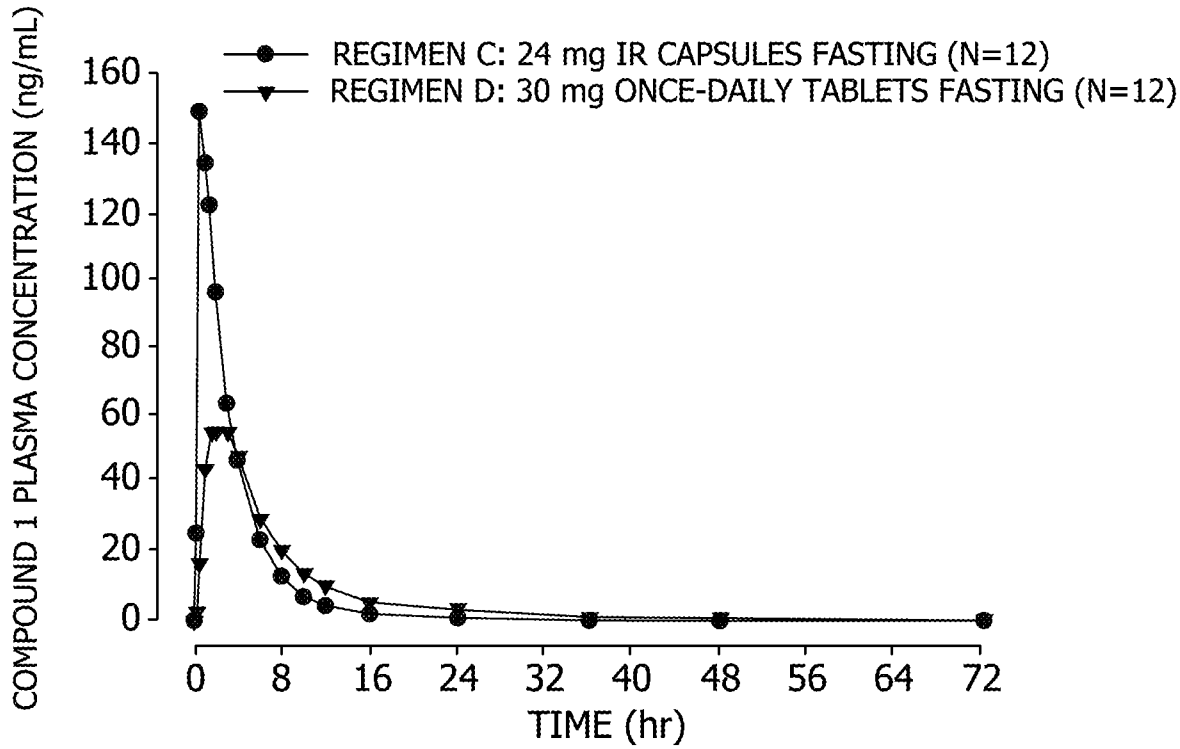


FIG. 17A

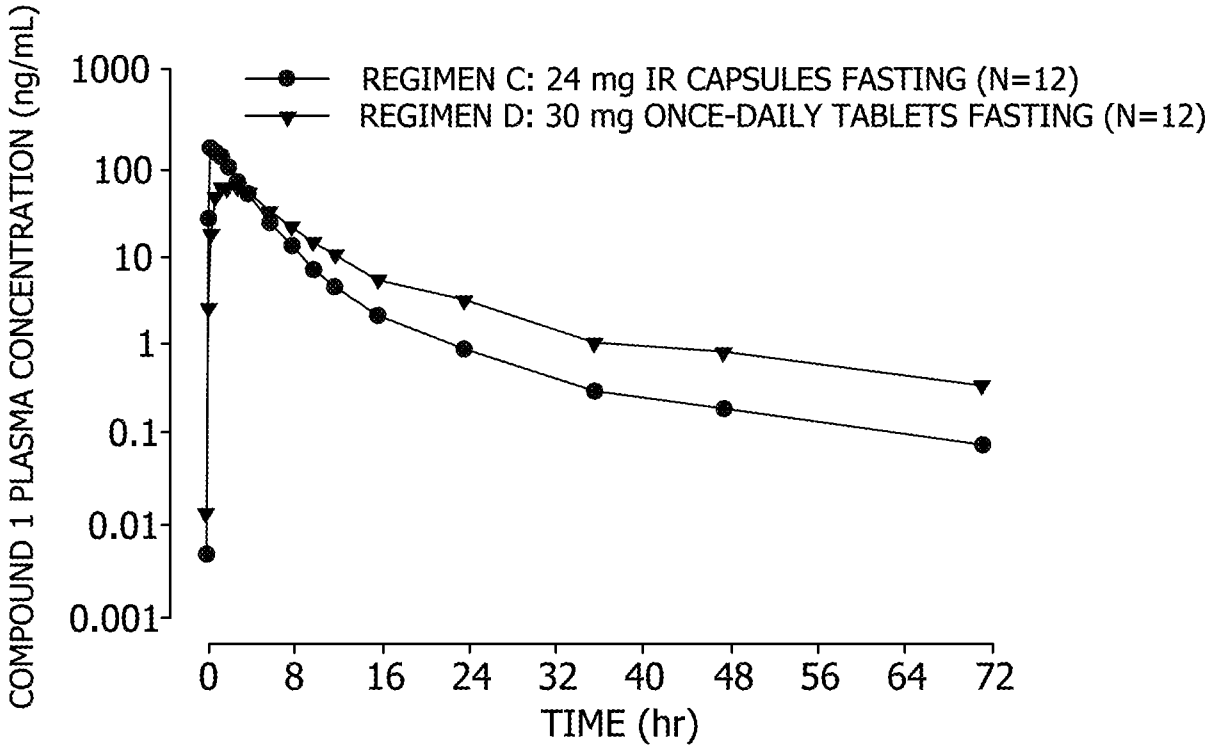


FIG. 17B

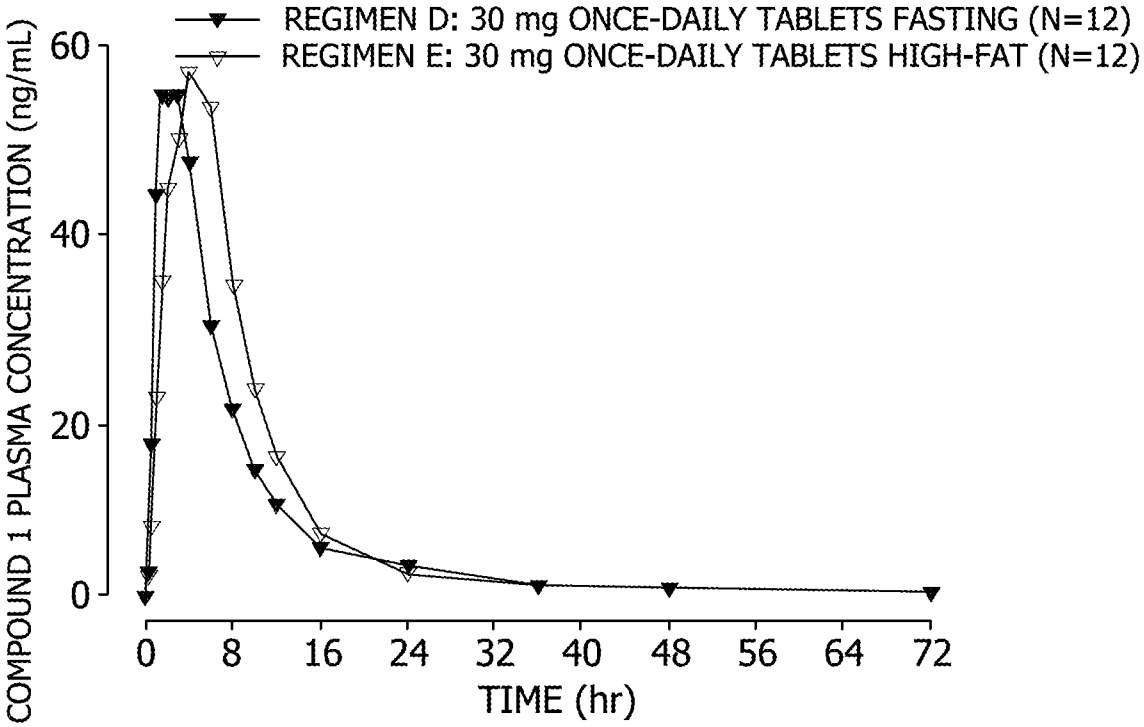


FIG. 18A

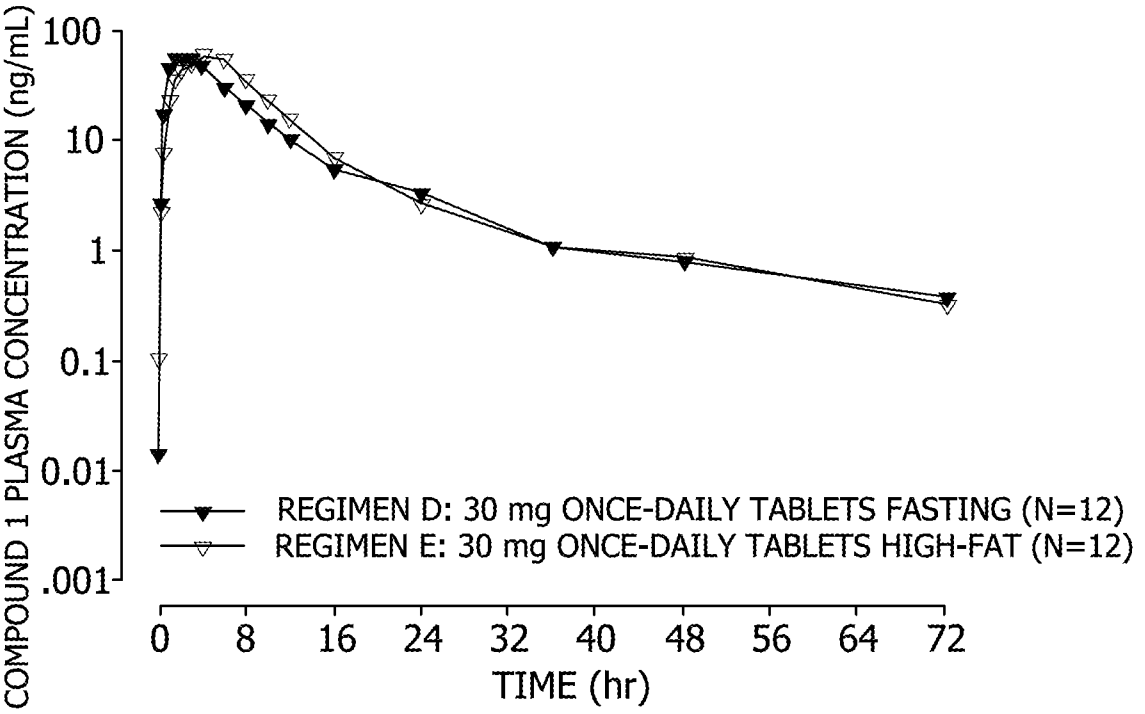


FIG. 18B

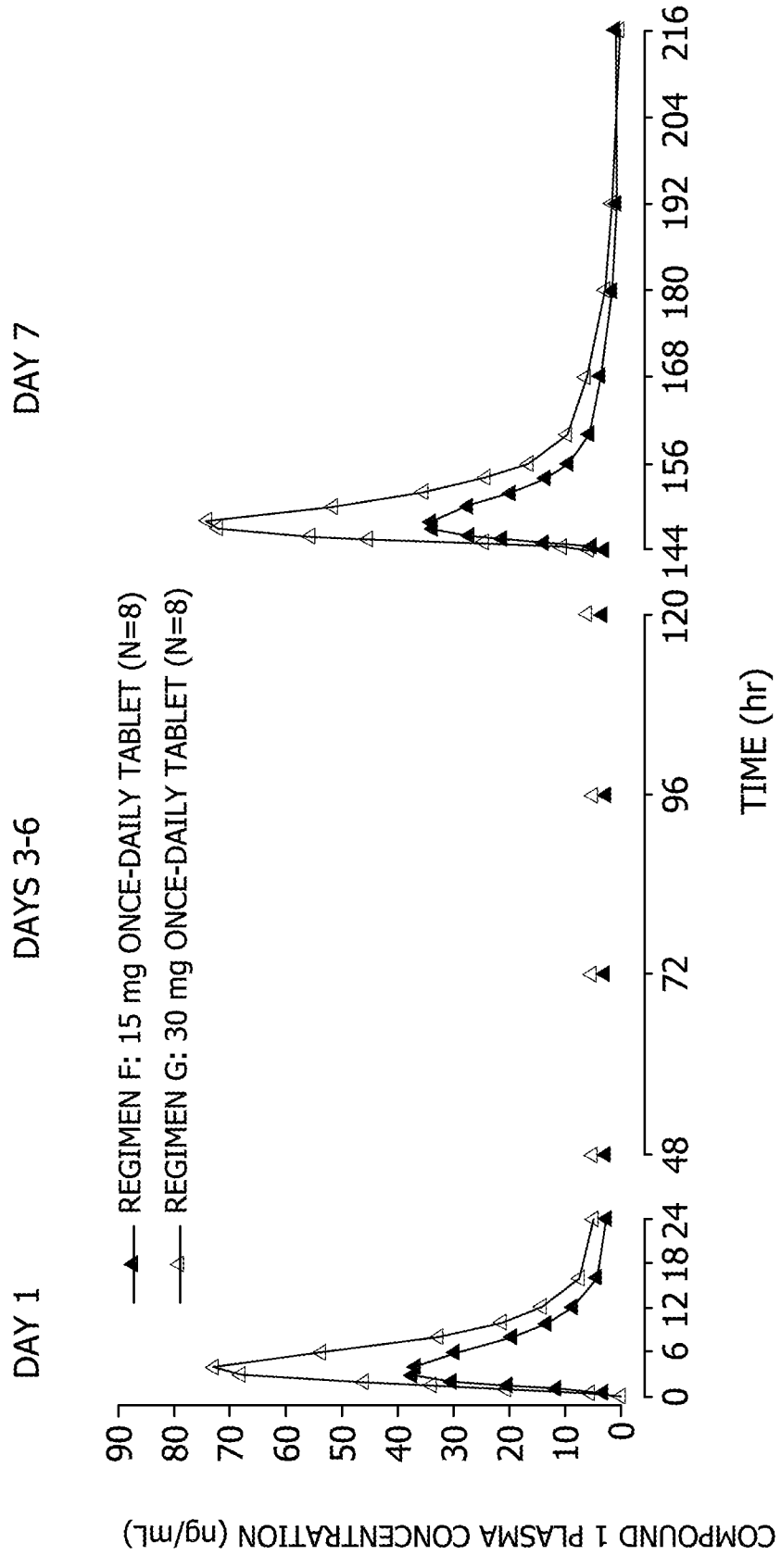

DAY 1
DAYS 3-6
DAY 7
REGIMEN F: 15 mg ONCE-DAILY TABLET (N=8)
REGIMEN G: 30 mg ONCE-DAILY TABLET (N=8)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
10
20
30
40
50
60
70
80
90
0 6 12 18 24 48 72 96 120 144 156 168 180 192 204 216
TIME (hr)

FIG. 19

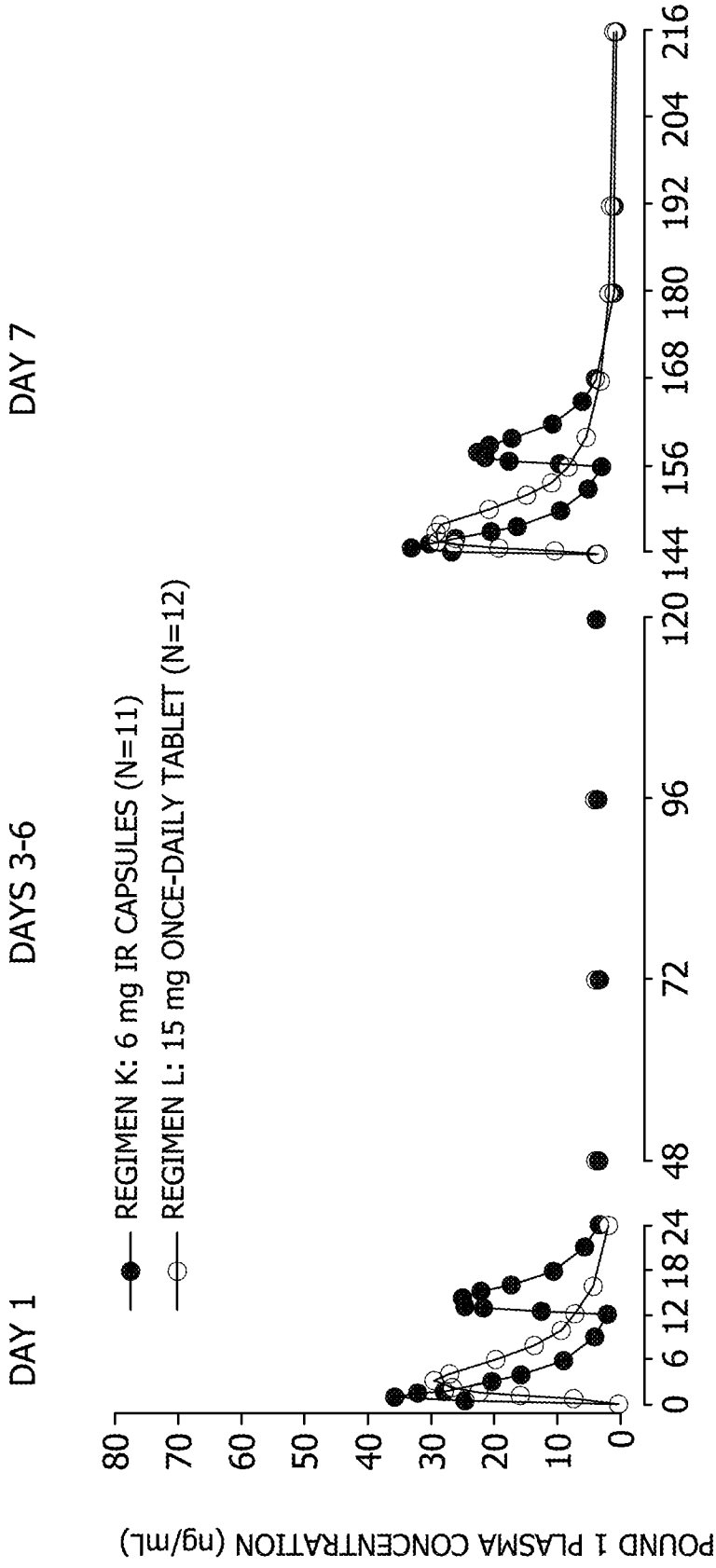

DAY 1
DAYS 3-6
DAY 7
REGIMEN K: 6 mg IR CAPSULES (N=11)
REGIMEN L: 15 mg ONCE-DAILY TABLET (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
TIME (hr)
0
10
20
30
40
50
60
70
80
0 6 12 18 24 48 72 96 120 144 156 168 180 192 204 216

FIG. 20

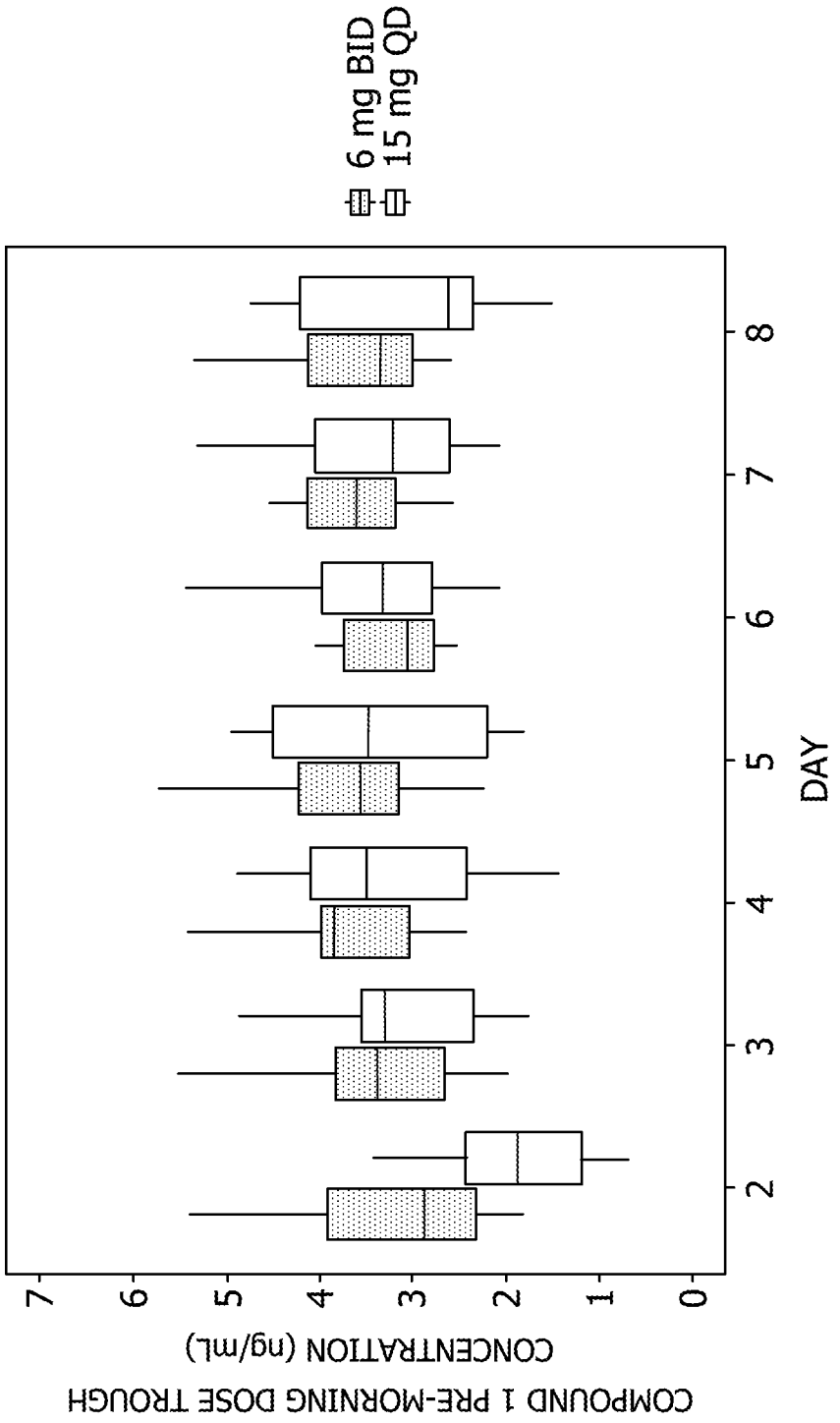

6 mg BID
15 mg QD
COMPOUND 1 PRE-MORNING DOSE TROUGH
CONCENTRATION (ng/mL)
0
1
2
3
4
5
6
7
DAY
2
3
4
5
6
7
8

FIG. 21

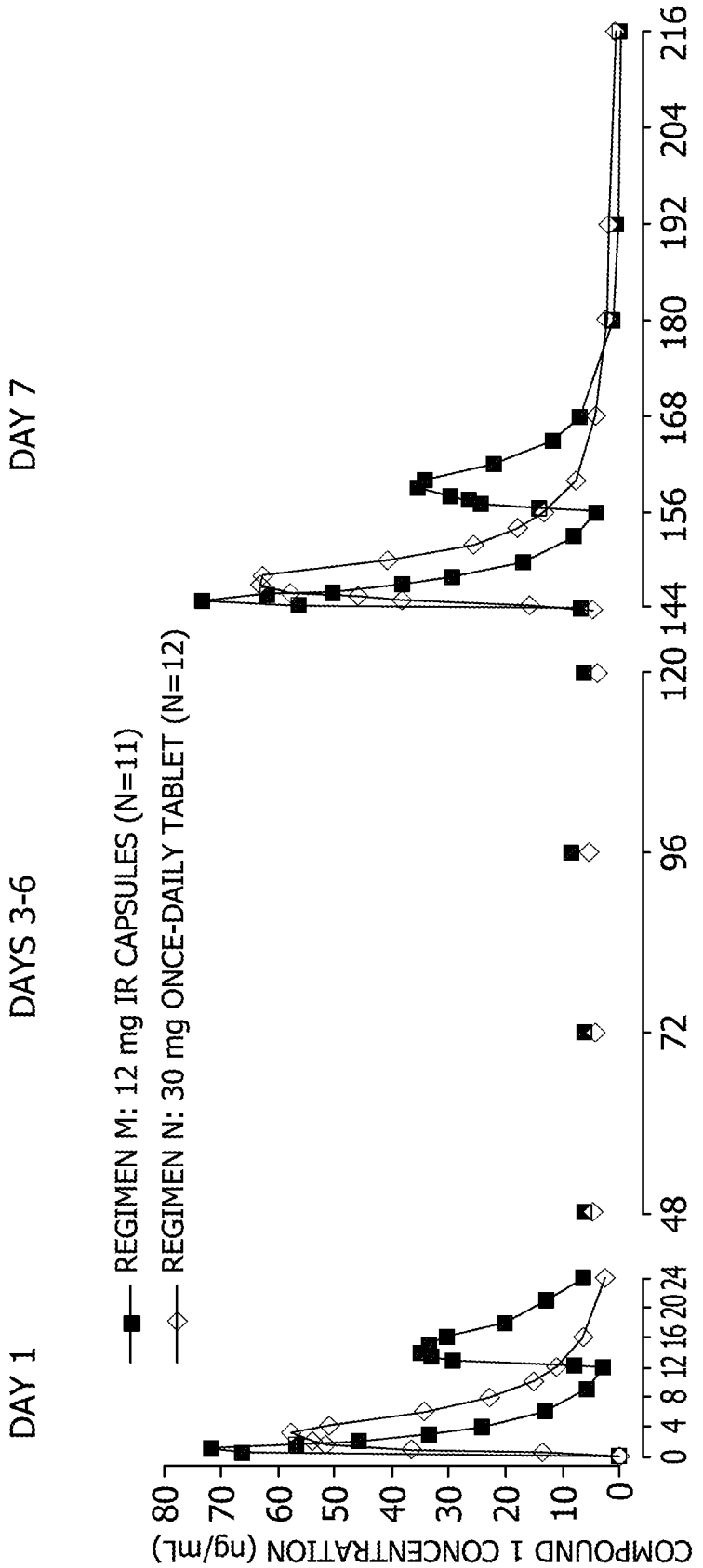

DAY 1
DAYS 3-6
DAY 7
REGIMEN M: 12 mg IR CAPSULES (N=11)
REGIMEN N: 30 mg ONCE-DAILY TABLET (N=12)
COMPOUND 1 CONCENTRATION (ng/mL)
0
10
20
30
40
50
60
70
80
0 4 8 12 16 20 24
48
72
96
120 144
156
168
180
192
204
216
TIME (hr)

FIG. 22

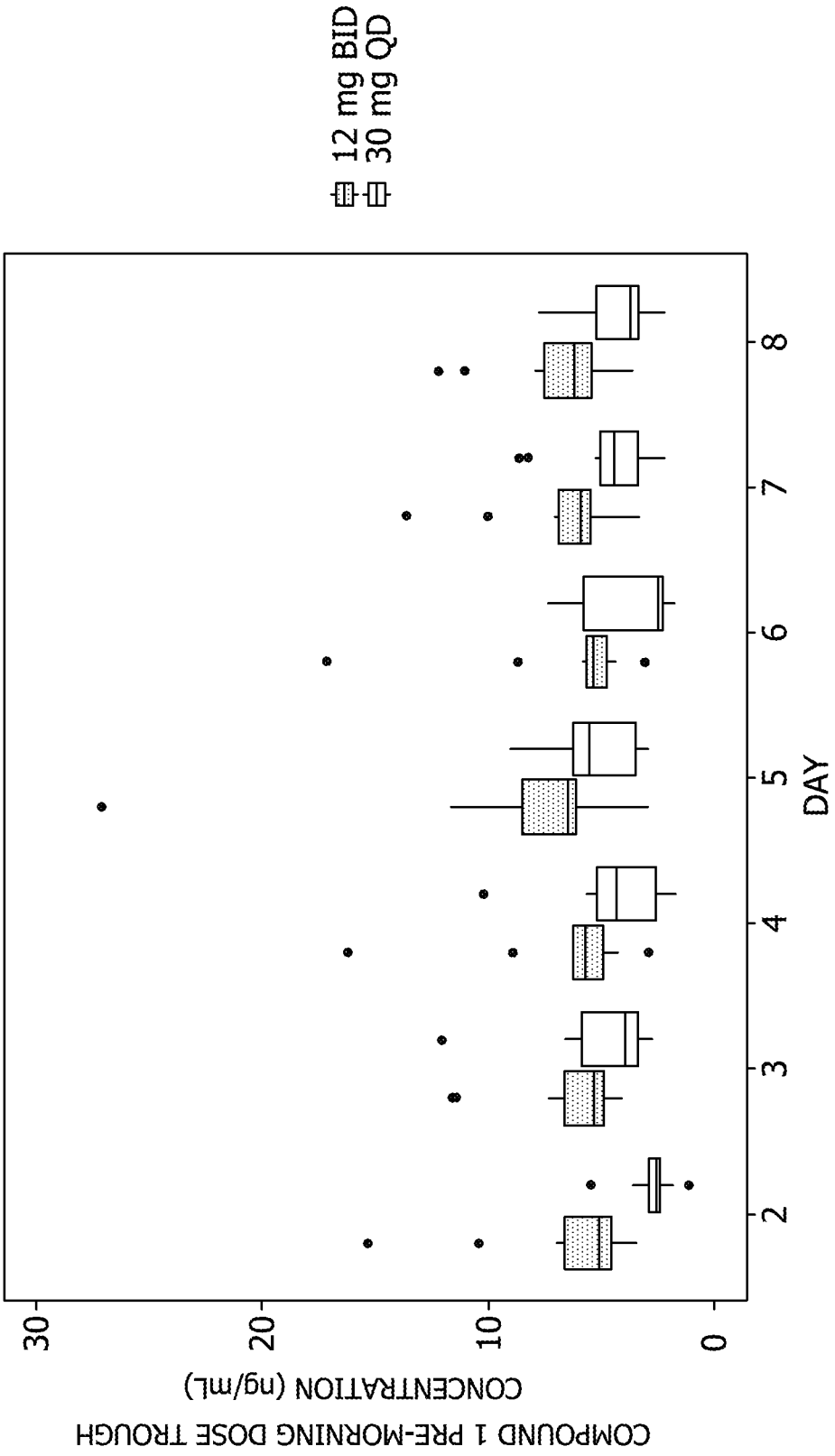

12 mg BID
30 mg QD
COMPOUND 1 PRE-MORNING DOSE TROUGH
CONCENTRATION (ng/mL)
0
10
20
30
2
3
4
5
6
7
8
DAY

FIG. 23

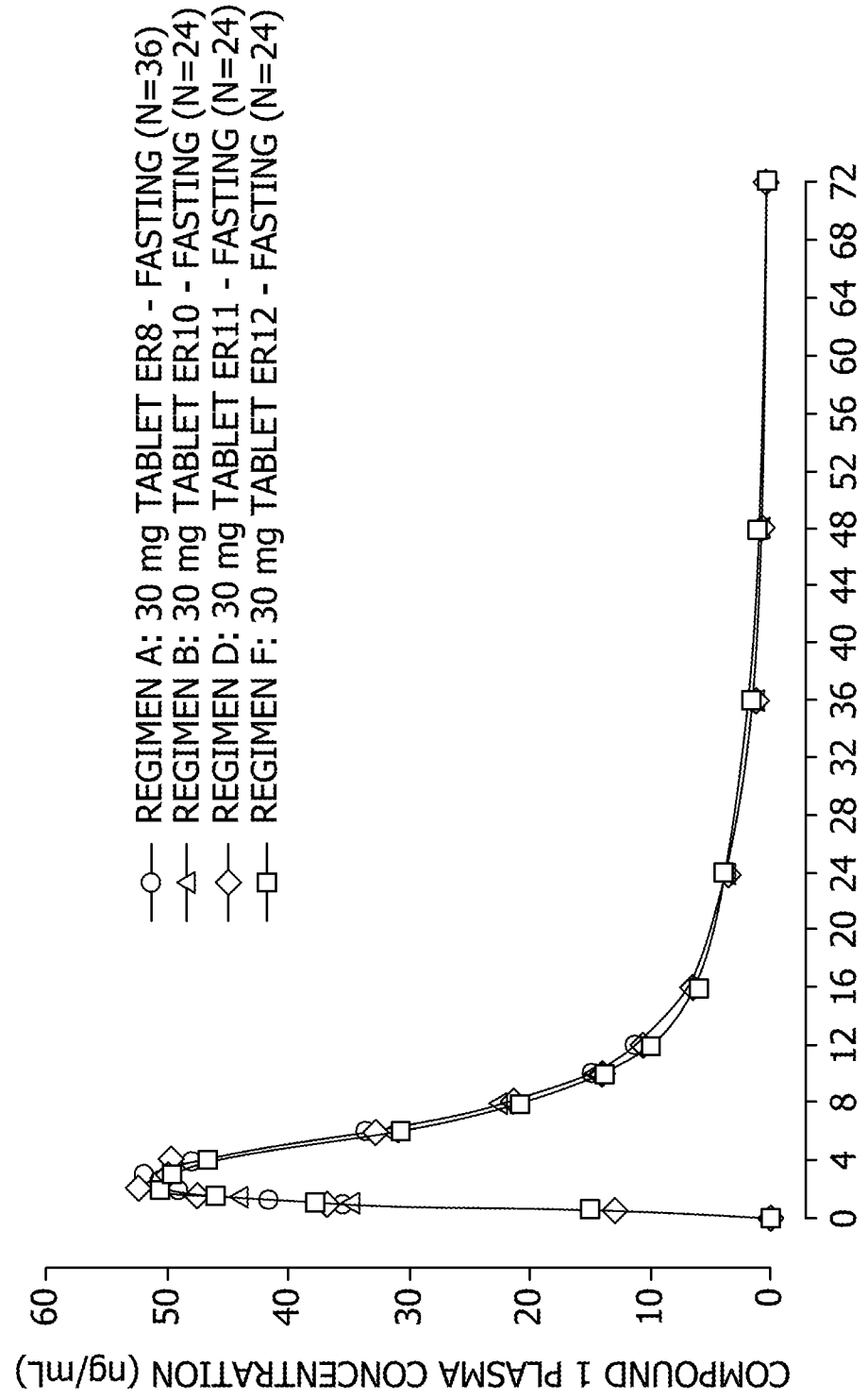

REGIMEN A: 30 mg TABLET ER8 - FASTING (N=36)
REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
10
20
30
40
50
60
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 24A

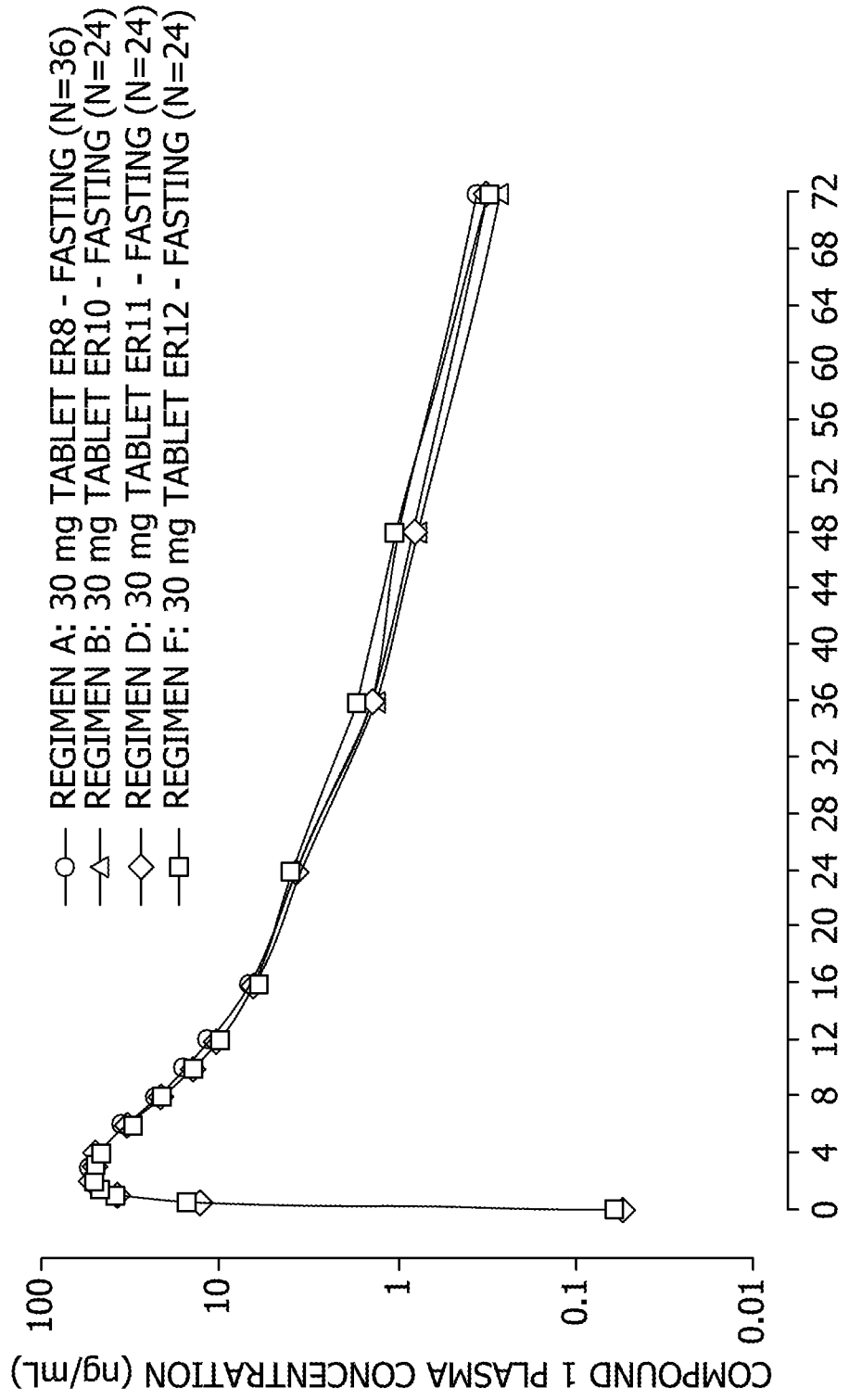

REGIMEN A: 30 mg TABLET ER8 - FASTING (N=36)
REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72
TIME (hr)

FIG. 24B

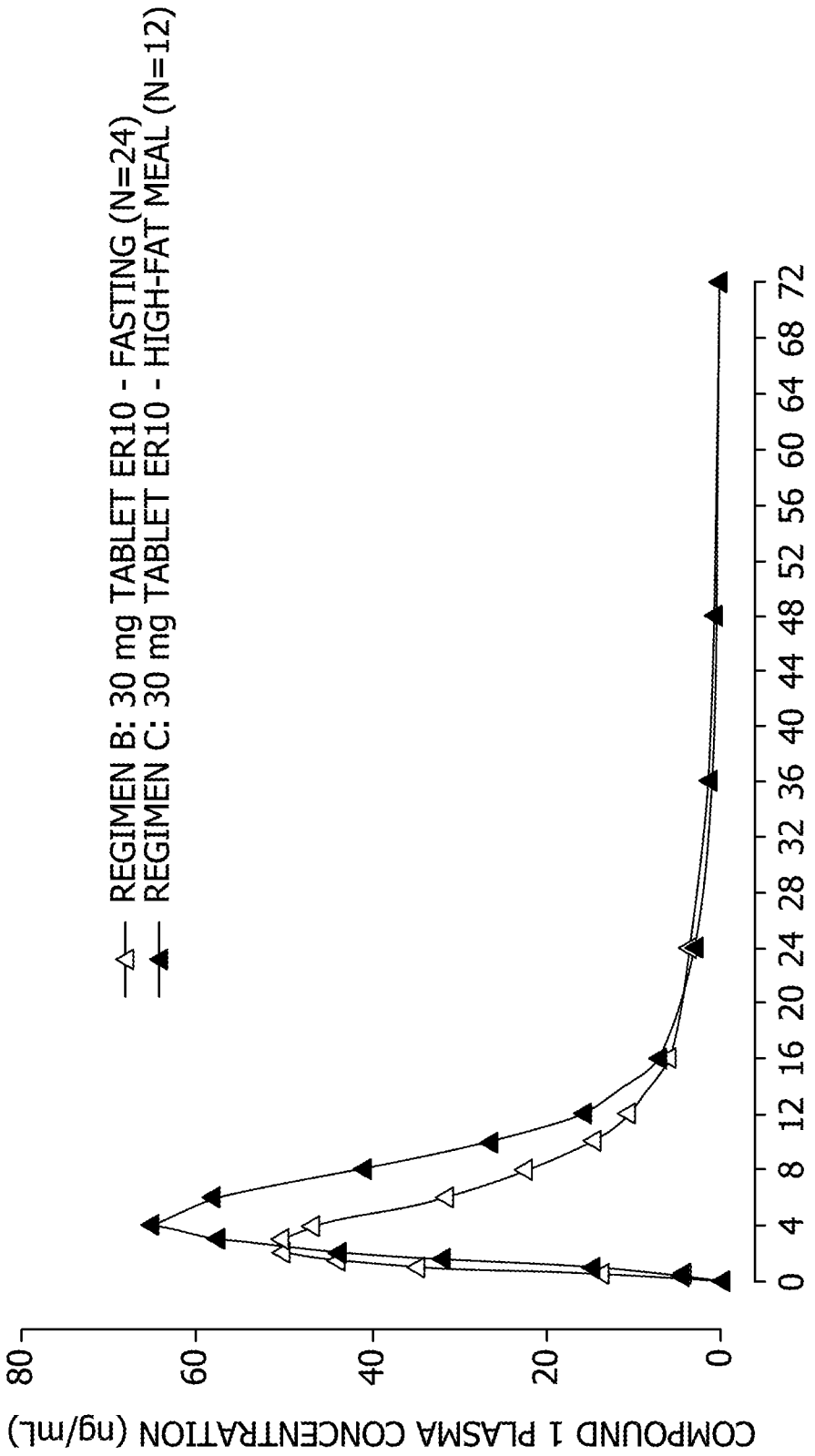

REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN C: 30 mg TABLET ER10 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 25A

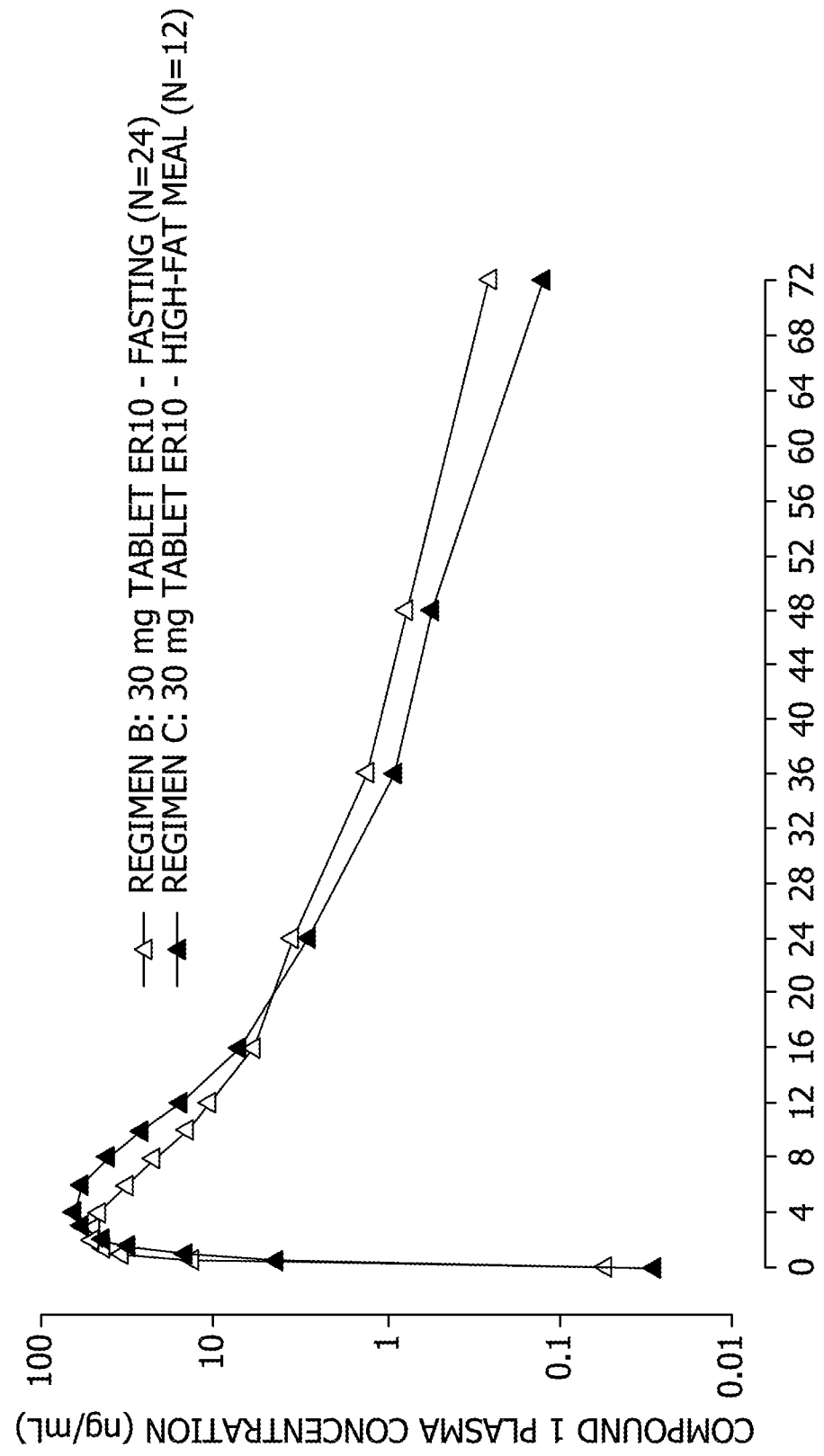

REGIMEN B: 30 mg TABLET ER10 - FASTING (N=24)
REGIMEN C: 30 mg TABLET ER10 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72
TIME (hr)

FIG. 25B

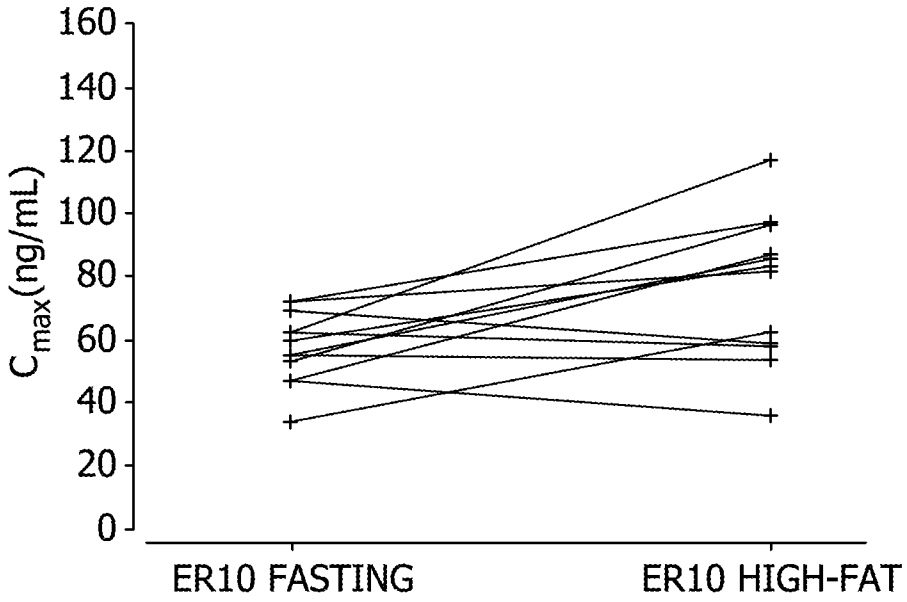


FIG. 26A

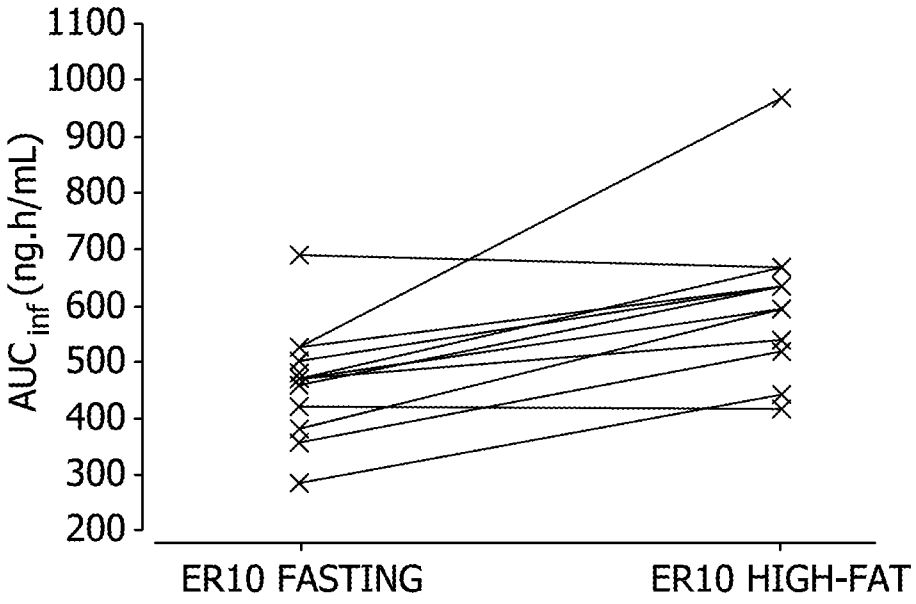


FIG. 26B

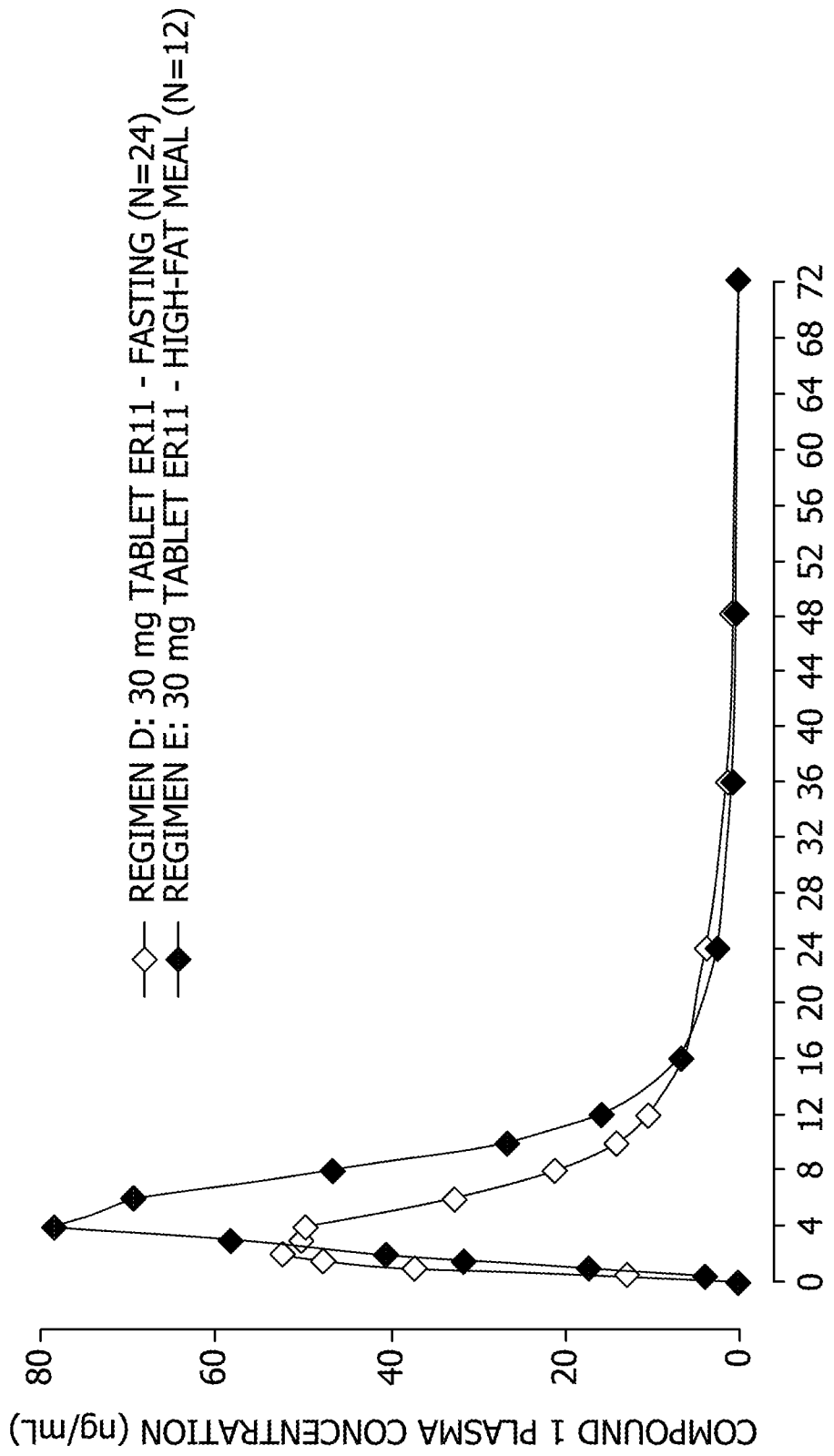

REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN E: 30 mg TABLET ER11 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 27A

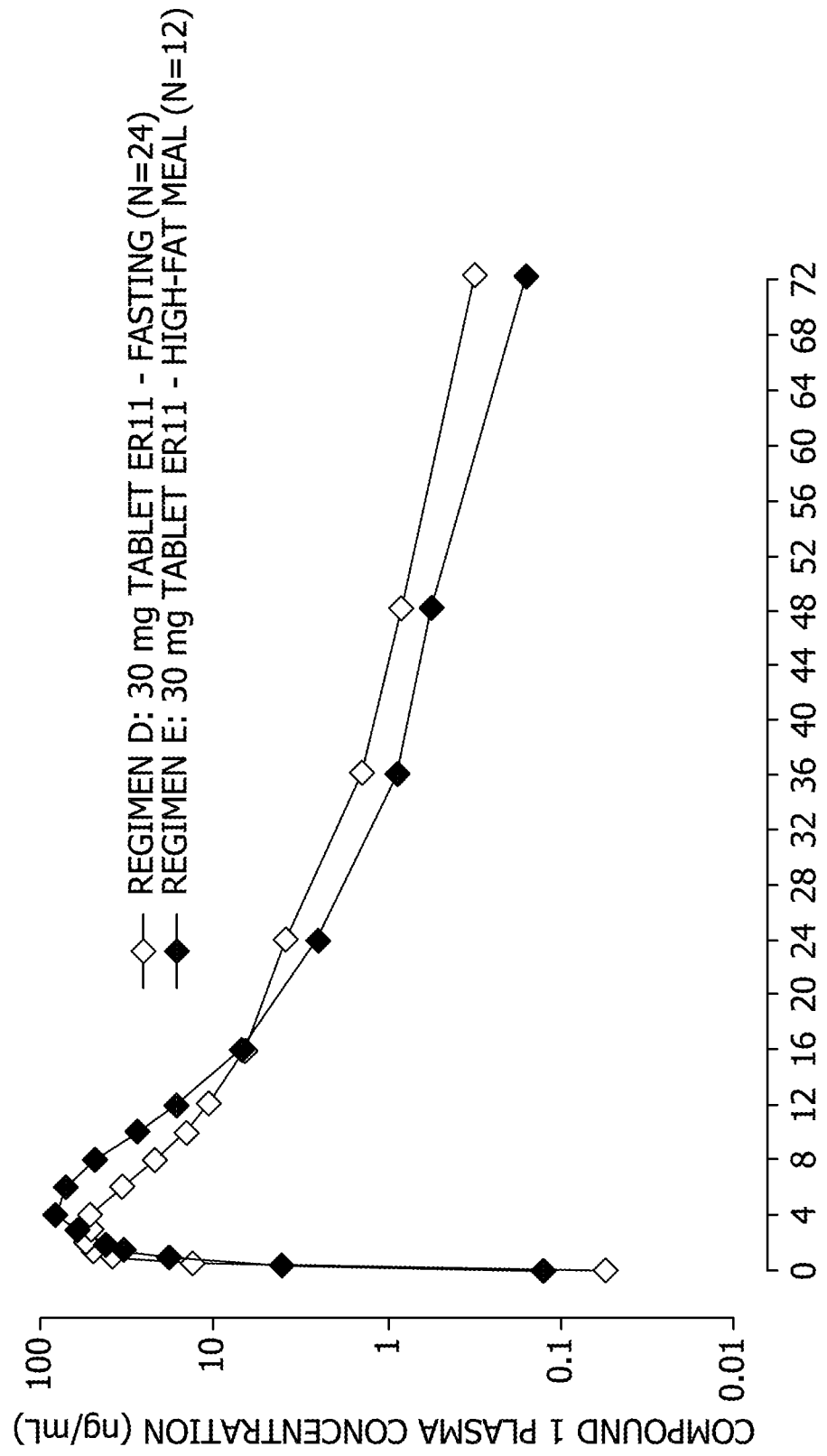

REGIMEN D: 30 mg TABLET ER11 - FASTING (N=24)
REGIMEN E: 30 mg TABLET ER11 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 27B

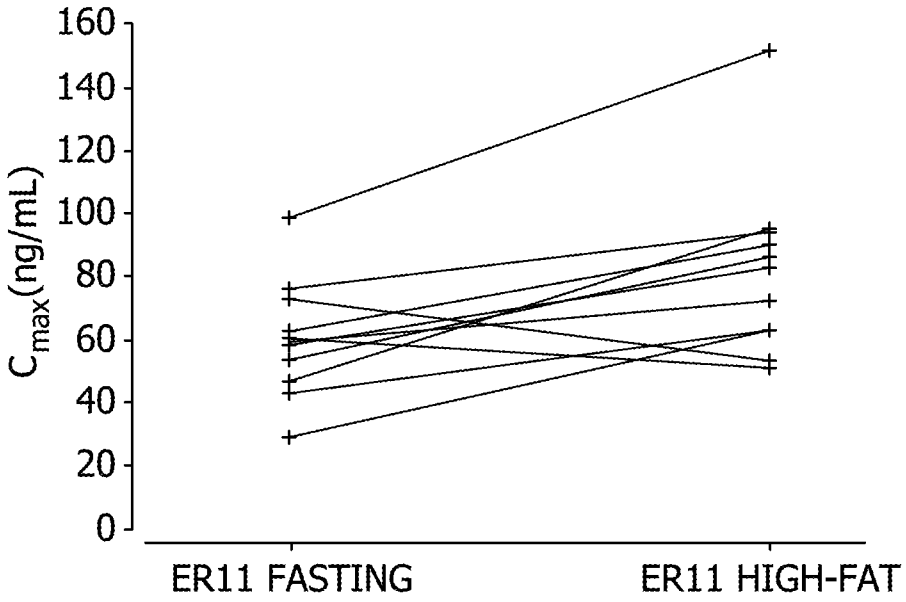


FIG. 28A

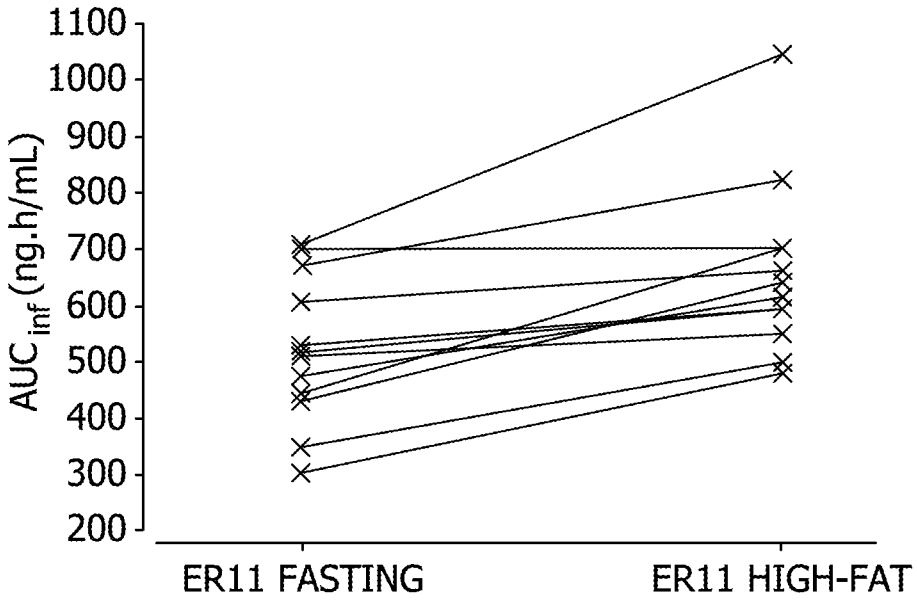


FIG. 28B

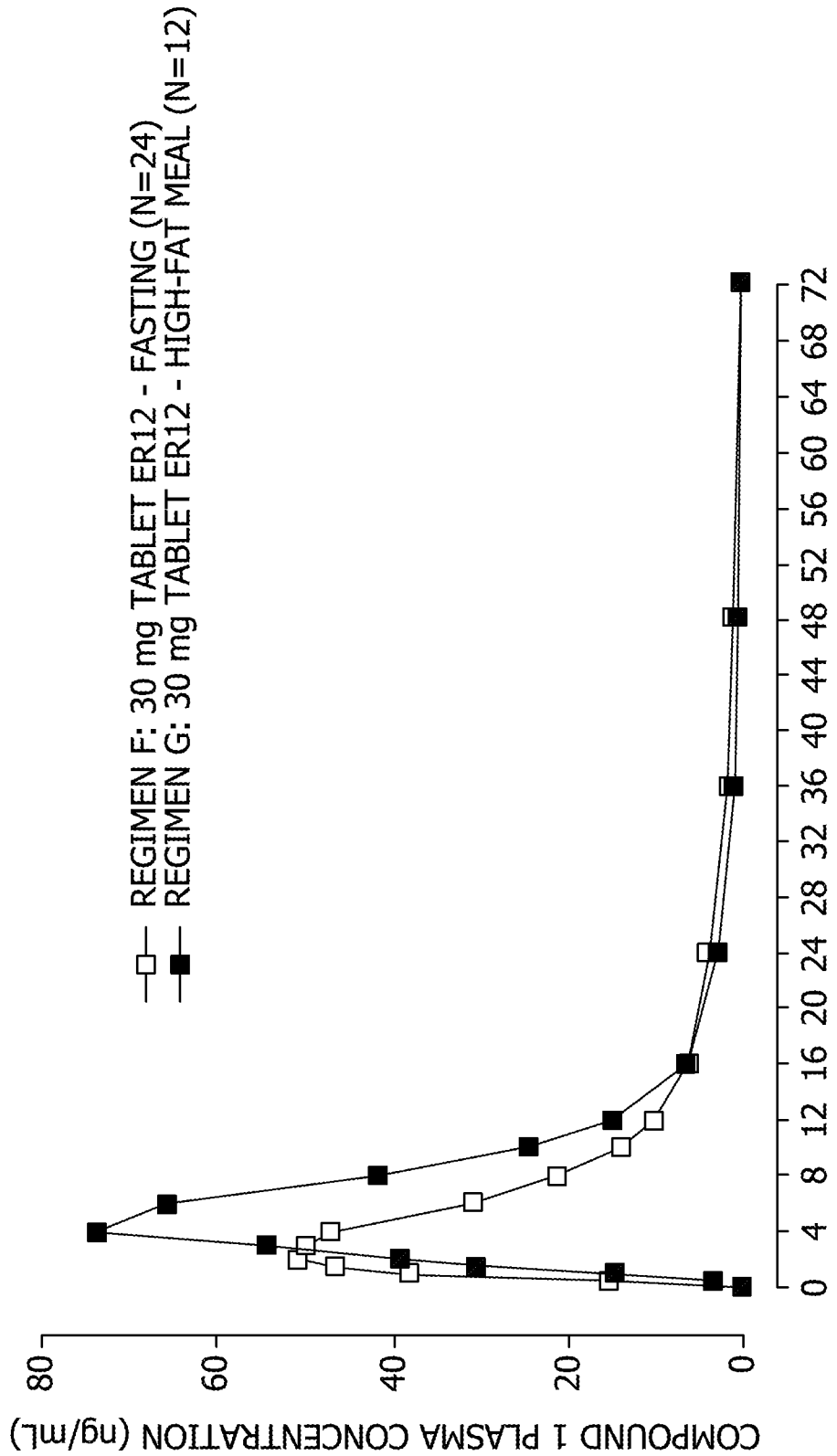

REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
REGIMEN G: 30 mg TABLET ER12 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 29A

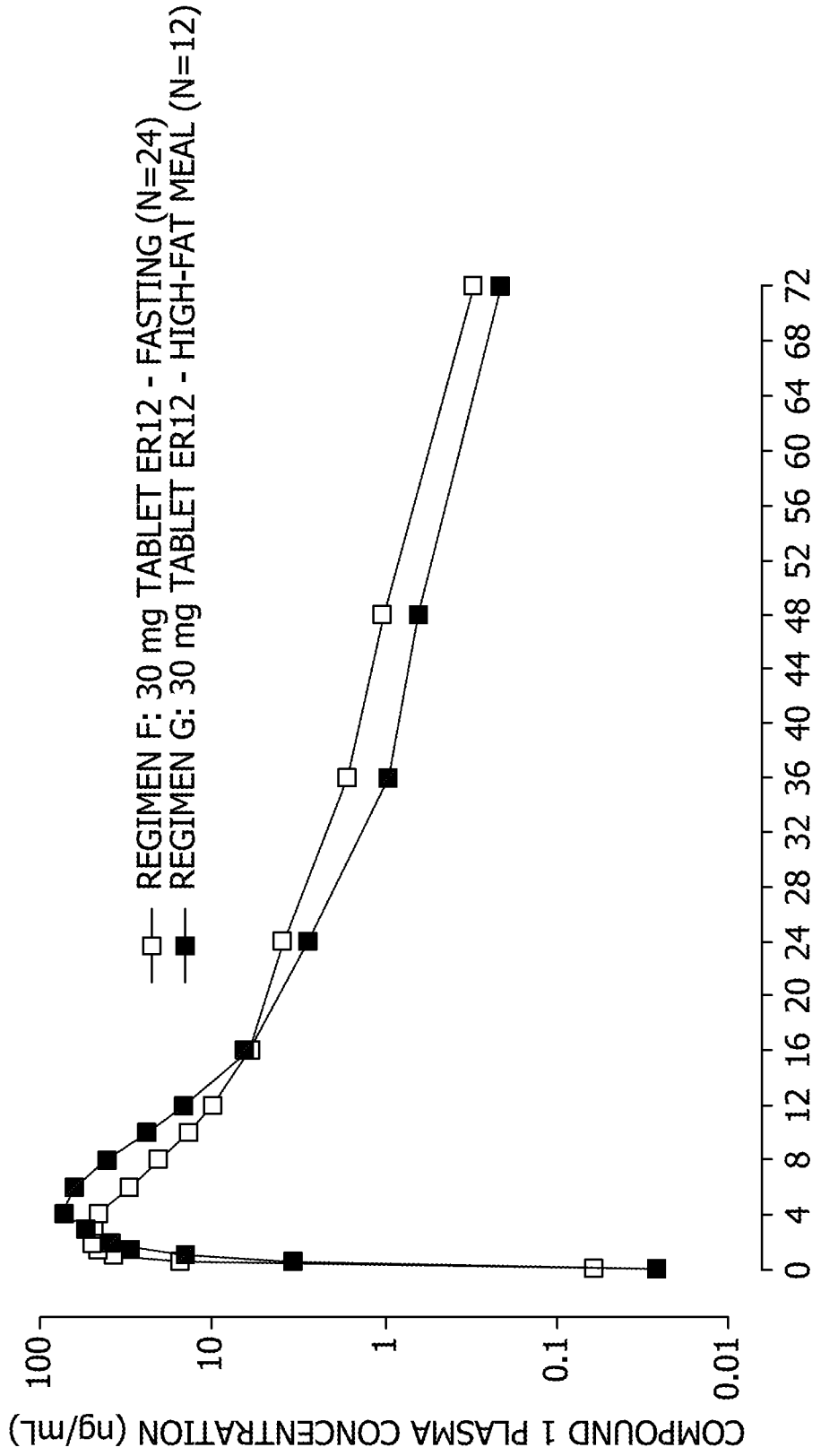

REGIMEN F: 30 mg TABLET ER12 - FASTING (N=24)
REGIMEN G: 30 mg TABLET ER12 - HIGH-FAT MEAL (N=12)
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
100
10
1
0.1
0.01
TIME (hr)
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72

FIG. 29B

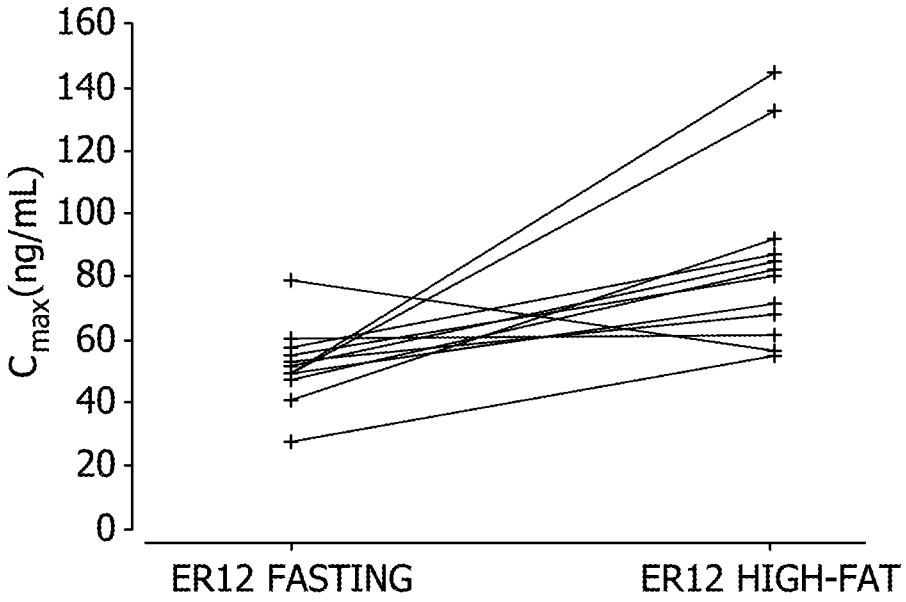


FIG. 30A

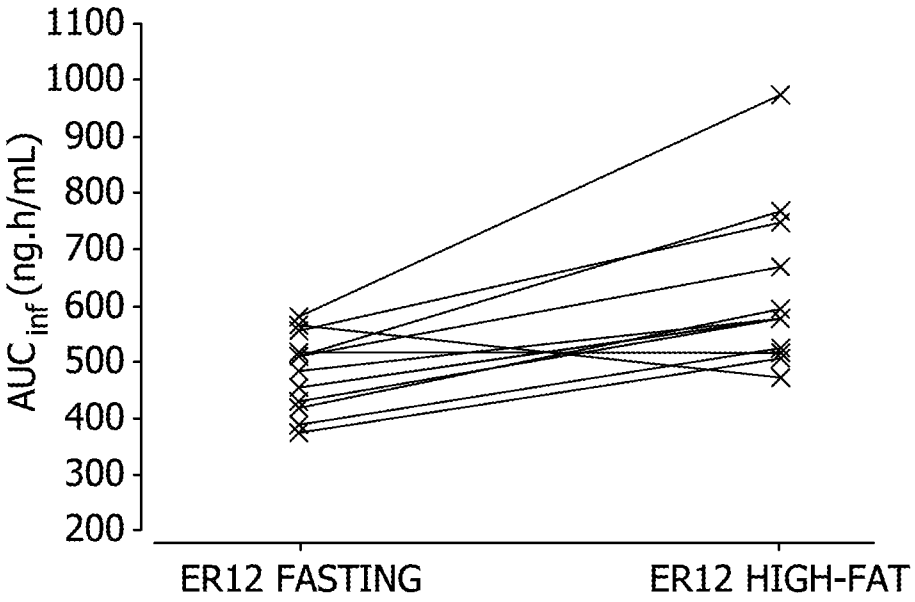


FIG. 30B

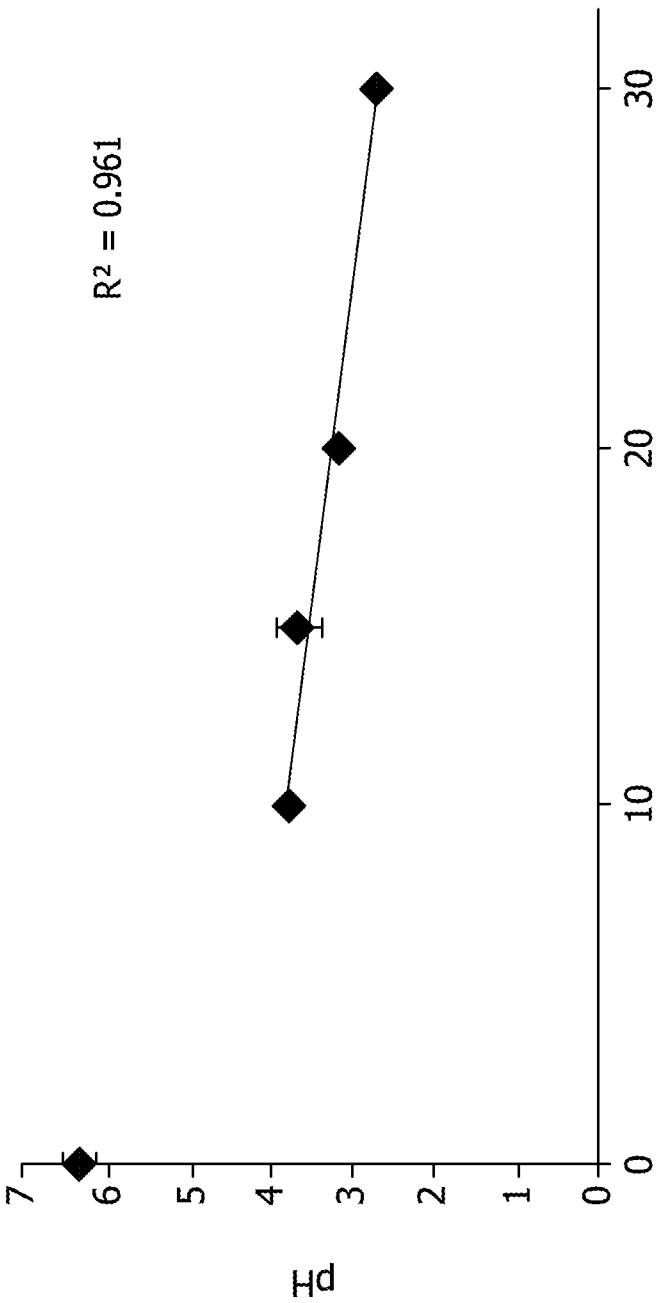


FIG. 31

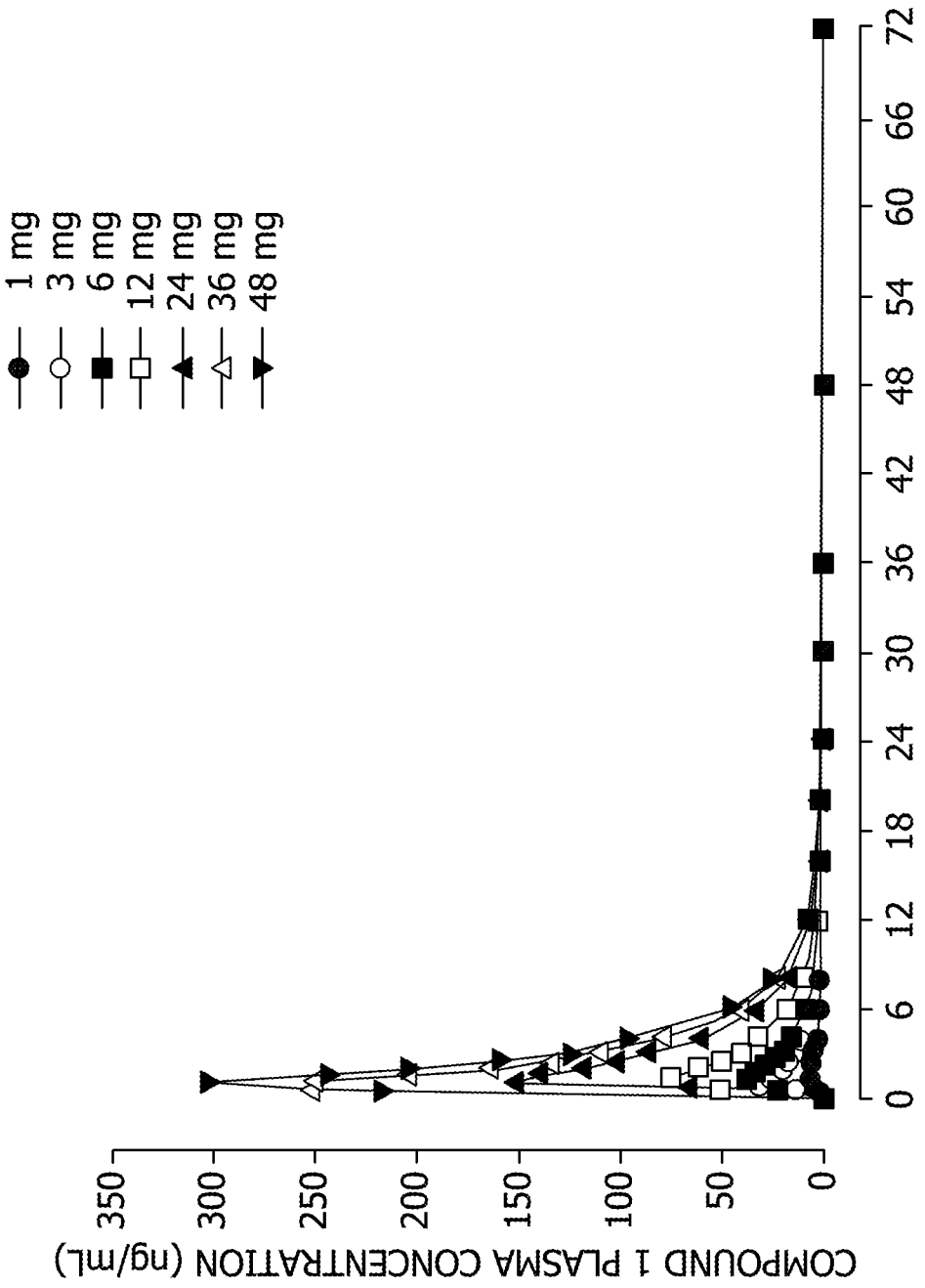

1 mg
3 mg
6 mg
12 mg
24 mg
36 mg
48 mg
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
50
100
150
200
250
300
350
TIME (hr)
0
6
12
18
24
30
36
42
48
54
60
66
72

FIG. 32A

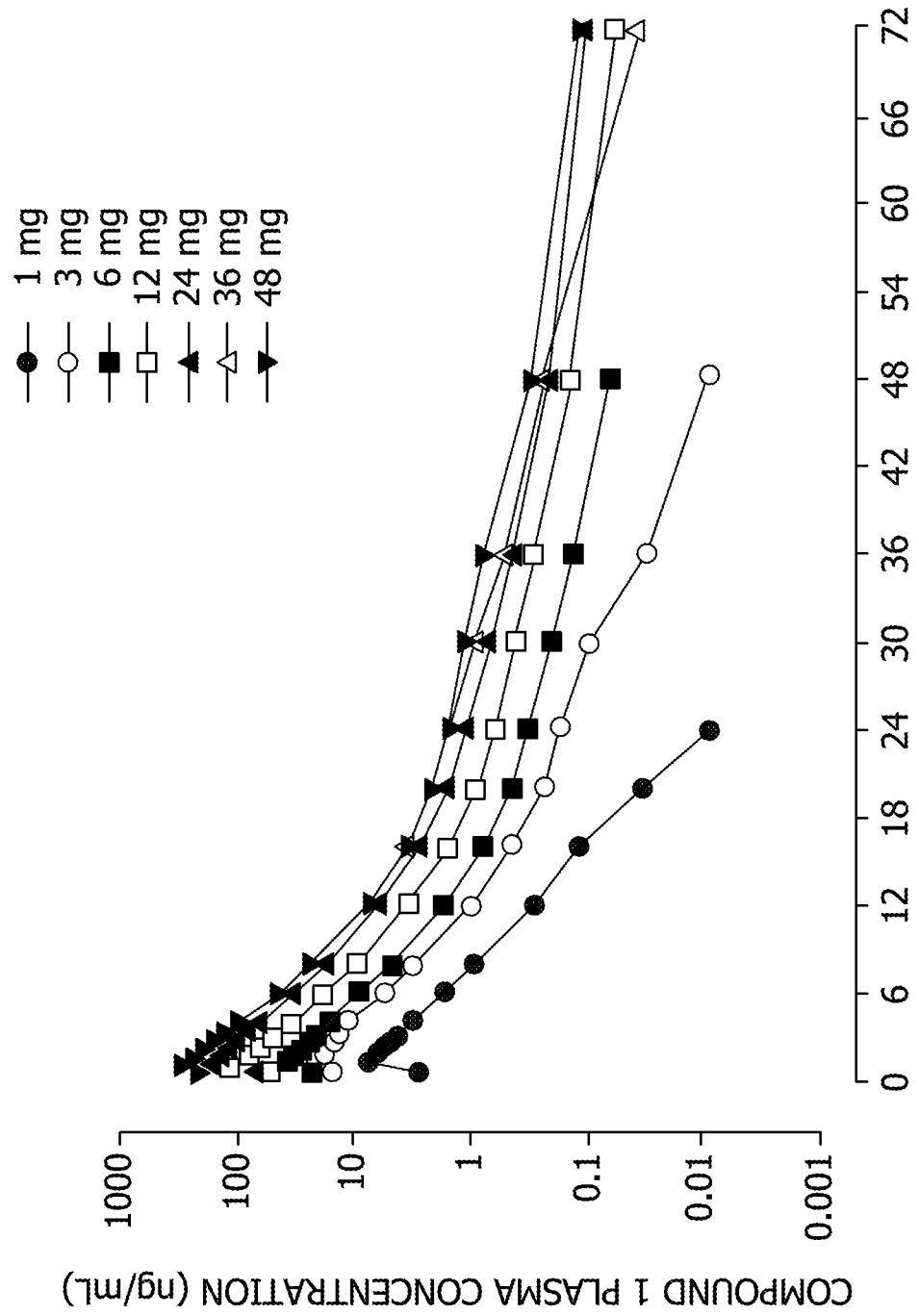

1 mg
3 mg
6 mg
12 mg
24 mg
36 mg
48 mg
1000
100
10
1
0.1
0.01
0.001
COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
6
12
18
24
30
36
42
48
54
60
66
72
TIME (hr)

FIG. 32B

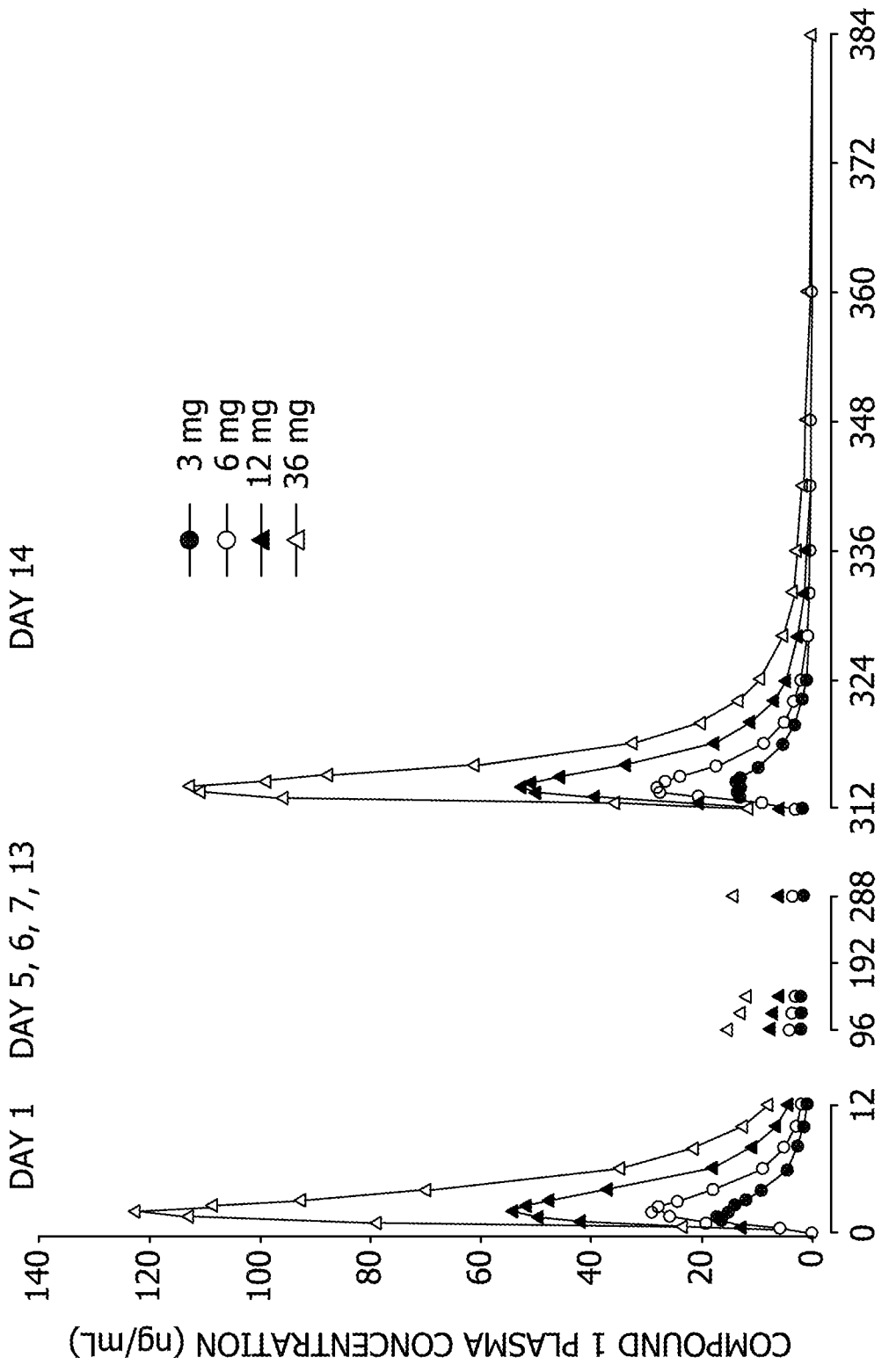

COMPOUND 1 PLASMA CONCENTRATION (ng/mL)
0
20
40
60
80
100
120
140
DAY 1
DAY 5, 6, 7, 13
DAY 14
0
12
96
192
288
312
324
336
348
360
372
384
TIME (hr)
3 mg
6 mg
12 mg
36 mg

FIG. 33

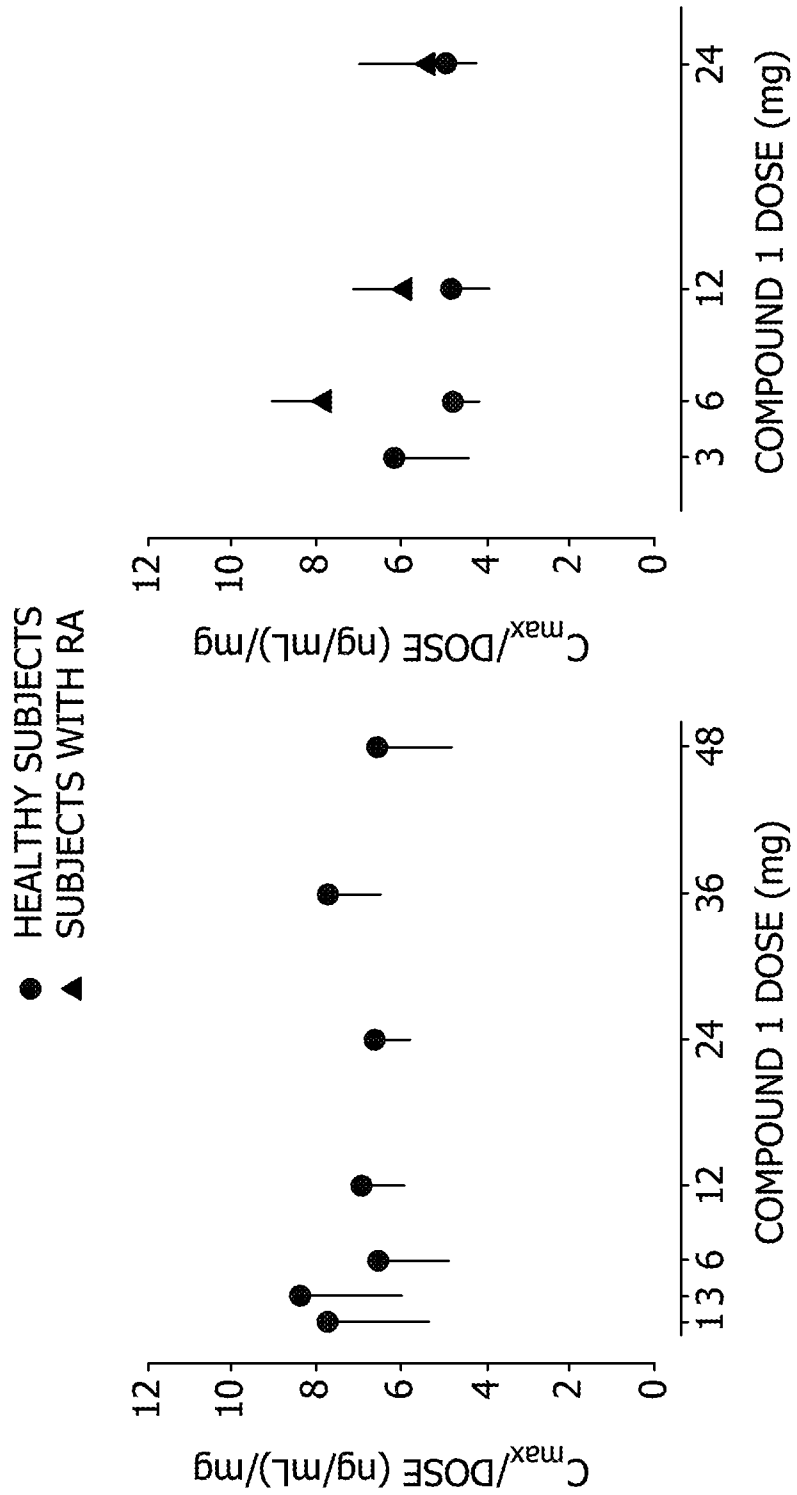


FIG. 34A

FIG. 34B

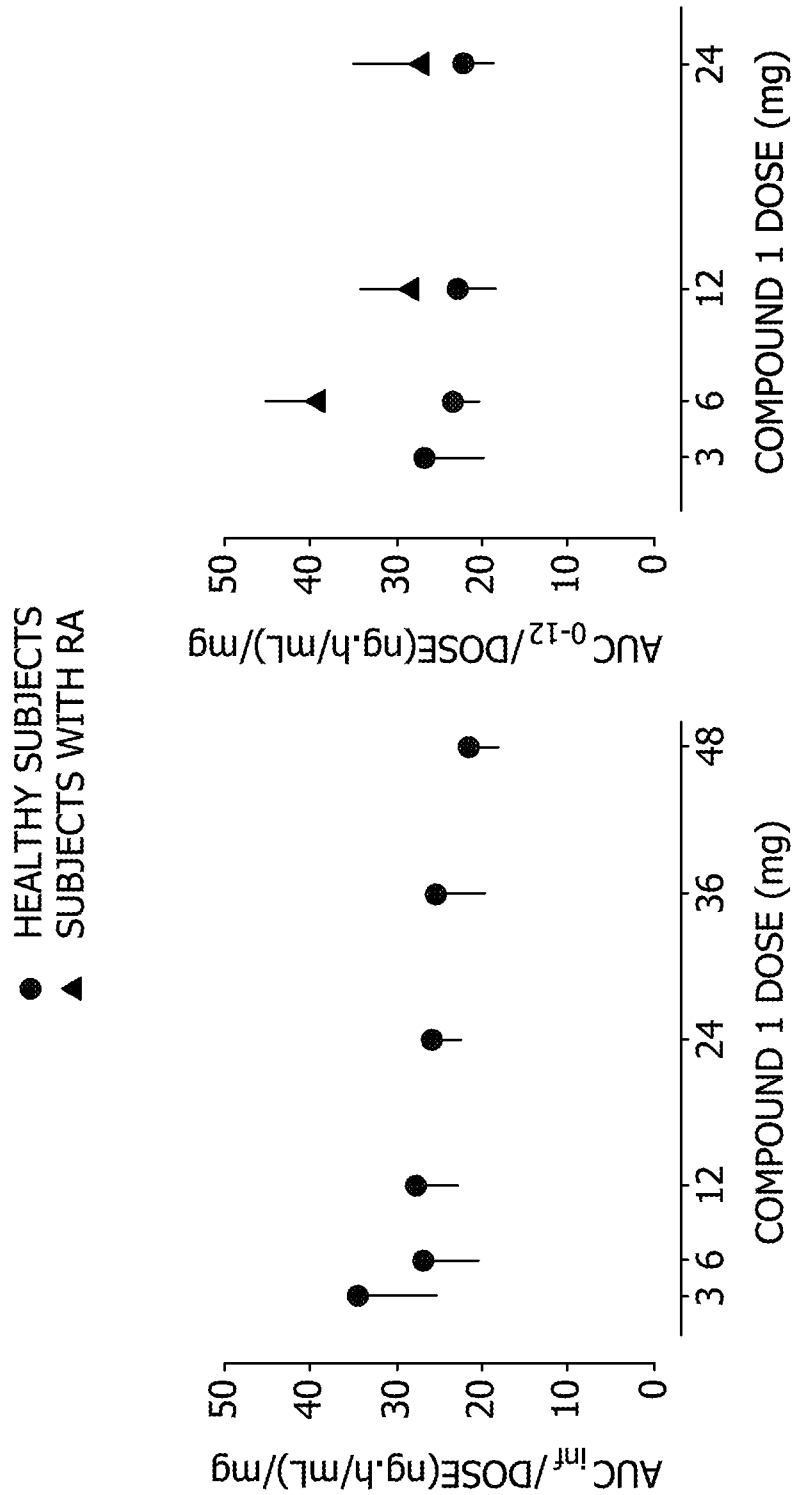


FIG. 34C

FIG. 34D

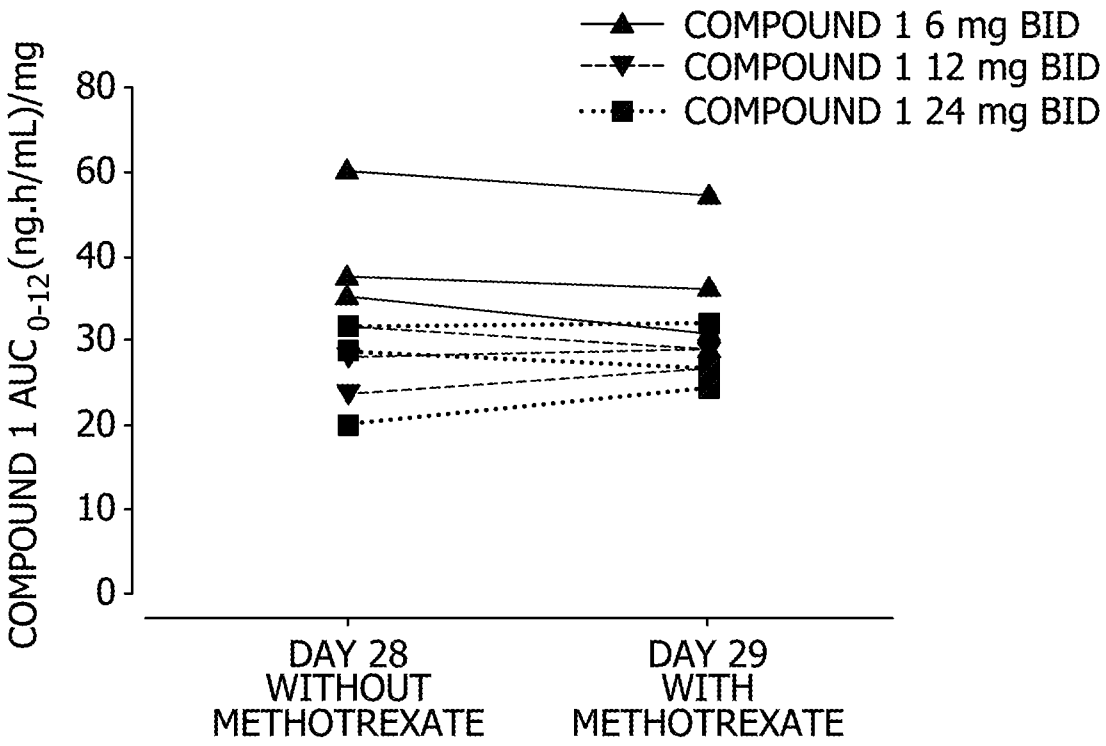


FIG. 35A

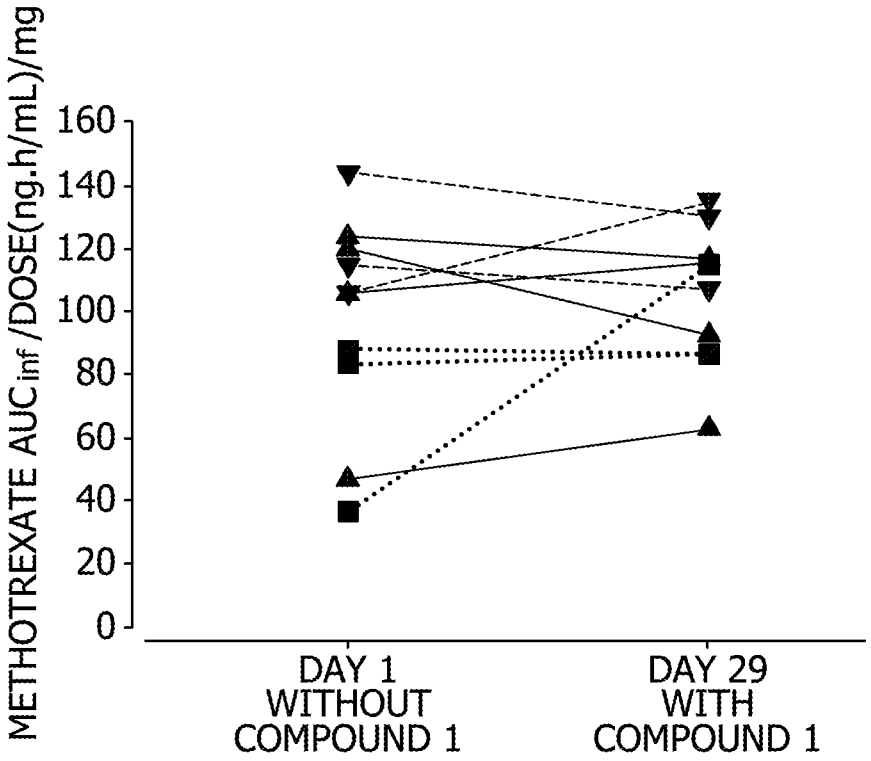


FIG. 35B

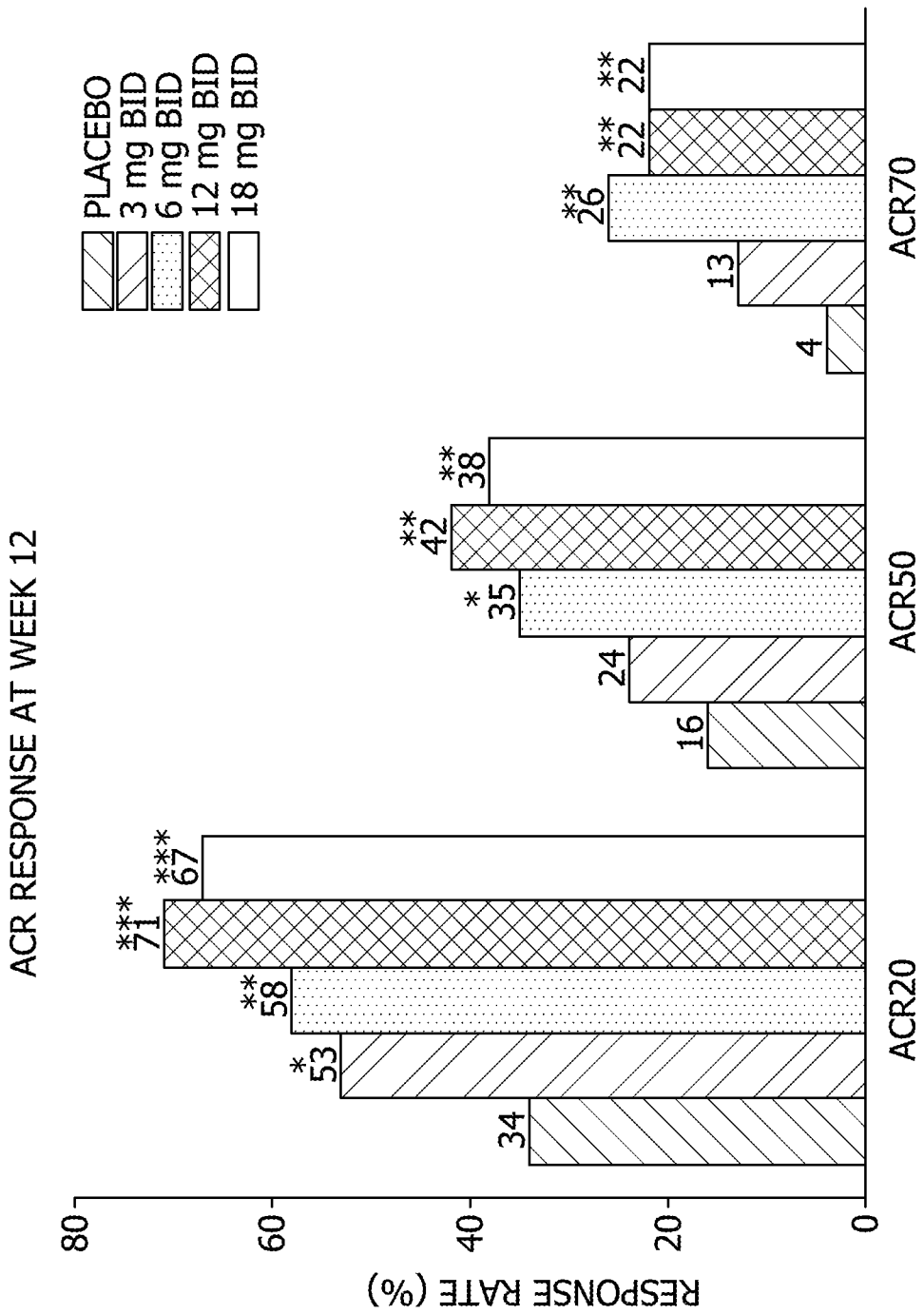

ACR RESPONSE AT WEEK 12
PLACEBO
3 mg BID
6 mg BID
12 mg BID
18 mg BID
RESPONSE RATE (%)
0
20
40
60
80
ACR20
ACR50
ACR70
34
*53
**58
***71
***67
16
24
*35
**42
**38
4
13
**26
**22
**22

FIG. 36A

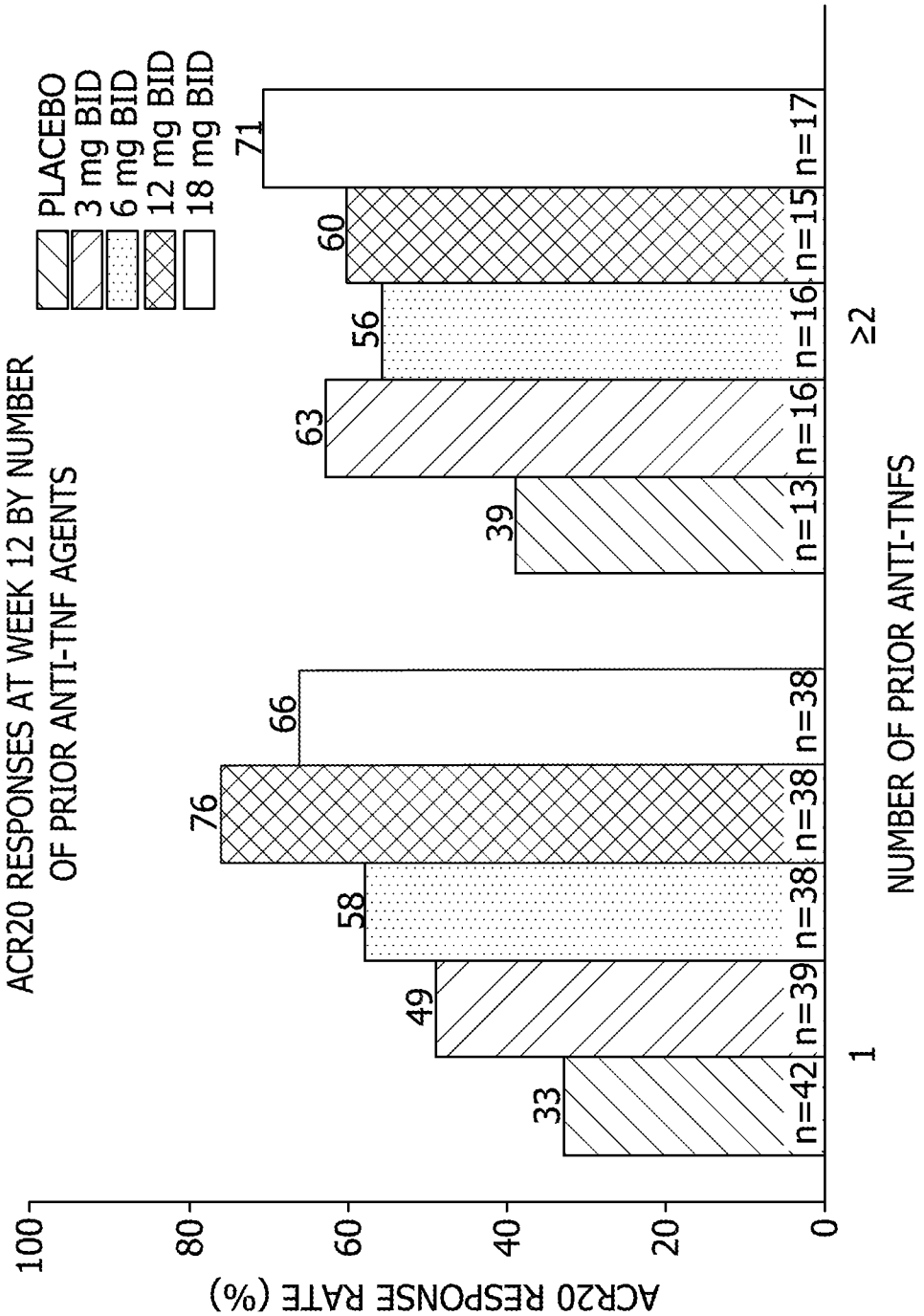

ACR20 RESPONSES AT WEEK 12 BY NUMBER OF PRIOR ANTI-TNF AGENTS
PLACEBO
3 mg BID
6 mg BID
12 mg BID
18 mg BID
ACR20 RESPONSE RATE (%)
0
20
40
60
80
100
33
49
58
76
66
39
63
56
60
71
n=42
n=39
n=38
n=38
n=38
n=13
n=16
n=16
n=15
n=17
1
≥2
NUMBER OF PRIOR ANTI-TNFS

FIG. 36B

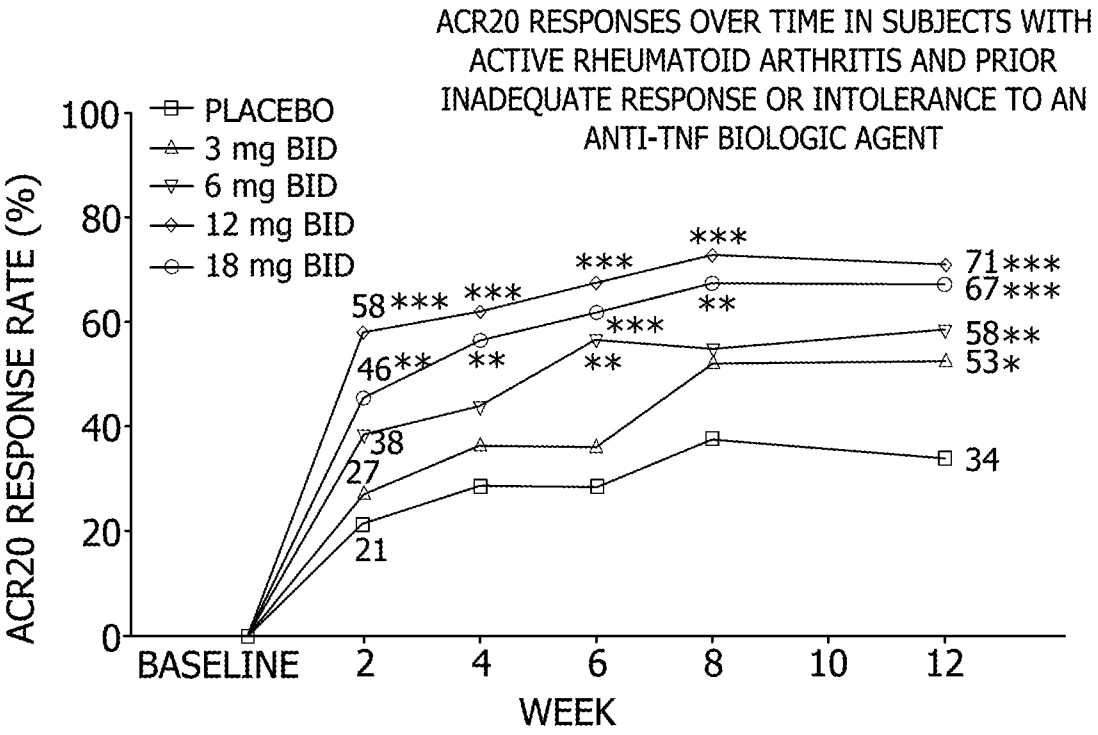


FIG. 37A

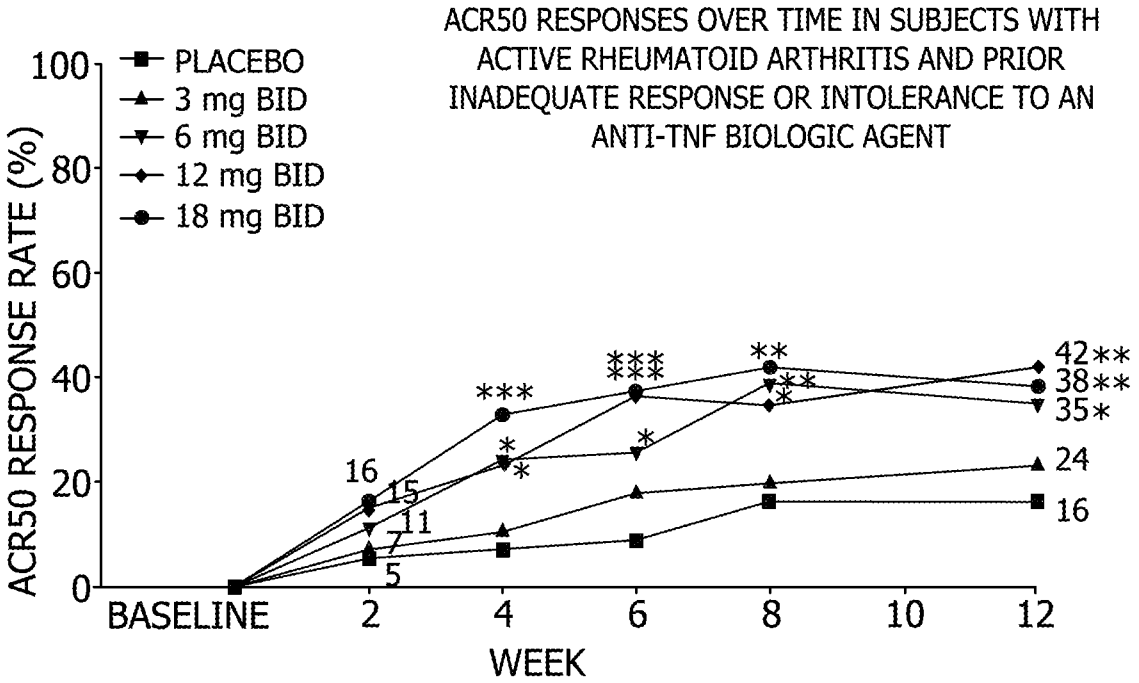


FIG. 37B

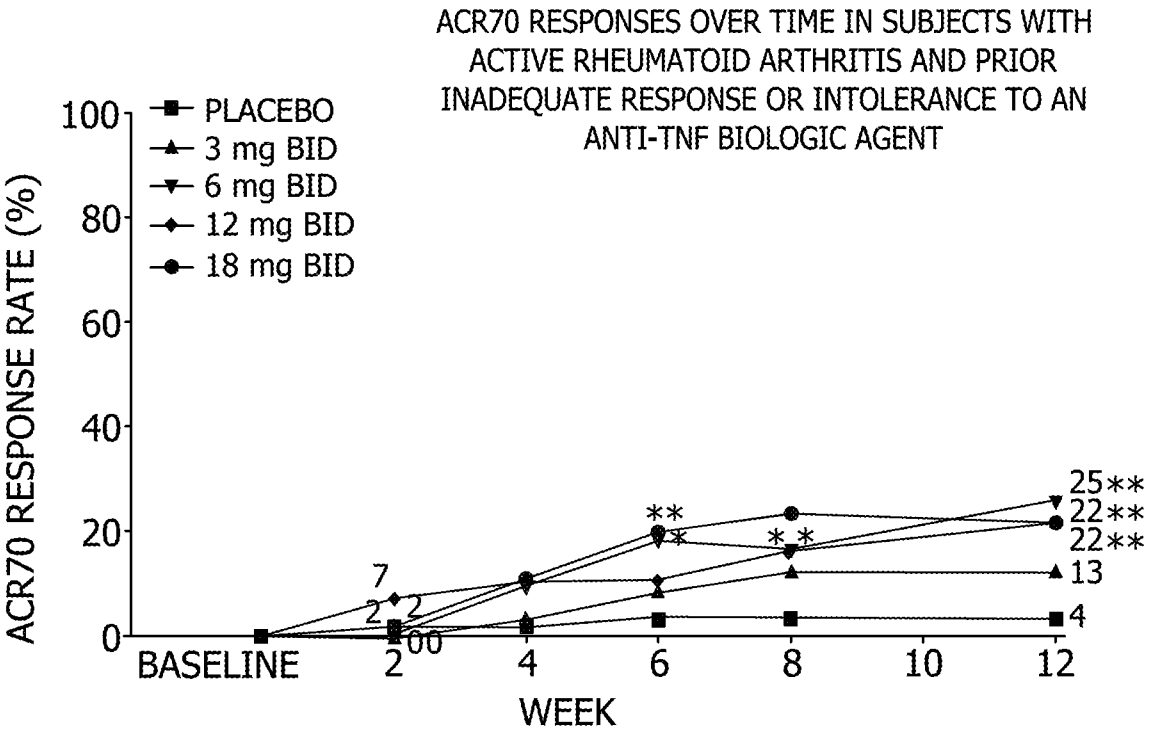


FIG. 37C

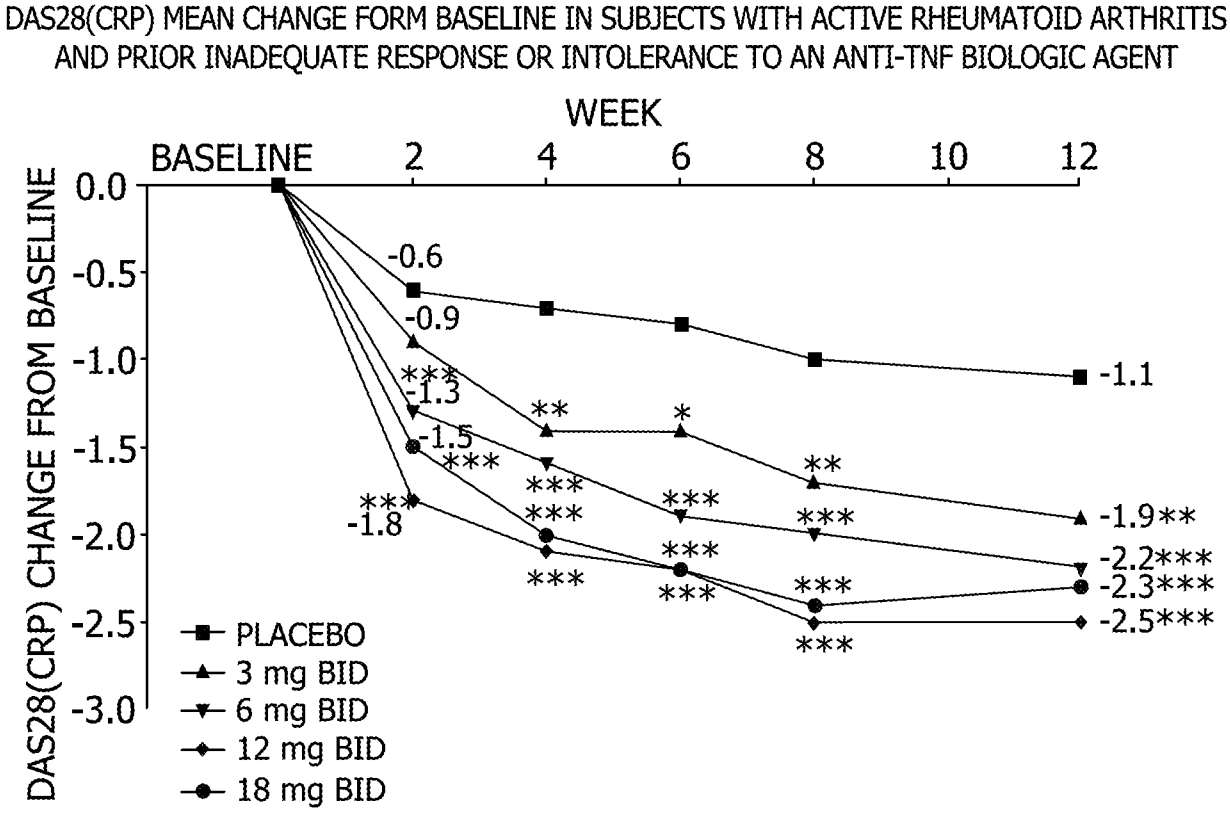


FIG. 37D

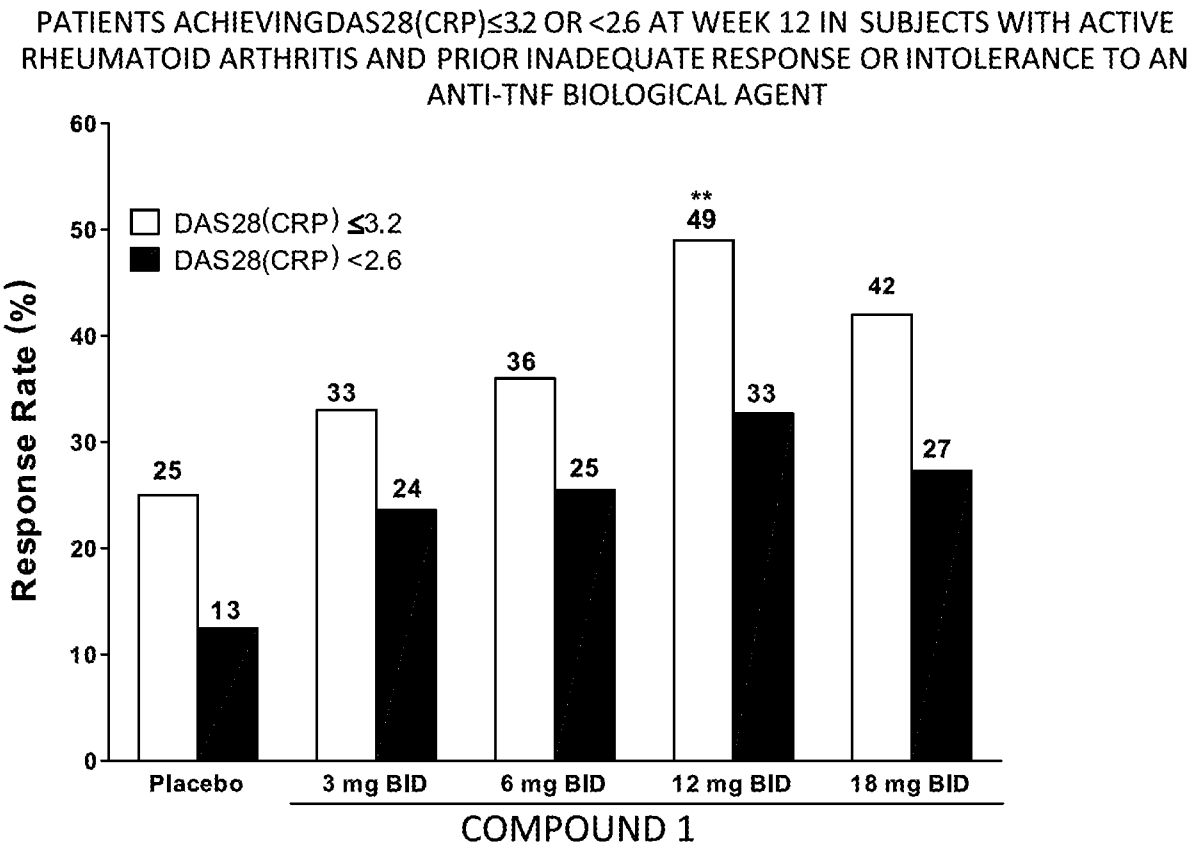


FIG. 37E

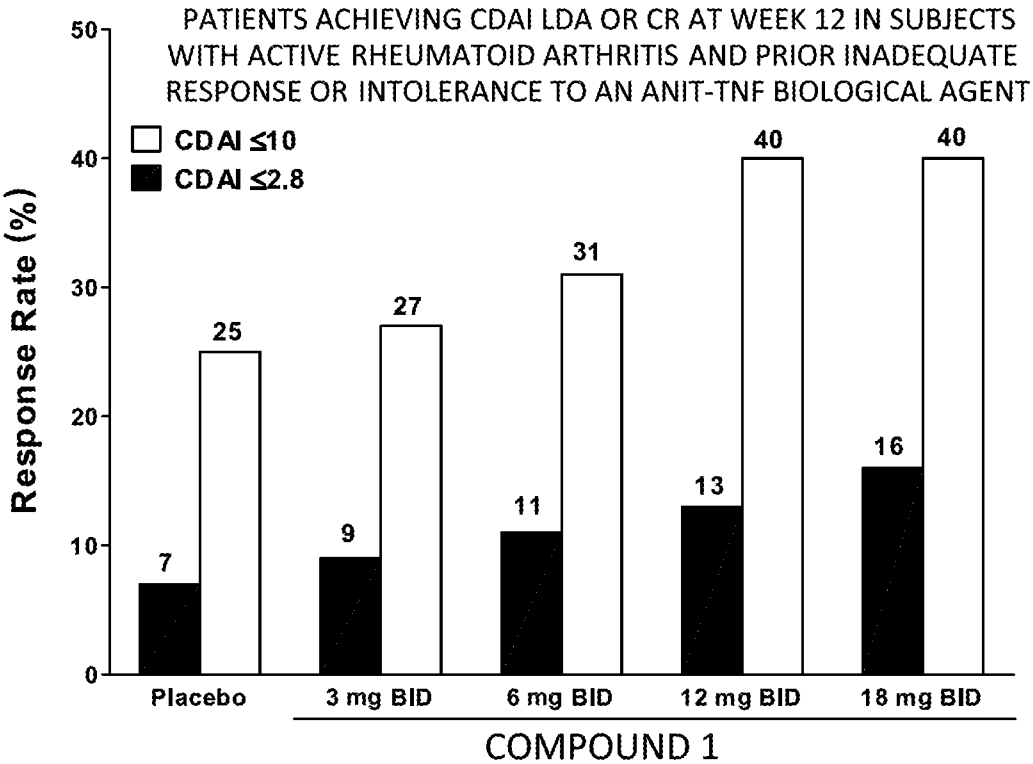


FIG. 37F

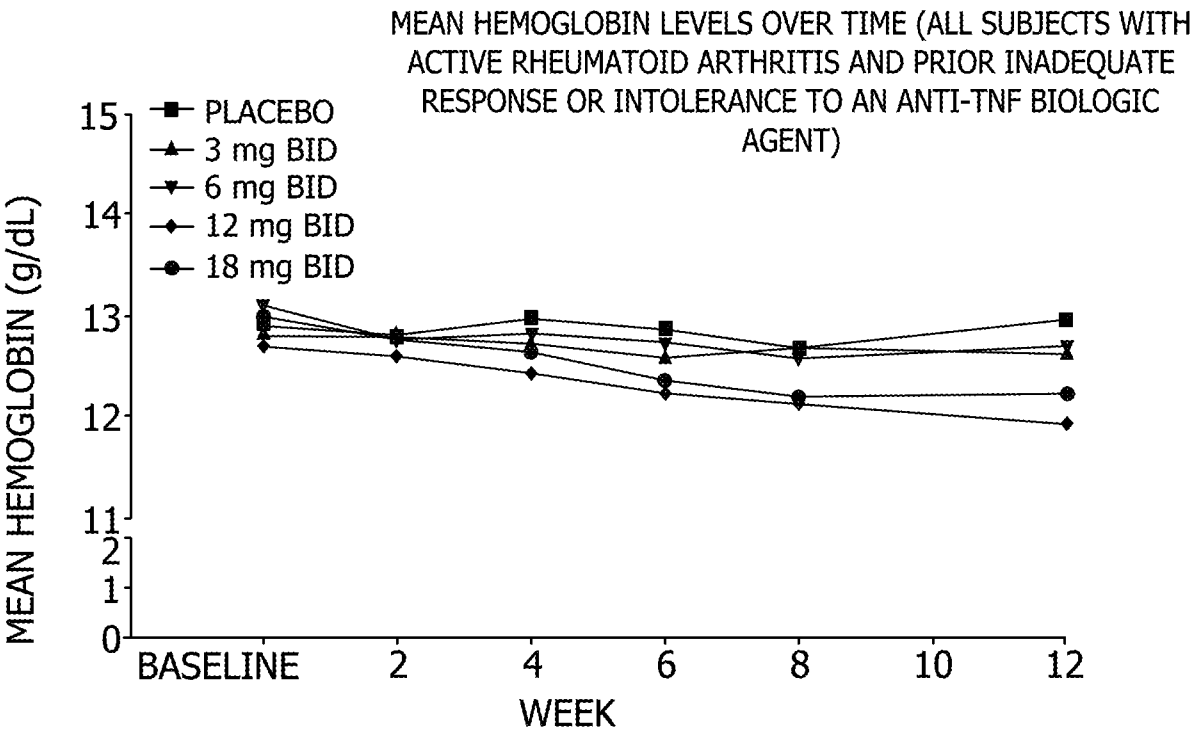


FIG. 38A

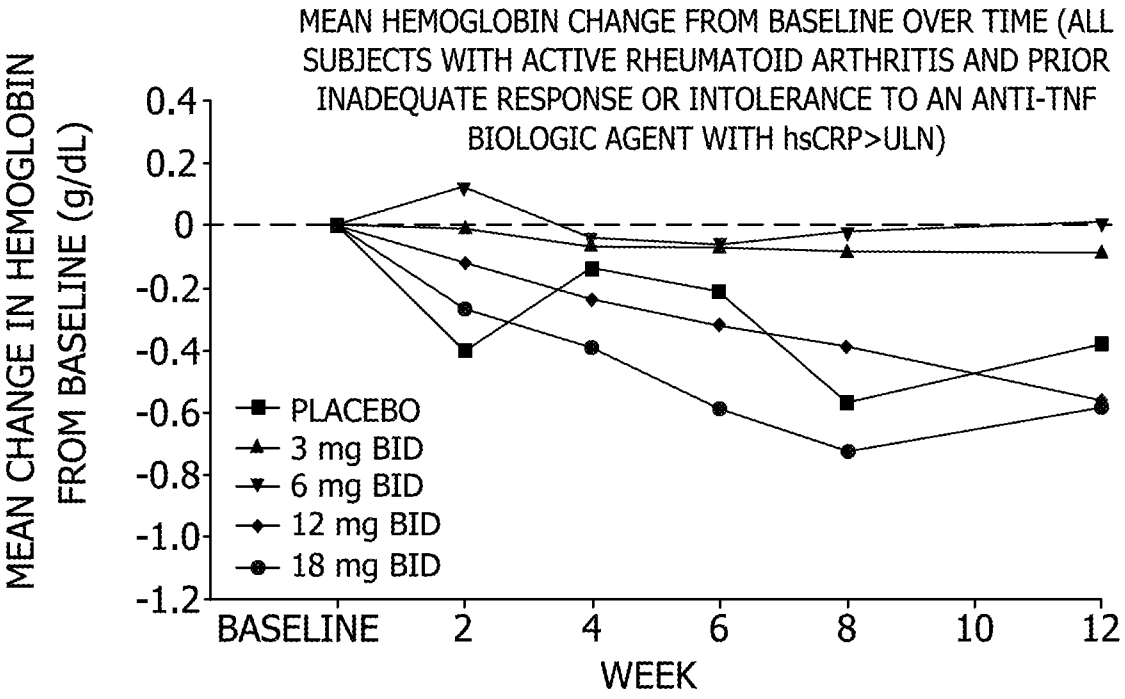


FIG. 38B

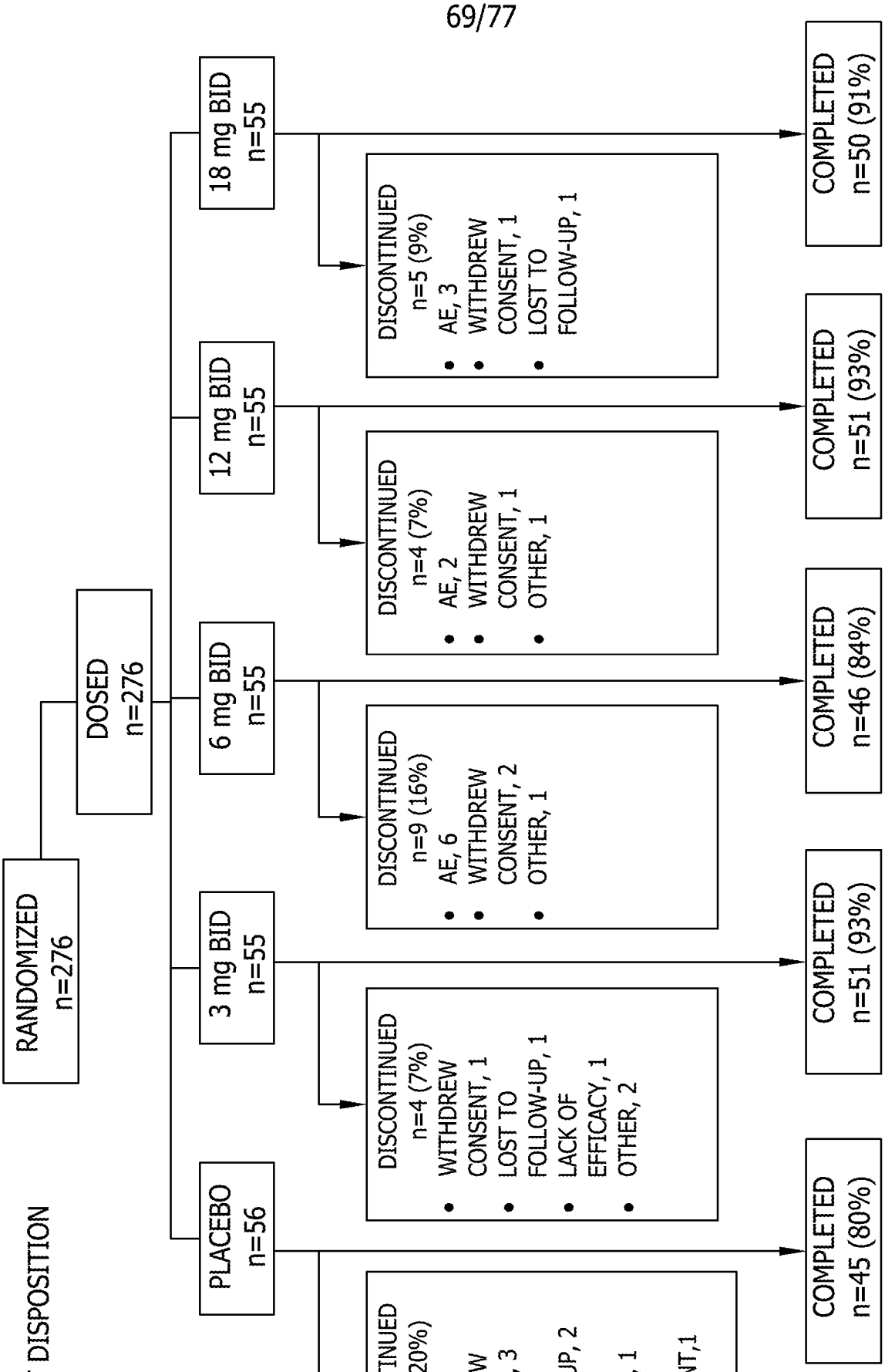

PATIENT DISPOSITION
RANDOMIZED n=276
DOSED n=276
PLACEBO n=56
3 mg BID n=55
6 mg BID n=55
12 mg BID n=55
18 mg BID n=55
DISCONTINUED n=11 (20%)
• AE, 2
• WITHDREW CONSENT, 3
• LOST TO FOLLOW-UP, 2
• LACK OF EFFICACY, 1
• NOT COMPLIANT,1
• OTHER, 2
DISCONTINUED n=4 (7%)
• WITHDREW CONSENT, 1
• LOST TO FOLLOW-UP, 1
• LACK OF EFFICACY, 1
• OTHER, 2
DISCONTINUED n=9 (16%)
• AE, 6
• WITHDREW CONSENT, 2
• OTHER, 1
DISCONTINUED n=4 (7%)
• AE, 2
• WITHDREW CONSENT, 1
• OTHER, 1
DISCONTINUED n=5 (9%)
• AE, 3
• WITHDREW CONSENT, 1
• LOST TO FOLLOW-UP, 1
COMPLETED n=45 (80%)
COMPLETED n=51 (93%)
COMPLETED n=46 (84%)
COMPLETED n=51 (93%)
COMPLETED n=50 (91%)

FIG. 39

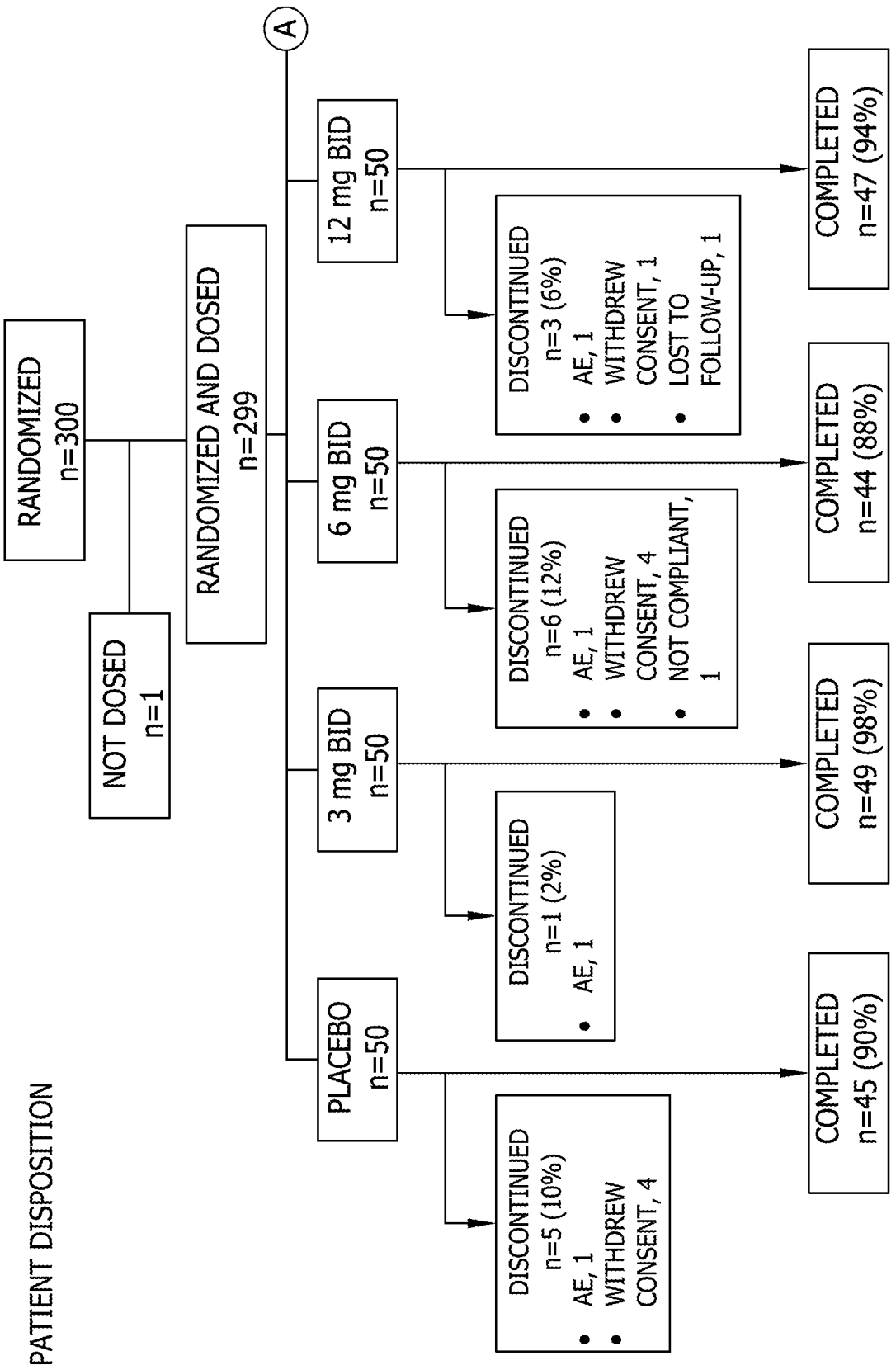

PATIENT DISPOSITION
RANDOMIZED n=300
NOT DOSED n=1
RANDOMIZED AND DOSED n=299
A
PLACEBO n=50
3 mg BID n=50
6 mg BID n=50
12 mg BID n=50
DISCONTINUED n=5 (10%)
AE, 1
WITHDREW CONSENT, 4
DISCONTINUED n=1 (2%)
AE, 1
DISCONTINUED n=6 (12%)
AE, 1
WITHDREW CONSENT, 4
NOT COMPLIANT, 1
DISCONTINUED n=3 (6%)
AE, 1
WITHDREW CONSENT, 1
LOST TO FOLLOW-UP, 1
COMPLETED n=45 (90%)
COMPLETED n=49 (98%)
COMPLETED n=44 (88%)
COMPLETED n=47 (94%)

FIG. 40A

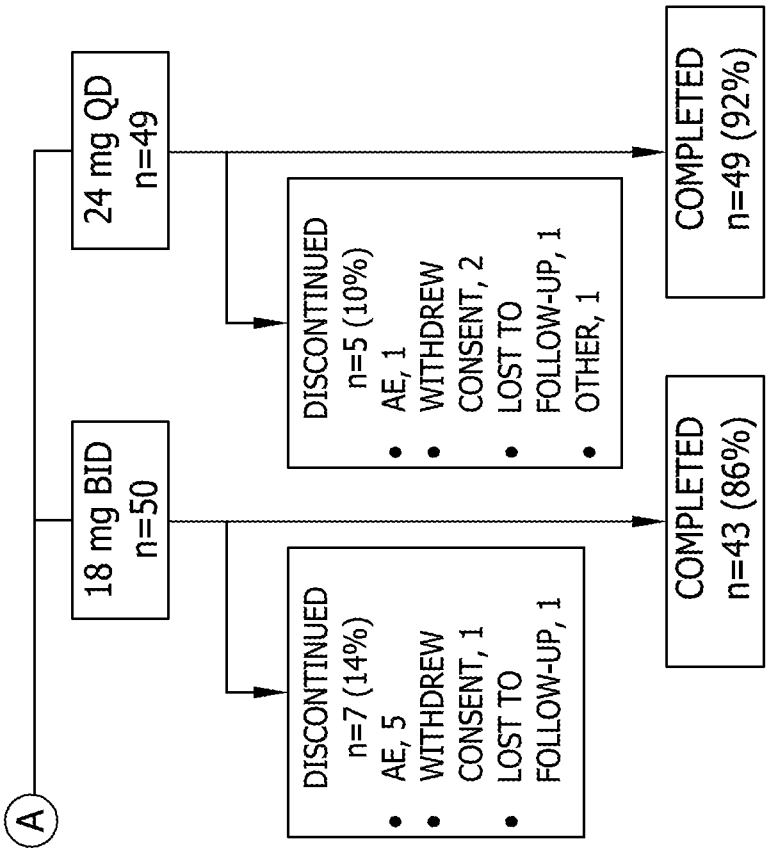

A
18 mg BID n=50
24 mg QD n=49
DISCONTINUED n=7 (14%)
• AE, 5
• WITHDREW CONSENT, 1
• LOST TO FOLLOW-UP, 1
DISCONTINUED n=5 (10%)
• AE, 1
• WITHDREW CONSENT, 2
• LOST TO FOLLOW-UP, 1
• OTHER, 1
COMPLETED n=43 (86%)
COMPLETED n=49 (92%)

FIG. 40B

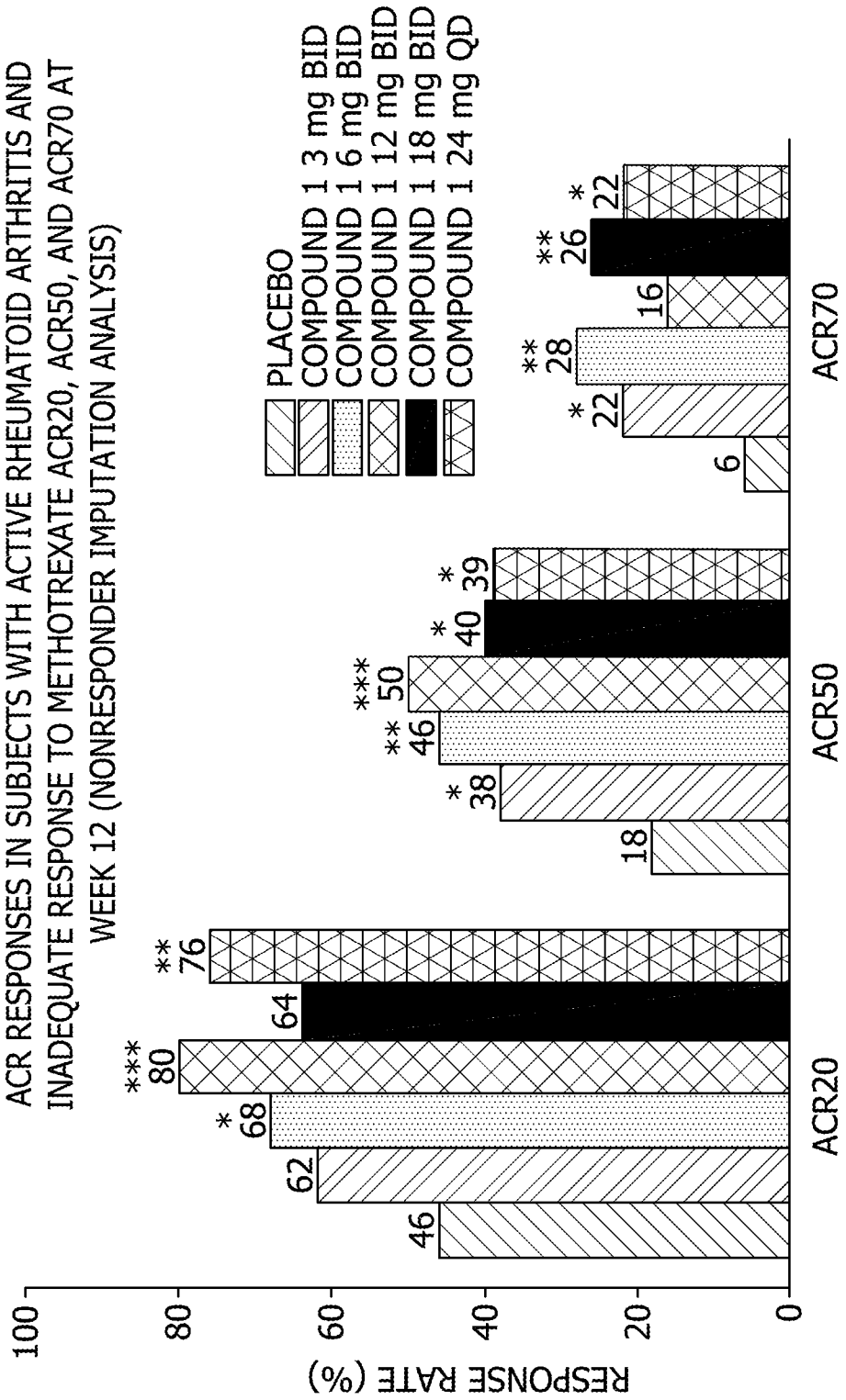

ACR RESPONSES IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE ACR20, ACR50, AND ACR70 AT WEEK 12 (NONRESPONDER IMPUTATION ANALYSIS)
PLACEBO
COMPOUND 1 3 mg BID
COMPOUND 1 6 mg BID
COMPOUND 1 12 mg BID
COMPOUND 1 18 mg BID
COMPOUND 1 24 mg QD
RESPONSE RATE (%)
0
20
40
60
80
100
46
62
*** 80
* 68
** 76
64
18
* 38
** 46
*** 50
* 40
* 39
6
* 22
** 28
16
** 26
* 22
ACR20
ACR50
ACR70

FIG. 41

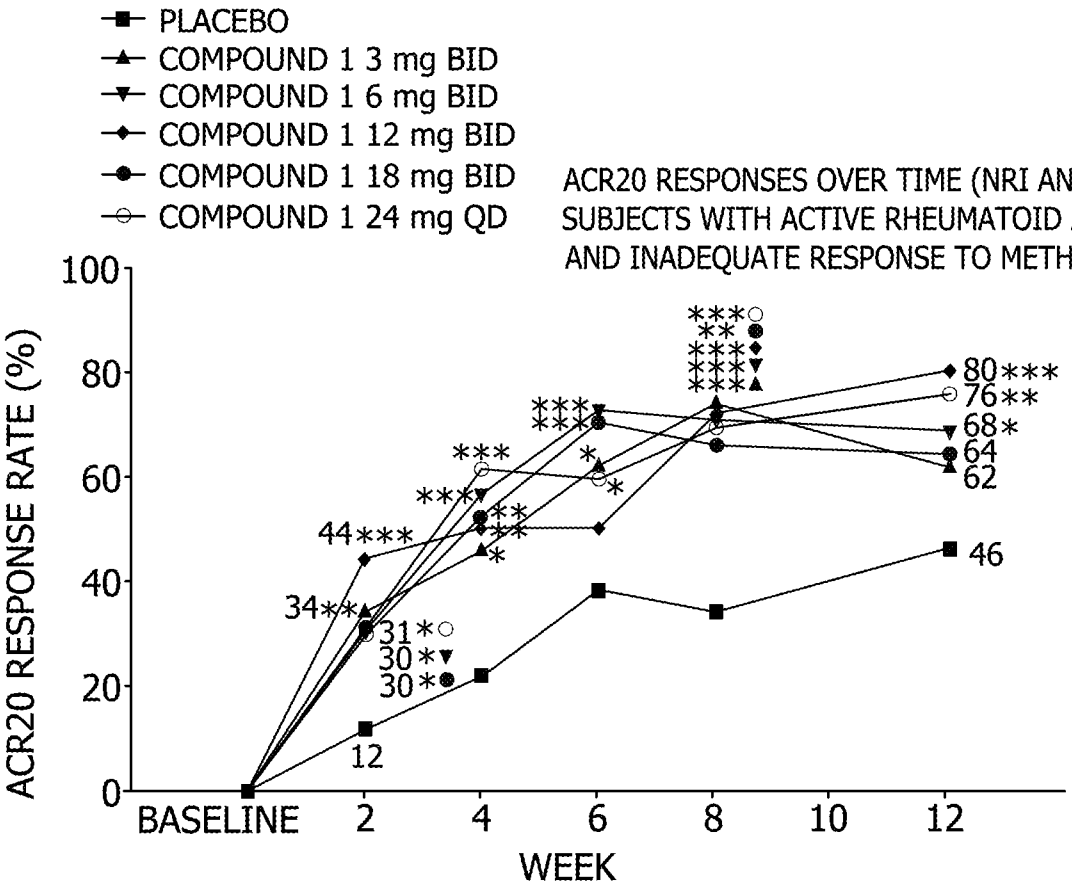


FIG. 42A

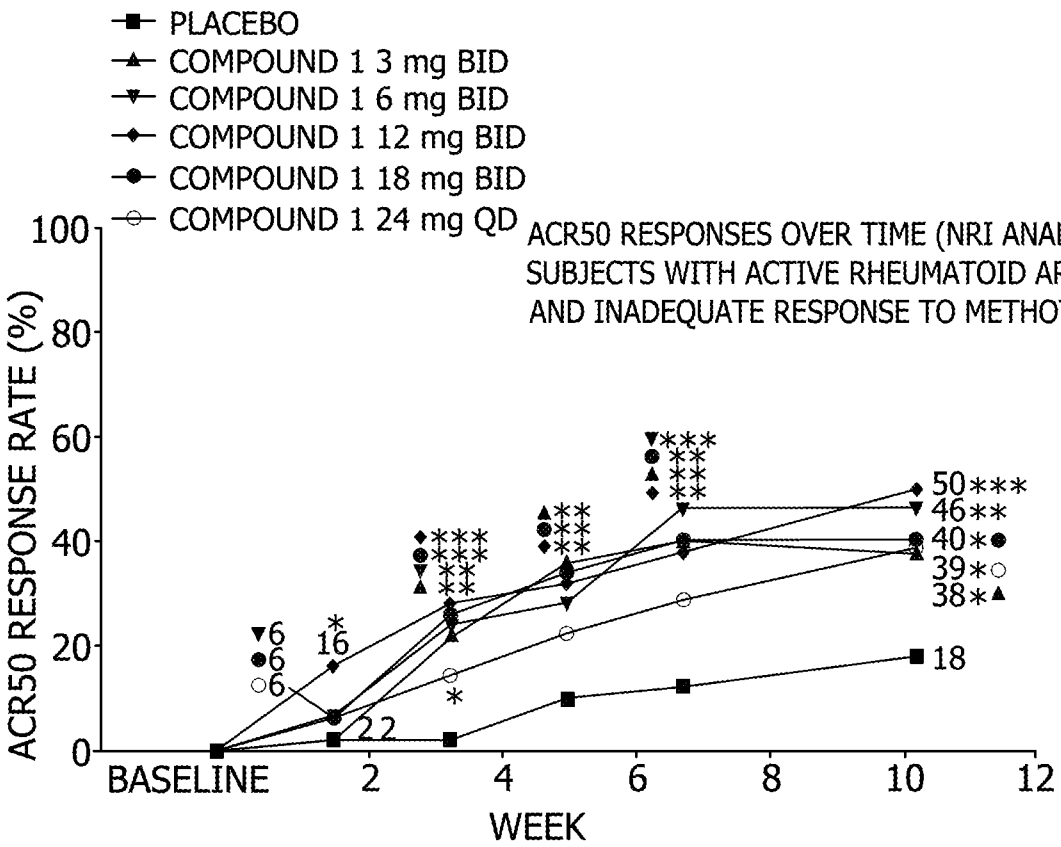


FIG. 42B

ACR70 RESPONSES OVER TIME (NRI ANALYSIS) IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE

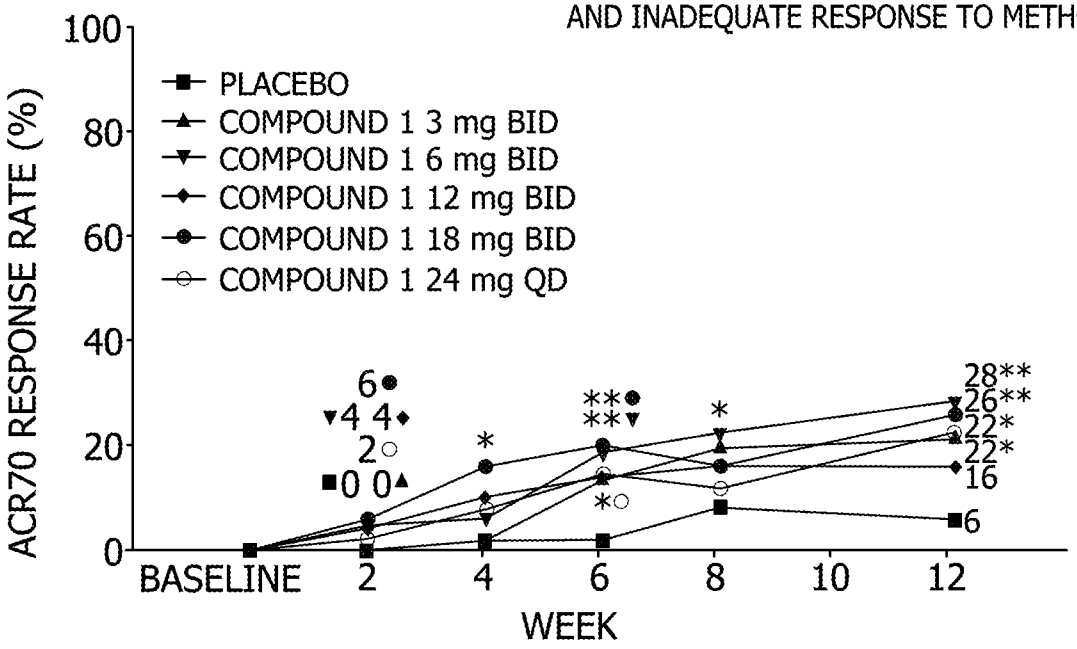


FIG. 42C

DAS28(CRP) MEAN CHANGE FROM BASELINE OVER TIME (OBSERVED CASES) IN SUBJECTS WITH ACTIVE RHEMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE

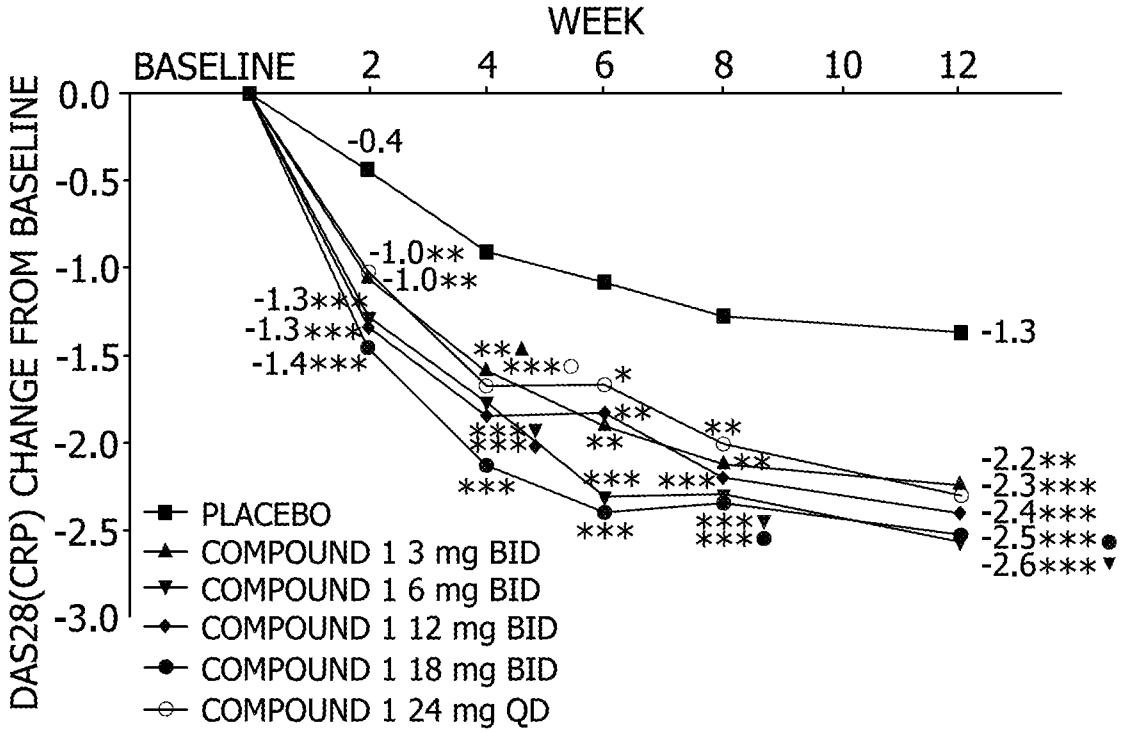


FIG. 42D

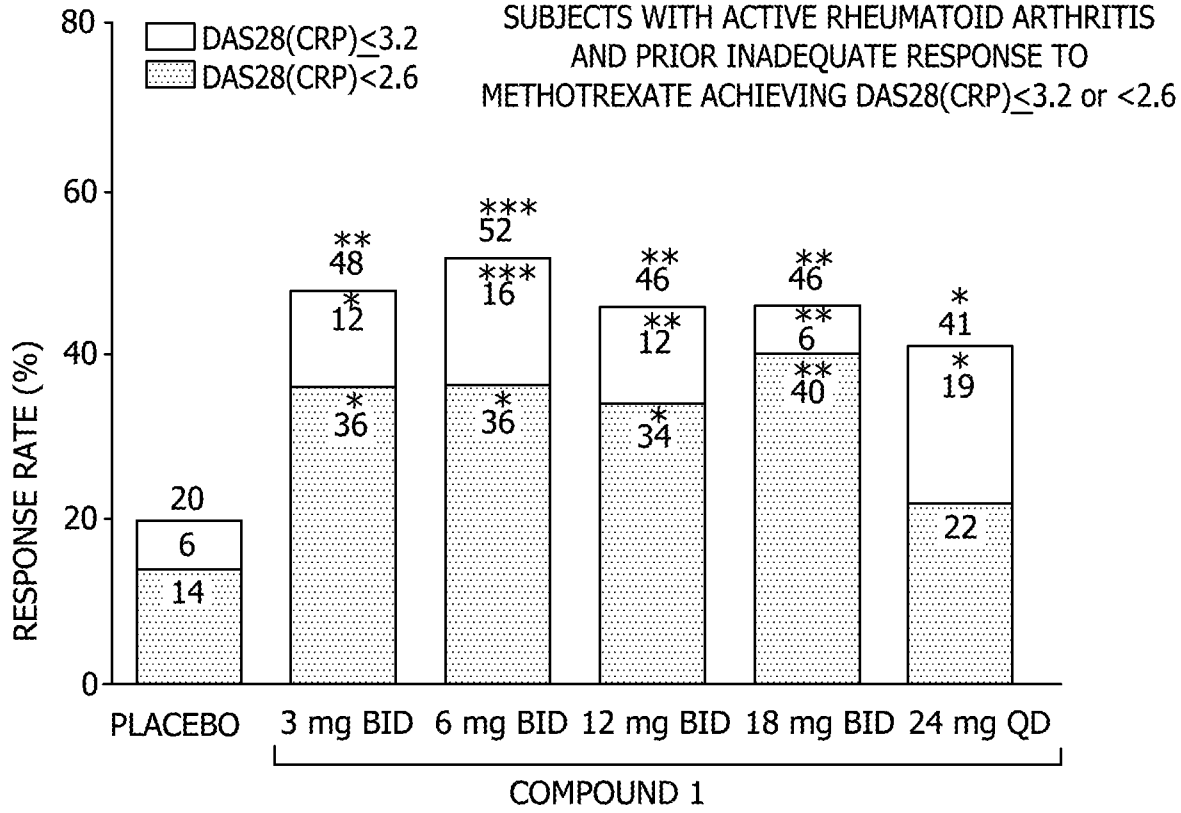


FIG. 43A

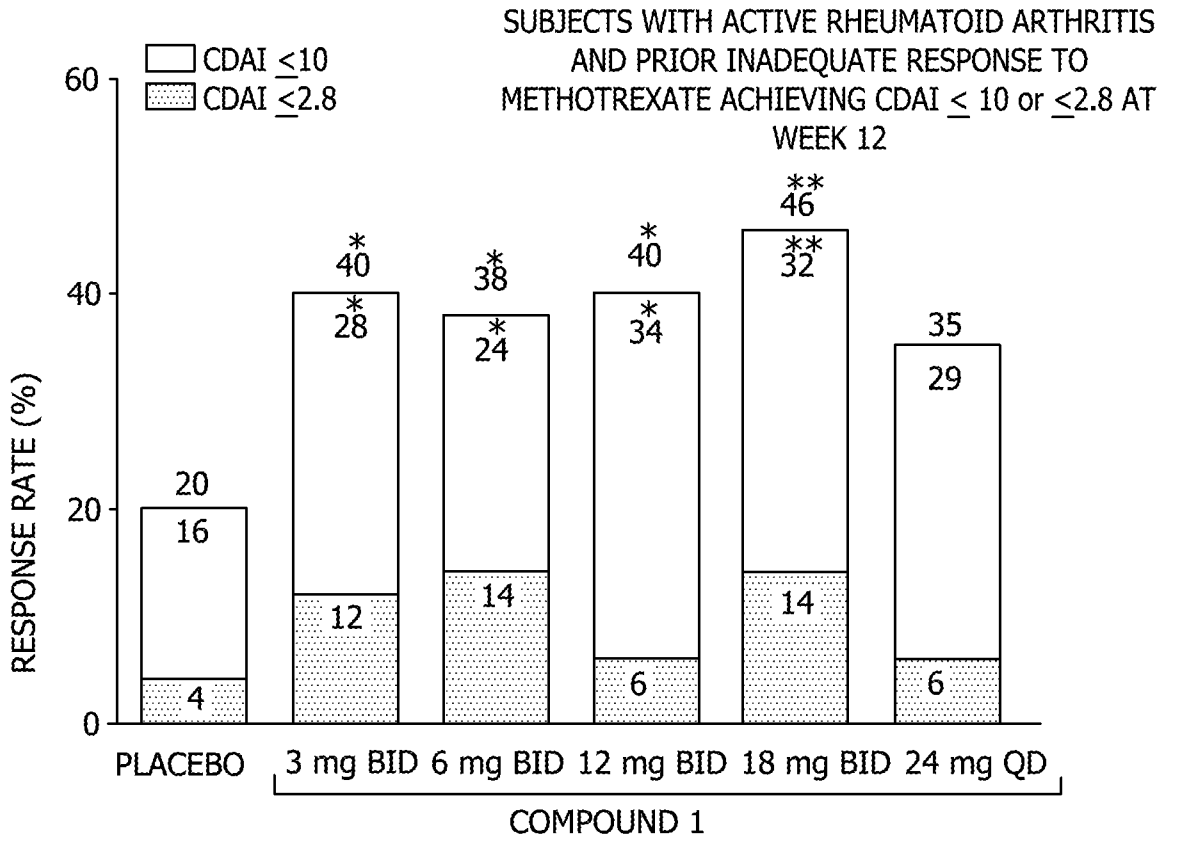


FIG. 43B

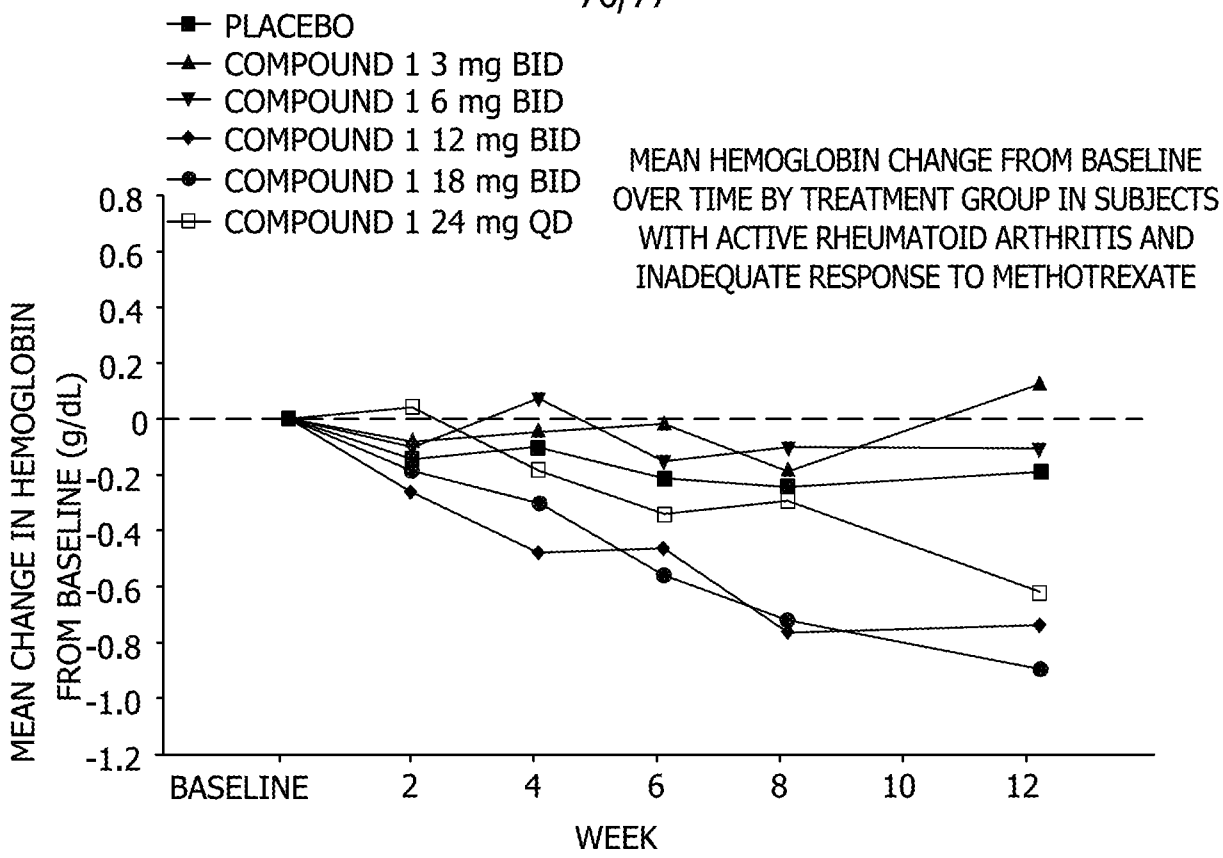


FIG. 44A

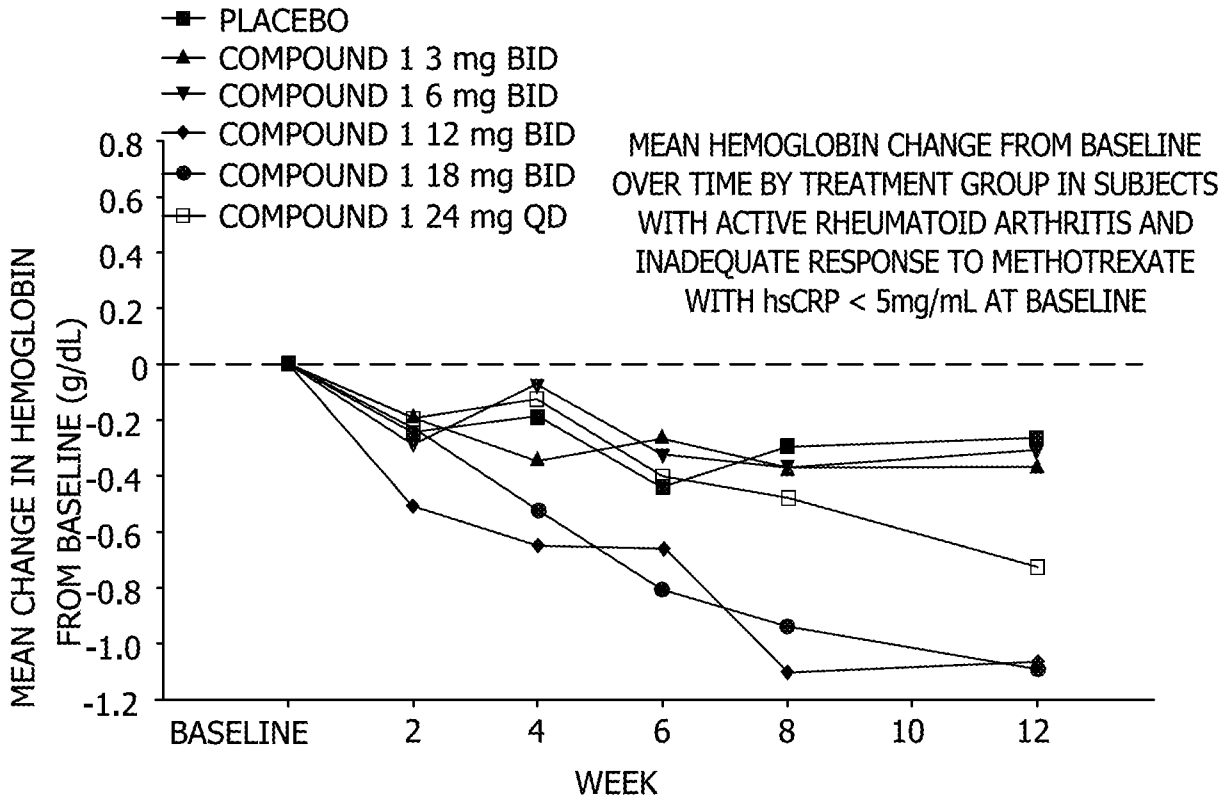


FIG. 44B

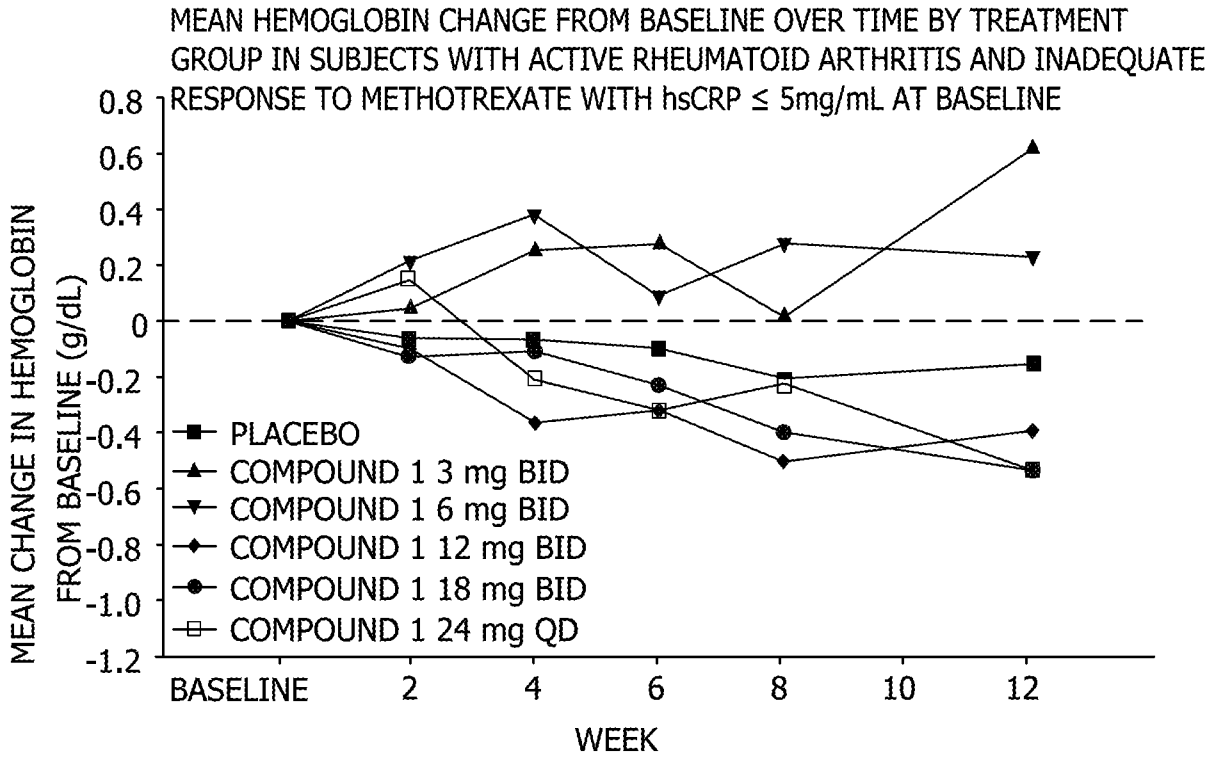

MEAN HEMOGLOBIN CHANGE FROM BASELINE OVER TIME BY TREATMENT GROUP IN SUBJECTS WITH ACTIVE RHEUMATOID ARTHRITIS AND INADEQUATE RESPONSE TO METHOTREXATE WITH hsCRP ≤ 5mg/mL AT BASELINE
MEAN CHANGE IN HEMOGLOBIN FROM BASELINE (g/dL)
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
PLACEBO
COMPOUND 1 3 mg BID
COMPOUND 1 6 mg BID
COMPOUND 1 12 mg BID
COMPOUND 1 18 mg BID
COMPOUND 1 24 mg QD
BASELINE
2
4
6
8
10
12
WEEK

FIG. 44C