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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 December 2018 (27.12.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/237207 A1

(51) International Patent Classification:
A61K 9/20 (2006.01) *A61K 31/454* (2006.01)
A61K 9/28 (2006.01)

(21) International Application Number:
PCT/US2018/038853

(22) International Filing Date:
21 June 2018 (21.06.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/523,204 21 June 2017 (21.06.2017) 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, JO, JP, KE, KG, KH, 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.

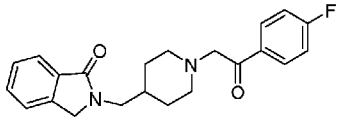
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

WO 2018/237207 A1

(54) Title: GASTRO-RESISTANT CONTROLLED RELEASE ORAL DOSAGE FORMS



(I)

(57) Abstract: This disclosure relates to gastro-resistant, controlled release dosage forms comprising Compound (I): (I), or a pharmaceutically acceptable salt and/or solvate thereof, the pharmacokinetic properties of these dosage forms, and the preparation of the same. The novel dosage forms disclosed herein are useful in reducing the risk of QT prolongation in a subject and in treating a disorder in a subject in need thereof, e.g., a subject diagnosed with schizophrenia, for example, in treating the negative symptoms in a subject diagnosed with schizophrenia having the CYP2D6 EM genotype.

GASTRO-RESISTANT CONTROLLED RELEASE ORAL DOSAGE FORMS

RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 62/523,204, filed June 21, 2017. The contents of which are incorporated herein by reference in their entirety.

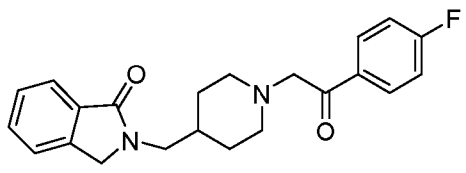
FIELD OF THE DISCLOSURE

[0002] The present disclosure relates generally to oral gastro-resistant (GR) controlled release (CR) dosage forms that reduce the risk of QT prolongation in patients treated with the compound identified as 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2), and to the use of these dosage forms for treating schizophrenia and other diseases.

BACKGROUND

[0003] The QT interval is a measurement of the duration of ventricular de- and repolarization. Prolongation of the QT interval, referred to as QT prolongation, can result in increased risk for ventricular arrhythmias, including torsades de pointes (TdP). Since a number of drugs have been shown to induce QT prolongation, development of new drugs typically includes assessment of their QT prolongation potential.

[0004] An investigational medicine, roluperidone hydrochloride, with the code name MIN-101 is being developed by Minerva Neurosciences, Inc. (Waltham, MA) for treating negative symptoms in schizophrenia patients. The active ingredient in MIN-101 (previously known as CYR-101 and MT-210) has the chemical name 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2). Formula I below shows the structure of the free base (Compound (I)):



(I).

[0005] As disclosed in US Patent No. 9,458,130, the contents of which are incorporated herein in their entirety, QT prolongation in patients treated with MIN-101 has been observed and appears to be related to plasma levels of Compound (I) and more specifically to a metabolite identified as BFB-520. The '130 patent discloses that QT prolongation induced by administration of MIN-101 can be reduced by administering this agent in a modified release (MR) formulation that provides a maximum plasma concentration (C_{max}) of Compound (I) and BFB-520 below 80 ng/mL and 12 ng/mL, respectively. However, a need exists for a formulation that further reduces the potential for QT prolongation after oral administration of MIN-101 in either a fasted state or a fed state, while maintaining a therapeutically effective level of Compound (I) throughout a dosing interval.

SUMMARY

[0006] The present disclosure is based, in part, on the finding that minimizing the release of Compound (I) during the first four hours after oral administration of a dosage form comprising Compound (I) is a key factor for maintaining low plasma levels of BFB-520.

[0007] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 2 mg to about 200 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent.

[0008] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 2 mg to about 200 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 4 hours and about 22 hours.

[0009] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent.

[0010] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 1 hours and about 22 hours.

[0011] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 1.5 hours and about 22 hours.

[0012] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 2 hours and about 22 hours.

[0013] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 2.5 hours and about 22 hours.

[0014] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 3 hours and about 22 hours.

[0015] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 3.5 hours and about 22 hours.

[0016] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 4 hours and about 22 hours.

[0017] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising Compound (I), wherein the amount of Compound (I) is 4 mg to 8 mg, 8

mg to 16 mg, 16 mg to 32 mg, 32 mg to 40 mg, 40 mg to 64 mg, 64 mg to 80 mg, or 80 mg to 100 mg.

[0018] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising Compound (I), wherein the amount of Compound (I) is 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, or 100 mg.

[0019] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising Compound (I), wherein the amount of Compound (I) is 4 mg, 8 mg, 16 mg, 24 mg, 32 mg, 40 mg, 64 mg, 80 mg, 96 mg, or 100 mg.

[0020] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 32 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent.

[0021] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 32 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 4 hours and about 22 hours.

[0022] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 64 of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent.

[0023] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

i. about 64 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent;

wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 4 hours and about 22 hours.

[0024] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the AUC_{0-4H} of Compound (I) is less than about 68 h*ng/mL.

[0025] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 16 ng/mL.

[0026] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 17 ng/mL.

[0027] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 18 ng/mL.

[0028] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 19 ng/mL.

[0029] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 20 ng/mL.

[0030] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 21 ng/mL.

[0031] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 22 ng/mL.

[0032] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the C_{max} of Compound (I) is less than about 23 ng/mL.

[0033] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the $AUC_{0\text{-}24hr}$ of Compound (I) is between about 50 h*ng/mL to about 400 h*ng/mL.

[0034] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the $AUC_{0\text{-}24hr}$ of Compound (I) is between about 75 h*ng/mL to about 350 h*ng/mL.

[0035] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the $AUC_{0\text{-}24hr}$ of Compound (I) is between about 75 h*ng/mL to about 300 h*ng/mL.

[0036] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the $AUC_{0\text{-}24hr}$ of Compound (I) is between about 100 h*ng/mL to about 300 h*ng/mL.

[0037] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 32 mg and the plasma pharmacokinetic profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 3.0 ng/mL, below 2.5 ng/mL, below 2.0 ng/mL, below 1.5 ng/mL or below 1.0 ng/mL.

[0038] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 50 h*ng/mL.

[0039] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 60 h*ng/mL.

[0040] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 70 h*ng/mL.

[0041] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 80 h*ng/mL.

[0042] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 90 h*ng/mL.

[0043] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 100 h*ng/mL.

[0044] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 110 h*ng/mL.

[0045] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 120 h*ng/mL.

[0046] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}4H}$ of Compound (I) is less than about 130 h*ng/mL.

[0047] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the C_{max} of Compound (I) is less than about 36 ng/mL or less than about 25 ng/mL.

[0048] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the $AUC_{0\text{-}24hr}$ of Compound (I) is between about 200 h*ng/mL to about 600 h*ng/mL.

[0049] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage forms comprising Compound (I) disclosed herein, wherein the amount of Compound (I) is about 64 mg and the plasma pharmacokinetic profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 4.0 ng/mL, below 3.5 ng/mL, below 3.0 ng/mL, or below 2.5 ng/mL.

[0050] In one embodiment, the gastro-resistant, controlled release dosage forms disclosed herein are in the form of a tablet which comprises a core tablet and an enteric coating.

[0051] In one embodiment, the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein comprises Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, and a controlled release agent.

[0052] In one embodiment, the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein comprises Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, a controlled release agent, a filler, a glidant, and a lubricant.

[0053] In one embodiment, the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein comprises Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, a controlled release agent, a filler, a glidant, a lubricant and a coating.

[0054] In one embodiment, the controlled release agent in the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein comprises one or more hypromelloses.

[0055] In one embodiment, the controlled release agent in the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein comprises one or more hypromelloses selected from the group consisting of Metolose® 90SH K15M 100 SR, Metolose® 90SH 100 SR, Methocel™ K100M CR, Methocel™ K15M CR, Methocel™ K4M CR, and Methocel™ K100LV CR, or equivalent grade.

[0056] In one embodiment, the controlled release agent in the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein comprises a mixture of (i) a low viscosity hypromellose with a viscosity of between about 15 millipascal-seconds (mPa·s) to about 100 mPa·s and (ii) a high viscosity hypromellose with a viscosity of about 100,000 mPa·s,

wherein each of the low and high viscosity hypromelloses is a controlled release or sustained-release grade and is further characterized by a methoxy content of 19.0% to 24.0% and a hydroxypropoxy content of 4.0% to 12.0%.

[0057] In one embodiment, the glidant in the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein is silica colloidal anhydrous.

[0058] In one embodiment, the lubricant in the core tablet of the gastro-resistant, controlled release dosage forms disclosed herein is magnesium stearate.

[0059] In one embodiment, the enteric coating of the gastro-resistant, controlled release dosage forms disclosed herein comprises at least one polymeric controlled release agent with a dissolution property of greater than pH 5.5, 6.0 or 6.5, and an anti-tacking agent.

[0060] In one embodiment, the enteric coating of the gastro-resistant, controlled release dosage forms disclosed herein further comprises a plasticizer.

[0061] In one embodiment, the polymeric controlled release agent of the enteric coating of the gastro-resistant, controlled release dosage forms disclosed herein comprises Eudragit L30D55.

[0062] In one embodiment, the anti-tacking agent of the enteric coating of the gastro-resistant, controlled release dosage forms disclosed herein is Plasacryl HTP20.

[0063] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 7 to about 17% w/w compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Metolose® 90SH K15M 100 SR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 25 to about 35% w/w microcrystalline cellulose;

about 13 to about 23% w/w lactose monohydrate

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% magnesium stearate;

about 1 to about 10% w/w Eudragit L30D55; and

about 0.5 to about 5% w/w Plasacryl HTP20.

[0064] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 12 % w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Metolose® 90SH K15M 100 SR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate

about 0.5% w/w silica colloidal anhydrous;

about 1 % magnesium stearate;

about 5 % w/w Eudragit L30D55; and

about 1 % w/w Plasacryl HTP20.

[0065] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 7 to about 17% w/w compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Methocel™ K15M CR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 25 to about 35% w/w microcrystalline cellulose;

about 13 to about 23% w/w lactose monohydrate;

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% w/w magnesium stearate;

about 1 to about 10% Eudragit L30D55;

about 0.5 to about 5% w/w Plasacryl HTP20; and

about 0.5 to about 5% w/w Surelease E-7-19040.

[0066] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 12% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Methocel™ K15M CR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate;

about 0.5 % w/w silica colloidal anhydrous;

about 1 % w/w magnesium stearate;

about 5 % w/w Eudragit L30D55;

about 1 % w/w Plasacryl HTP20; and

about 1 % w/w Surelease E-7-19040.

[0067] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 7 to about 17% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Methocel™ K100LV CR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 25 to about 35% w/w microcrystalline cellulose;

about 13 to about 23% w/w lactose monohydrate

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% magnesium stearate;

about 1 to about 10% w/w Eudragit L30D55; and

about 0.5 to about 5% w/w Plasacryl HTP20.

[0068] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 12% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Methocel™ K100LV CR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate;

about 0.5 % w/w silica colloidal anhydrous;

about 0.5 % w/w magnesium stearate;

about 5 % w/w Eudragit L30D55; and

about 1 % w/w Plasacryl HTP20.

[0069] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 12% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Methocel™ K100LV CR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate;

about 0.5 % w/w silica colloidal anhydrous;

about 1 % w/w magnesium stearate;

about 5 % w/w Eudragit L30D55; and

about 1 % w/w Plasacryl HTP20.

[0070] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 19 to about 29% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Methocel™ K100LV CR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 19 to about 29% w/w microcrystalline cellulose;

about 8 to about 18% w/w lactose monohydrate

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% magnesium stearate;

about 1 to about 10% w/w Eudragit L30D55; and

about 0.5 to about 5% w/w Plasacryl HTP20.

[0071] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 24% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9% w/w hypromellose (Methocel™ K100LV CR);

about 23% w/w hypromellose (Methocel™ K100M CR);

about 24% w/w microcrystalline cellulose;

about 13% w/w lactose monohydrate;

about 0.5% w/w silica colloidal anhydrous;

about 0.5% w/w magnesium stearate;

about 5% w/w Eudragit L30D55; and

about 1% w/w Plasacryl HTP20.

[0072] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form comprising:

about 24% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9% w/w hypromellose (Methocel™ K100LV CR);

about 23% w/w hypromellose (Methocel™ K100M CR);

about 24% w/w microcrystalline cellulose;

about 13% w/w lactose monohydrate;

about 0.5% w/w silica colloidal anhydrous;

about 1% w/w magnesium stearate;

about 5% w/w Eudragit L30D55; and

about 1% w/w Plasacryl HTP20.

[0073] In one aspect, the present disclosure provides a method of reducing a risk of QT prolongation when treating a subject with Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, the method comprising oral administration to the subject of a gastro-resistant, controlled release dosage form described herein.

[0074] In one aspect, the present disclosure provides a method of treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, the method comprising an oral administration to the subject of a gastro-resistant, controlled release dosage form described herein, wherein the subject has a diagnosis of the disorder, e.g., schizophrenia.

[0075] In one aspect, the present disclosure provides a method of treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, the method comprising a once daily oral administration to the subject of a gastro-resistant, controlled release dosage form described herein, wherein the subject has a diagnosis of the disorder, e.g., schizophrenia.

[0076] In one aspect, the present disclosure provides a method of treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, the method comprising an oral administration to the subject of a gastro-resistant, controlled release dosage form described

herein, wherein the subject has a diagnosis of, e.g., schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype.

[0077] In one aspect, the present disclosure provides a method of treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, the method comprising a once daily oral administration to the subject of a gastro-resistant, controlled release dosage form described herein, wherein the subject has a diagnosis of, e.g., schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype.

[0078] In one aspect, the present disclosure provides a method of treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, the method comprising an oral administration to the subject of a gastro-resistant, controlled release dosage form described herein (e.g., including a low dose of Compound (I), such as about 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, or about 16 mg), wherein the subject has a diagnosis of, e.g., schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype.

[0079] In one aspect, the present disclosure provides a method of treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, the method comprising a once daily oral administration to the subject of a gastro-resistant, controlled release dosage form described herein (e.g., including a low dose of Compound (I), such as about 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, or about 16 mg), wherein the subject has a diagnosis of, e.g., schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype.

[0080] In one aspect, for any of the methods disclosed herein, the subject is in fed state prior to oral administration of the gastro-resistant, controlled release dosage form described herein.

[0081] In one aspect, for any of the methods disclosed herein, the subject is in fasted state prior to oral administration of the gastro-resistant, controlled release dosage form described herein.

[0082] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in reducing a risk of QT prolongation.

[0083] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia.

[0084] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of

schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype.

[0085] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, or about 16 mg.

[0086] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in reducing a risk of QT prolongation, wherein the gastro-resistant, controlled release dosage form is administered once daily.

[0087] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the gastro-resistant, controlled release dosage form is administered once daily.

[0088] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype, wherein the gastro-resistant, controlled release dosage form is administered once daily.

[0089] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, or about 16 mg, wherein the gastro-resistant, controlled release dosage form is administered once daily

[0090] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject is in fed state prior to oral administration of the dosage form.

[0091] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject is in fasted state prior to oral administration of the dosage form.

[0092] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype, wherein the subject is in fed state prior to oral administration of the dosage form.

[0093] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype, wherein the subject is in fasted state prior to oral administration of the dosage form

[0094] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, or about 16 mg, wherein the subject is in fed state prior to oral administration of the dosage form.

[0095] In one aspect, the present disclosure provides a gastro-resistant, controlled release dosage form disclosed herein for use in treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, or about 16 mg, wherein the subject is in fasted state prior to oral administration of the dosage form.

[0096] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for reducing a risk of QT prolongation.

[0097] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia.

[0098] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype.

[0099] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, or about 8 mg.

[00100] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for reducing a risk of QT prolongation, wherein the gastro-resistant, controlled release dosage form is administered once daily.

[00101] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the gastro-resistant, controlled release dosage form is administered once daily.

[00102] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype, wherein the gastro-resistant, controlled release dosage form is administered once daily.

[00103] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, or about 8 mg, wherein the gastro-resistant, controlled release dosage form is administered once daily.

[00104] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject is in fasted state prior to oral administration of the dosage form.

[00105] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype, wherein the subject is in fasted state prior to oral administration of the dosage form.

[00106] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, or about 8 mg, wherein the subject is in fasted state prior to oral administration of the dosage form.

[00107] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject is in fed state prior to oral administration of the dosage form.

[00108] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype, wherein the subject is in fed state prior to oral administration of the dosage form.

[00109] In one aspect, the present disclosure provides for a use of a gastro-resistant, controlled release dosage form disclosed herein in the manufacture of medicament for the treatment of a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, e.g., the subject has a diagnosis of schizophrenia, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 IM or PM genotype and the dosage form has a low dose of Compound (I), e.g., about 4 mg, 5 mg, 6 mg, 7 mg, or about 8 mg, wherein the subject is in fed state prior to oral administration of the dosage form.

[00110] Thus, in one aspect, the present disclosure provides a gastro-resistant, controlled release oral dosage form, which comprises (i) about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and (ii) at least one controlled release agent, wherein the dosage form produces, upon oral administration to a subject, a plasma pharmacokinetic (PK) profile for Compound (I) which comprises a T_{max} of between about 4 and about 11 hours. In an embodiment, the T_{max} of Compound (I) in the plasma PK profile is between about 5 and about 10 hours; between about 6 and about 9 hours, between about 7 and about 9 hours, or between about 6 and about 8 hours.

[00111] In some embodiments, the amount of Compound (I) in the oral dosage form is 4 mg to 8mg, 8 to 16 mg, 16 mg to 32 mg, 32 mg to 40 mg, 40 mg to 64 mg, 64 mg to 80 mg, 80 mg to 100 mg or is about any of 4 mg, 8 mg, 16 mg, 24 mg, 32 mg, 40 mg, 64 mg, 80 mg, 96 mg, or 100 mg.

[00112] In an embodiment, the dosage form comprises about 32 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 68 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 16 ng/mL, 17 ng/mL,18 ng/mL, 19 ng/mL, 20 ng/mL, 21 ng/mL, 22 ng/mL, or 23 ng/mL; and (c) an AUC_{0-24hr} of between about 75 h*ng/mL to about 350

h*ng/mL or between about 100 h*ng/mL to 300 h*ng/mL. In an embodiment, the plasma PK profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 3.0 ng/mL, below 2.5 ng/mL, below 2.0 ng/mL, below 1.5 ng/mL or below 1.0 ng/mL.

[00113] In an embodiment, the dosage form comprises about 4 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 8 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 2.5 ng/mL; and (c) an AUC_{0-24hr} of between about 12 h*ng/mL to 35 h*ng/mL. In an embodiment, the plasma PK profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 2.0 ng/mL, below 1.5 ng/mL, below 1.0 ng/mL, or below 0.5 ng/mL.

[00114] In an embodiment, the dosage form comprises about 8 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 16 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 5 ng/mL; and (c) an AUC_{0-24hr} of between about 25 h*ng/mL to 75 h*ng/mL. In an embodiment, the plasma PK profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 2.5 ng/mL, below 2.0 ng/mL, below 1.5 ng/mL, or below 1.0 ng/mL.

[00115] In an embodiment, the dosage form comprises about 16 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 32 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 10 ng/mL or less than about 6 ng/mL; and (c) an AUC_{0-24hr} of between about 50 h*ng/mL to 150 h*ng/mL. In an embodiment, the plasma PK profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 2.5 ng/mL, below 2.0 ng/mL, below 1.5 ng/mL, or below 1.0 ng/mL.

[00116] In an embodiment, the dosage form comprises about 40 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 80 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 24 ng/mL or less than about 20 ng/mL; and (c) an AUC_{0-24hr} of between about 125 h*ng/mL to 375 h*ng/mL. In an embodiment, the plasma PK profile for the

BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 3.5 ng/mL, below 3.0 ng/mL, below 2.5 ng/mL, or below 2.0 ng/mL.

[00117] In an embodiment, the dosage form comprises about 64 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 50, 60, 70, 80, 90, 100, 110, 120, or 130 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 36 ng/mL or less than about 25 ng/mL; and (c) an AUC_{0-24hr} of between about 200 h*ng/mL to 600 h*ng/mL. In an embodiment, the plasma PK profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 4.0 ng/mL, below 3.5 ng/mL, below 3.0 ng/mL, or below 2.5 ng/mL.

[00118] In an embodiment, the dosage form comprises about 80 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 160 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 48 ng/mL or less than about 40 ng/mL; and (c) an AUC_{0-24hr} of between about 250 h*ng/mL to 750 h*ng/mL. In an embodiment, the plasma PK profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 4.5 ng/mL, below 4.0 ng/mL, below 3.5 ng/mL, or below 3.0 ng/mL.

[00119] In an embodiment, the dosage form comprises about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma PK profile further comprises: (a) an AUC_{0-4H} of less than about 220 h*ng/mL; (b) a C_{max} of Compound (I) of less than about 72 ng/mL; and (c) an AUC_{0-24hr} of between about 325 h*ng/mL to 975 h*ng/mL. In an embodiment, the plasma PK profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 5.0 ng/mL, below 4.5 ng/mL, below 4.0 ng/mL, or below 3.5 ng/mL.

[00120] In some embodiments of any of the above dosage forms, the plasma PK parameters are values determined after two once daily administrations of a single unit of the dosage form. In an embodiment, the PK parameter is determined after the 3rd or 4th administration.

[00121] In an embodiment, the dosage form comprises about 32 mg of Compound (I) and, when administered to a subject, produces a plasma pharmacokinetic (PK) profile for Compound (I) which is similar to the target profile shown in Figure 1.

[00122] In some embodiments of any of the above dosage forms, the plasma PK profile for one or both of Compound (I) and the metabolite BFB-520 is produced after the 1st, 2nd, 3rd, or 4th once daily administration of a single unit of the dosage form.

[00123] In some embodiments, the plasma PK profile for one or both of Compound (I) and the metabolite BFB-520 is produced when administered to a subject in the fasted state. In other embodiments, the plasma PK profile for one or both of Compound (I) and the metabolite BFB-520 is produced when administered to a subject in the fed state.

[00124] In an embodiment, a controlled release dosage form of the disclosure comprises about 4 to about 100 mg of Compound (I) and produces a target *in vitro* dissolution profile using a 24-hour, two-stage *in vitro* dissolution method which comprises a 2-hour acid stage and a 22-hour buffer stage. The target *in vitro* dissolution profile comprises (a) no detectable release of Compound (I) during the first 2.0 hours of the dissolution method and (b) release of at least 80% of the total amount of Compound (I) in the dosage form over a time period of 16-19 hours. In an embodiment, the target *in vitro* dissolution profile comprises release of at least 85%, 90% or 95% of the amount of Compound (I) in the dosage form by hour 24 of the dissolution method.

[00125] In an embodiment, the target *in vitro* dissolution profile further comprises release of Compound (I) at a release rate that produces each of the following cumulative percentages of the starting total amount:

(i) less than 0.6 % by 2.5 hours;
(ii) from 0.2 to 7.9% by 3.0 hours;
(iii) from 2.5 to 19.2% by 4 hours;
(iv) from 12.7 to 34.0% by 6 hours;
(v) from 22.8 to 44.3% by 8 hours;
(vi) from 35.5 to 75.7% by 13 hours;
(vii) from 43.3 to 89.0% by 16 hours; and
(viii) from 59.3 to 96.9% by 19 hours.

[00126] In an embodiment, the target *in vitro* dissolution profile further comprises release of Compound (I) at a release rate that produces each of the following cumulative percentages of the starting total amount:

(i) less than about 0.5 % by 2.5 hours;

(ii) from about 2.8 to about 3.1 % by 3.0 hours;

(iii) from about 9.0 to about 11.0 % by 4 hours;

(iv) from about 14.5 to about 18.0 % by 5 hours;

(v) from about 19.5 to about 24.5 % by 6 hours;

(vi) from about 30.5 to about 38.0 % by 8 hours;

(vii) from about 41.5 to about 51.0 % by10 hours;

(viii) from about 54.5 to about 67.0 % by 13 hours;

(ix) from about 58.5 to about 71.5 % by 14 hours;

(x) from about 61.5 to about 75.5 % by 15 hours;

(xi) from about 70.0 to about 86.0 % by 18 hours; and

(xii) from about 77.5 to about 95.0 % by 21 hours.

[00127] In an embodiment, the CR dosage form comprises 32 mg of Compound (I) and generates *in vitro* cumulative dissolution and dissolution rate profiles that are substantially similar to the target profile shown in Figure 1 or to the target profile shown in Tables 6 and 7 in the Examples below.

[00128] In an embodiment, the target *in vitro* dissolution profile further comprises release of Compound (I) at a release rate that produces each of the following cumulative percentages of the starting total amount:

(xiii) less than about 0.5 % by 2 hours;

(xiv) from about 19 to about 29 % by 4 hours;

(xv) from about 54 to about 64 % by 8 hours; and

(xvi) from about 83 to about 93 % by 16 hours.

[00129] In an embodiment, the target *in vitro* dissolution profile further comprises release of Compound (I) at a release rate that produces each of the following cumulative percentages of the starting total amount:

(xvii) less than about 0.5 % by 2 hours;

(xviii) about 24.1% by 4 hours;

(xix) about 59.2 % by 8 hours; and

(xx) about 88.6 % by 16 hours.

[00130] In each of the above embodiments, the dissolution method is preferably conducted according to the dissolution method described in the Examples below.

[00131] In an embodiment, the CR oral dosage form is a tablet which comprises a core tablet and an enteric coating. The core tablet comprises a desired amount of Compound (I), a controlled release agent, a filler, a glidant and a lubricant and the enteric coating comprises at least one polymeric controlled release agent with a dissolution property of greater than pH 5.5, and an anti-tacking agent. In an embodiment, the enteric coating dissolves at a pH greater than 6.0 or 6.5.

[00132] In an embodiment, the CR oral dosage form is a tablet which comprises a core tablet and an enteric coating. The core tablet comprises a desired amount of Compound (I) or a pharmaceutically acceptable salt and/or solvate thereof (e.g., MIN-101), a controlled release agent, a filler, a glidant and a lubricant and the enteric coating comprises at least one polymeric controlled release agent with a dissolution property of greater than pH 5.5, and an anti-tacking agent. In an embodiment, the enteric coating dissolves at a pH greater than 6.0 or 6.5.

[00133] In some embodiments, the controlled release agent in the core tablet comprises a mixture of (i) a low viscosity hypromellose with a viscosity of between about 15 millipascal-seconds (mPa·s) to about 100 mPa·s and (ii) a high viscosity hypromellose with a viscosity of about 100,000 mPa·s, wherein each of the low and high viscosity hypromelloses is a controlled release or sustained-release grade and is further characterized by a methoxy content of 19.0% to 24.0% and a hydroxypropoxy content of 4.0% to 12.0%. In an embodiment, the high viscosity hypromellose is characterized by a methoxy content of 22.0% to 24.0% and a hydroxypropoxy content of 9.5% to 11.5%. In an embodiment, the low viscosity hypromellose comprises about 10% of the weight of the core tablet and the high viscosity hypromellose comprises about 24% of the weight of the core tablet.

[00134] In an embodiment, the core tablet comprises 38.4 mg of 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2) and the controlled release agent in the core table consists essentially of (i) 9.45% w/w of a hypromellose having the chemical and physical characteristics of the hypromellose product marketed as METOLOSE® 90 SH 100 SR by Shin-Etsu Chemical Co., Ltd., or METHOCEL™ K100LV CR; and (ii) 22.67% w/w of a hypromellose having the chemical and physical

characteristics of the hypromellose product marketed as METHOCEL™ K100M CR by The Dow Chemical Company.

[00135] In an embodiment, the dosage form further comprises a controlled release coating located between the core tablet and the enteric coating. The controlled release coating comprises at least one controlled release reagent. In an embodiment, the controlled release coating comprises a semipermeable membrane which comprises ethylcellulose as the controlled release agent.

[00136] In an embodiment of the dosage form that comprises a controlled release coating, the core tablet comprises 38.4 mg of 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2) and the controlled release agent in the core table consists essentially of 9.36% w/w of a hypromellose having the chemical and physical characteristics of the hypromellose product marketed as METHOCEL™ K15M CR by The Dow Chemical Company, or METHOCEL™ K100LV CR; and 22.46% of a hypromellose having the chemical and physical characteristics of the hypromellose product marketed as METHOCEL™ K100M CR by The Dow Chemical Company and the controlled release agent in the controlled release coating consists essentially of 0.94 % w/w of an ethylcellulose having the chemical and physical characteristics of the ethylcellulose product marketed as Surelease® E-7-19040 by Colorcon.

[00137] In some embodiments of any of the above dosage forms, the enteric coating consists essentially of a mixture of (i) 4.68% w/w of a copolymer of methacrylic acid and ethyl acrylate having the same physical and chemical properties as the copolymer marketed as EUDRAGIT® L 30 D-55 by Evonik Industries AG and (ii) 0.80% w/w of an anti-tacking agent having the chemical and physical characteristics of the anti-tacking product marketed as PlasACRYL™ by Evonik Industries AG.

[00138] In an embodiment, the gastro-resistant CR tablet of the disclosure has a round shape, an oval shape, a capsule shape or an oblong shape. In an embodiment, the tablet is round, with a diameter of 10 mm and a curvature radius (R) of 10.

[00139] In other aspects, the present disclosure provides a batch composition and a process for manufacturing a gastro-resistant CR oral dosage form described herein.

[00140] In yet another aspect, the present disclosure provides a method of reducing a risk of QT prolongation when treating a subject with Compound (I), the method comprising administering to the subject a gastro-resistant CR oral dosage form described herein.

[00141] In a still further aspect, the present disclosure provides a method of treating a disorder (e.g., negative symptoms of schizophrenia) in a subject in need thereof, the method comprising a once daily administration to the patient of a gastro-resistant CR oral dosage form described herein. In one embodiment, the subject, e.g., a patient, has a diagnosis of schizophrenia. In an embodiment, the patient has a diagnosis of schizophrenia, a CYP2D6 extensive metabolizer (EM) genotype and the oral dosage form comprises 32 mg to 64 mg of Compound (I). In another embodiment, the patient has a diagnosis of schizophrenia, a CYP2D6 poor metabolizer (PM) genotype and the gastro-resistant CR oral dosage form comprises 4 mg to 16 mg of Compound (I). In another embodiment, the patient has a diagnosis of schizophrenia, a CYP2D6 intermediate metabolizer (IM) genotype and the gastro-resistant CR oral dosage form comprises 8 mg to 32 mg of Compound (I).

[00142] In another aspect, the present disclosure provides a gastro-resistant CR oral dosage form described herein for use in treating negative symptoms in a patient. In an embodiment, the patient has a diagnosis of schizophrenia. In an embodiment, the dosage form is intended for use in improving one or both of negative symptoms and cognitive impairment in patients with a diagnosis of schizophrenia.

[00143] In another aspect, the present disclosure provides the use of a gastro-resistant CR oral dosage form described herein for the preparation of a medicament for treating negative symptoms in a patient. In an embodiment, the patient has a diagnosis of schizophrenia.

[00144] In another aspect, the present disclosure provides a kit for use in treating negative symptoms in a patient, the kit comprising a gastro-resistant CR oral dosage form described herein and instructions for use of the dosage form. In an embodiment, the instructions include instructions for testing the patient to determine the patient's CYP2D6 genotype. In an embodiment, the instructions include instructions for administrating the dosage form to the patient in a fed state or in a fasted state.

[00145] In all of the above aspects and embodiments of the invention, Compound (I) may be provided in the gastro-resistant CR oral dosage form as 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2).

BRIEF DESCRIPTION OF THE DRAWINGS

[00146] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[00147] In the Drawings, various graphs are shown which include the plasma concentrations time profile of various compounds, including, for example, 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, i.e., Compound (I). In these Drawings, the use of the "MIN-101" or "MIN101" is intended to refer to the free base, i.e., Compound (I).

[00148] The foregoing summary, as well as the following detailed description of the disclosure, will be better understood when read in conjunction with the appended drawings.

[00149] Figure 1 shows an exemplary target plasma PK profile for Compound (I) produced by oral administration of a gastro-resistant, controlled release dosage form comprising 32 mg of Compound (I) ("Prediction new formulation") compared to the observed plasma PK profile for Compound (I) produced by a previous 32 mg modified release MIN-101 tablet (described in Example 1) ("MR 32 mg"). The time profile is through 24 hours.

[00150] Figure 2 compares target *in vitro* dissolution profiles for Compound (I) (Target, red curve) with observed dissolution profiles for two exemplary gastro-resistant CR 32 mg tablets of the present disclosure, with the left graph showing cumulative dissolution profiles and the right graph showing dissolution rate profiles. The time profile is through 24 hours.

[00151] Figure 3 shows another exemplary target plasma PK profile for Compound (I) produced by oral administration of a gastro-resistant, controlled release dosage form comprising 32 mg of Compound (I) to a subject in either the fed state or fasted state ("Optimal formulation") compared to the observed plasma PK profiles for Compound (I) produced by a previous 32 mg

modified release MIN-101 tablet (described in Example 1) in patients in the fasted state or fed state. The time profile is through 24 hours.

[00152] Figure 4 is a graph of Compound (I) plasma concentrations time profile for subjects administered a MR 32 mg tablet. The time profile is through 36 hours.

[00153] Figure 5 is a graph of Compound (I) plasma concentrations time profile for subjects administered a GR-01 tablet. The time profile is through 36 hours.

[00154] Figure 6 is a graph of Compound (I) plasma concentrations time profile for subjects administered a GR-02 tablet. The time profile is through 36 hours.

[00155] Figure 7 is a graph of mean Compound (I) plasma concentrations time profile for subjects administered MR 32 mg tablets, GR-01 tablets, or GR-02 tablets. The time profile is through 48 hours.

[00156] Figure 8 is a graph of the rates of increase or decrease in Compound (I) plasma concentrations time profile for subjects administered MR 32 mg tablets, GR-01 tablets, or GR-02 tablets. The time profile is through 8 hours.

[00157] Figure 9 is a graph of BFB-520 plasma concentrations time profile for subjects administered a MR 32 mg tablet. The time profile is through 36 hours.

[00158] Figure 10 is a graph of BFB-520 plasma concentrations time profile for subjects administered a GR-01 tablet. The time profile is through 36 hours.

[00159] Figure 11 is a graph of BFB-520 plasma concentrations time profile for subjects administered a GR-02 tablet. The time profile is through 36 hours.

[00160] Figure 12 is a graph of mean BFB-520 plasma concentrations time profile for subjects administered MR 32 mg tablets, GR-01 tablets, or GR-02 tablets. The time profile is through 48 hours.

[00161] Figure 13 is a graph of the rates of increase or decrease in BFB-520 plasma concentrations time profile for subjects administered MR 32 mg tablets, GR-01 tablets, or GR-02 tablets. The time profile is through 8 hours.

[00162] Figure 14 is a pair of graphs of predicted Compound (I) steady state plasma concentrations time profile for subjects administered 4 daily doses of a MR 32 mg tablet or a GR-01 tablet (32 mg) based on actual data observed following Day 1 dosing. The time profile is through 96 hours.

[00163] Figure 15 is a pair of graphs of predicted BFB-520 steady state plasma concentrations time profile for subjects administered 4 daily doses of a MR 32 mg tablet or a GR-01 tablet (32 mg) based on actual data observed following Day 1 dosing. The time profile is through 96 hours.

[00164] Figure 16 is a pair of graphs of predicted Compound (I) steady state plasma concentrations time profile for subjects administered 4 daily 64 mg (2x32mg) doses of a MR 32 mg tablet or a GR-01 tablet. The time profile is through 96 hours.

[00165] Figure 17 is a pair of graphs of predicted BFB-520 steady state plasma concentrations time profile for subjects administered 4 daily 64 mg (2x32mg) doses of a MR 32 mg tablet or a GR-01 tablet. The time profile is through 96 hours.

[00166] Figure 18 is a pair of graphs of predicted Compound (I) steady state plasma concentrations time profile for subjects administered 4 daily doses of a MR 32 mg tablet or a GR-02 tablet (32 mg) based on actual data observed following Day 1 dosing. The time profile is through 96 hours.

[00167] Figure 19 is a pair of graphs of predicted BFB-520 steady state plasma concentrations time profile for subjects administered 4 daily doses of a MR 32 mg tablet or a GR-02 tablet (32 mg) based on actual data observed following Day 1 dosing. The time profile is through 96 hours.

[00168] Figure 20 is a pair of graphs of predicted Compound (I) steady state plasma concentrations time profile for subjects administered 4 daily doses of a MR 32 mg tablet or a GR-02 tablet based on actual data observed following Day 1 dosing. The time profile is through 96 hours.

[00169] Figure 21 is a pair of graphs of predicted BFB-520 steady state plasma concentrations time profile for subjects administered 4 daily 64 mg (2x32 mg) doses of a MR 32 mg tablet or a GR-02 tablet. The time profile is through 96 hours.

[00170] Figure 22 is a graph of Compound (I) plasma concentrations time profile for subjects administered GR-01 tablets in fed state. The time profile is through 36 hours.

[00171] Figure 23 is a graph of Compound (I) plasma concentrations time profile for subjects administered GR-01 tablets in fasted state. The time profile is through 36 hours.

[00172] Figure 24 is graph comparing mean Compound (I) plasma concentrations time profile for subjects administered GR-01 tablets in fed or fasted state. The time profile is through 48 hours.

[00173] Figure 25 is a graph of BFB-520 plasma concentrations time profile for subjects administered GR-01 tablets in fed state. The time profile is through 48 hours.

[00174] Figure 26 is a graph of BFB-520 plasma concentrations time profile for subjects administered GR-01 tablets in fasted state. The time profile is through 48 hours.

[00175] Figure 27 is graph comparing mean BFB-520 plasma concentrations time profile for subjects administered GR-01 tablets in fed or fasted state. The time profile is through 48 hours.

[00176] Figure 28 is a pair of graphs of predicted Compound (I) steady state plasma concentrations time profile for subjects administered 4 daily doses of a GR-01 tablet (32 mg) based on actual data observed following Day 1 dosing in fed or fasted state. The time profile is through 96 hours.

[00177] Figure 29 is a pair of graphs of predicted BFB-520 steady state plasma concentrations time profile for subjects administered 4 daily doses of a GR-01 tablet (32 mg) based on actual data observed following Day 1 dosing in fed or fasted state. The time profile is through 96 hours.

[00178] Figure 30 is a pair of graphs of predicted Compound (I) steady state plasma concentrations time profile for subjects administered 4 daily 64 mg (2x32 mg) doses of a GR-01 tablet in fed or fasted state. The time profile is through 96 hours.

[00179] Figure 31 is a pair of graphs of predicted BFB-520 steady state plasma concentrations time profile for subjects administered 4 daily 64 mg (2x32 mg) doses of a GR-01 tablet (64 mg) in fed or fasted state. The time profile is through 96 hours.

DETAILED DESCRIPTION

[00180] The present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I) or a pharmaceutically acceptable salt and/or solvate thereof, bulk compositions and processes for manufacturing the dosage forms, and use of the dosage forms for therapeutic treatment of patients suffering from various disorders and conditions.

[00181] In one embodiment, the present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, wherein upon oral administration to a subject, the C_{max} of Compound (I) and its metabolite, BFB-520, are reduced while the $AUC_{(0\text{-}tau)}$ is maintained compared to previously disclosed formulations and/or dosage forms, e.g., those as disclosed in US Patent No. 9,458,130.

[00182] In one embodiment, the present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, wherein upon oral administration to a subject, similar AUC-based exposure of Compound (I) is maintained compared to a previous study with previously disclosed formulations and/or dosage forms, e.g., those as disclosed in US Patent No. 9,458,130, which achieved its primary endpoint of improving negative symptoms in patients with schizophrenia with both doses tested, 64 mg and 32 mg.

[00183] In one embodiment, the present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I) or a pharmaceutically acceptable salt and/or solvate thereof, wherein upon oral administration to a subject, the $t_{1/2}$ of Compound (I) is prolonged compared to previously disclosed formulations and/or dosage forms, e.g., those as disclosed in US Patent No. 9,458,130.

[00184] In one embodiment, the present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I) or a pharmaceutically acceptable salt and/or solvate thereof, wherein upon oral administration to a subject, the C_{max} of BFB-520 in the subject's plasma is reduced to promote drug safety.

[00185] In one embodiment, the present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I) or a pharmaceutically acceptable salt and/or solvate thereof, wherein upon oral administration to a subject, the C_{max} of BFB-520 is reduced by about 30% or more (e.g., 30%, 35%, or 40%) compared to previously disclosed formulations and/or dosage forms, e.g., those as disclosed in US Patent No. 9,458,130.

[00186] In one embodiment, the reduction of the C_{max} of BFB-520 in the subject leads to a reduction in the potential for transient QTc increases observed in a previous study at the higher dose but not at the lower dose. In one example, administration of novel gastro-resistant CR oral

dosage forms described herein comprising Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, does not result in an observable QTc prolongations.

[00187] In one embodiment, the present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I) or a pharmaceutically acceptable salt and/or solvate thereof, wherein the administration of the dosage form does not result in an observable food effect, i.e., the administration of the dosage form may occur with or without food without changing its pharmacokinetic properties.

[00188] In one embodiment, the present disclosure relates to novel gastro-resistant CR oral dosage forms comprising Compound (I) or a pharmaceutically acceptable salt and/or solvate thereof, wherein the dosage forms comprising Compound (I) retain previously established overall safety and tolerability profiles.

[00189] The novel gastro-resistant CR oral dosage forms disclosed herein allow for the delivery of Compound (I) to a lower part of the gastrointestinal tract, which unexpectedly reduced the highest concentration of BFB-520. This unexpected pharmacokinetic effect resulted in no observable QTc prolongations in the subjects who were administered these novel gastro-resistant CR oral dosage forms.

Definitions and Abbreviations

[00190] The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. Notwithstanding the foregoing, and except where stated otherwise, the following definitions apply throughout the specification and claims.

[00191] Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure is understood to predominate.

[00192] All references to Compound (I) herein include all pharmaceutically acceptable salts (such as MIN-101) and/or all solvates (e.g., including hydrates) and alternative physical forms thereof unless otherwise indicated. All doses recited herein are based on the molecular weight of the free base Compound (I), which is 366.43 g/mole, rather than the molecular weight

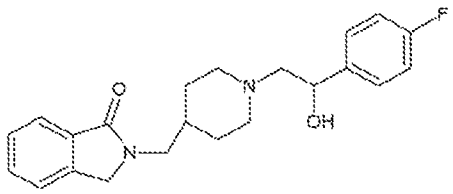
of the pharmaceutically acceptable salt or solvate (e.g., hydrate) thereof or any excipients in the composition, unless otherwise indicated.

[00193] All amounts of a component of an oral dosage form described herein that are indicated based on % w/w refer to the total weight of the oral dosage form, unless otherwise indicated.

[00194] The term "about" as part of a quantitative expression such as "about X", includes any value that is 10% higher or lower than X, and also includes any numerical value that falls between X-10% and X+10%. Thus, for example, a weight of about 40 g includes a weight of between 36 to 44 g.

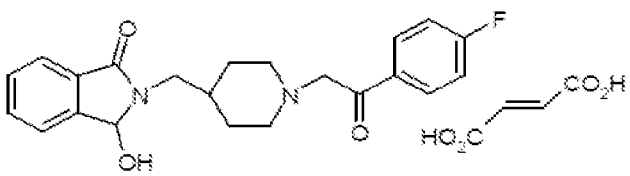
[00195] "Administration" refers to introducing an agent, such as a compound or dosage form described herein, into a subject. The related terms "administering" and "administration of" (and grammatical equivalents) refer both to direct administration, which may be administration to a subject by a medical professional or by self-administration by the subject, and/or to indirect administration, which may be the act of prescribing a drug such as a dosage form described herein. For example, a physician who instructs a patient to self-administer a drug and/or provides a patient with a prescription for a drug is administering the drug to the patient.

[00196] "BFB-520" is a metabolite of Compound (I) and has the structure shown in Formula II below:



(II).

[00197] "BFB-999" is a metabolite of Compound (I) and the structure of a maleate salt of BFB-999 shown in Formula III below:



(III).

[00198] "Similar PK profile" as used herein with respect to a plasma concentration time profile produced by oral administration to a subject of a dosage form of the disclosure is a plasma concentration time profile that is substantially similar to the target profile shown in Figure 1 such that a first dosage form comprising Compound (I) that produces the target plasma concentration time profile in Figure 1 and a second dosage form comprising Compound (I) that produces the similar plasma concentration time profile would result in a PK property, such as AUC, considered to be bioequivalent by a regulatory agency. In an embodiment, the regulatory agency is the U.S. Food and Drug Administration.

[00199] "BNSS" is the Brief Negative Symptom Scale.

[00200] "Comprising" or "comprises" as applied to a particular dosage form, composition, method or process described or claimed herein means that the dosage form, composition or method includes all of the recited elements in a specific description or claim, but does not exclude other elements. "Consists essentially of" and "consisting essentially of" means that the described or claimed composition, dosage form, method or process does not exclude other materials or steps that do not materially affect the recited physical, pharmacological, pharmacokinetic properties or therapeutic effects of the composition, dosage form, method or process. "Consists of" and "consisting of" means the exclusion of more than trace elements of other ingredients and substantial method or process steps.

[00201] "Controlled release" or "CR" as used herein with respect to an oral dosage form of the disclosure means that Compound (I) is released from the dosage form according to a pre-determined profile that may include when and where release occurs after oral administration and/or a specified rate of release over a specified time period.

[00202] "Controlled release agent" as used herein with respect to an oral dosage form of the disclosure refers to one or more substances or materials that modulate release of Compound (I) from the dosage form. Controlled release agents may be materials which are organic or inorganic, naturally occurring or synthetic, such as polymeric materials, triglycerides, derivatives of triglycerides, fatty acids and salts of fatty acids, talc, boric acid and colloidal silica.

[00203] "CYP2D6 allele" refers to one of over 100 named versions of the CYP2D6 gene that are present in the general population, and typically classified into one of three categories: active (functional); decreased activity (partially active or decreased function) and inactive (non-functional).

[00204] Active CYP2D6 alleles include: *1, *2, *2A, *33, *35, *39, *48, and *53.

[00205] Decreased activity CYP2D6 alleles include: *9, *10, *17, *29, *41, *49, *50, *54, *55, *59, *69, and *72.

[00206] Inactive CYP2D6 alleles include: *3, *4, *5 (deletion), *6, *7, *8, *11, *12, *13, *14A, *14B, *15, *18, *19, *20, *21, *38, *40, *42, *44, *56, *56A, *56B, and *68.

[00207] "CYP2D6 Extensive Metabolizer (EM)genotype" as applied to a subject means the subject has a CYP2D6 which results in CYP2D6 metabolic activity considered as normal. CYP2D6 EM genotypes include combinations of: (a) two active CYP2D6 alleles, (b) one active and one decreased activity CYP2D6 allele, and (c) one active and one inactive CYP2D6 allele.

[00208] "CYP2D6 Intermediate Metabolizer (IM) genotype" as applied to a subject means the subject has a CYP2D6 genotype, which results in reduced CYP2D6 metabolic activity. CYP2D6 IM genotypes include combinations of: (a) one inactive and one decreased activity CYP2D6 allele; and (c) two decreased activity CYP2D6 alleles.

[00209] "CYP2D6 PM genotype" as applied to a subject means the subject has a positive test result for a CYP2D6 poor metabolizer genotype and thus likely to have no CYP2D6 activity. A CYP2D6 PM genotype is 2 inactive alleles.

[00210] "CYP2D6 UM genotype" as applied to a subject means the subject has a positive test result for a CYP2D6 ultrarapid metabolizer genotype and thus likely to have higher than average CYP2D6 activity. A CYP2D6 UM genotype is 3 or more active alleles.

[00211] "Enteric coating" as used herein with respect to a dosage form of the disclosure refers to a pH-dependent material that surrounds a core comprising Compound (I) and which remains substantially intact in the acid environment of the stomach, but which dissolves in the pH environment of the intestines.

[00212] In one embodiment, in the dosage forms of the disclosure the filler is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, sucrose, glucose, and sorbitol.

[00213] "Glidant" as used herein refers to a substance used to promote powder flow by reducing interparticle cohesion. In one embodiment, in the dosage forms of the disclosure the glidant is selected from the group consisting of silica colloidal anhydrous, starch, and talc.

[00214] "Lubricant" as used herein refers to a substance that prevents ingredients from sticking and/or clumping together in the machines used in preparation of the dosage forms of the disclosure. In one embodiment, in the dosage forms of the disclosure the lubricant is selected from the group consisting of magnesium strearate, steric acid, and vegetable stearin.

[00215] "Fasted condition" or "fasted state" as used to describe a subject means the subject has not eaten for at least 4 hours before a time point of interest, such as the time of administering a dosage form described herein. In an embodiment, a subject in the fasted state has not eaten for at least any of 6, 8, 10 or 12 hours prior to administration of a dosage form described herein.

[00216] "Fed condition" or "fed state" as used to describe a subject herein means the subject has eaten less than 4 hours before a time point of interest, such as the time of administering a dosage form described herein. In an embodiment, a subject in the fed state has not eaten for at least any of 3, 2, 1 or 0.5 hours prior to administration of a dosage form described herein.

[00217] "Gastro-resistant" or "GR" as applied to a CR oral dosage form described herein means that release of Compound (I) in the stomach of a subject shall not exceed 5%, 2.5%, 1% or 0.5% of the total amount of Compound (I) in the dosage form.

[00218] "MIN-101" is a code name for 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2), with an alternative name of 2-{1-[2-(4-Fluorophenyl)-2-oxoethyl]piperidin-4-ylmethyl}-2,3-dihydroisoindol-1-one hydrochloride dihydrate.

[00219] "Oral dosage form" as used herein refers to a pharmaceutical drug product that contains a specified amount (dose) of Compound (I) as the active ingredient, or a

pharmaceutically acceptable salt and/or solvate thereof, and inactive components (excipients), formulated into a particular configuration that is suitable for oral administration, such as a tablet or capsule.

[00220] "Pharmaceutically acceptable salt" as used herein with respect to Compound (I), means a salt form of Compound (I) as well as hydrates of the salt form with one or more water molecules present. Such salt and hydrated forms retain the biological activity of Compound (I) and are not biologically or otherwise undesirable, i.e., exhibit minimal, if any, toxicological effects. In an embodiment, the pharmaceutically acceptable salt of Compound (I) has a single HCl molecule and two water molecules, i.e., 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2).

[00221] "PANSS" is Positive and Negative Syndrome Scale.

[00222] "Pharmacokinetic parameter" means a measurement or characteristic that describes the pharmacokinetic properties of a compound of interest. PK parameters used herein are defined below.

[00223] "AUC" is total area under the plasma concentration-time curve, which is a measure of exposure to a compound of interest, and is the integral of the concentration-time curve after a single dose or at steady state. AUC is expressed in units of ng·H/mL (ng x H/mL).

[00224] "$AUC_{(0\text{-}4H)}$" means the AUC from 0 hours to 4 hours after administration of a single dose.

[00225] "$AUC_{(0\text{-}24H)}$" means the AUC from 0 hours to 24 hours after administration of a single dose.

[00226] "AUC_{last}" means the AUC from time 0 to the last quantifiable concentration (C_{last}).

[00227] "$AUC_{(0\text{-}tau)}$" means the AUC from 0 hours to the end of a dosing interval.

[00228] "C_{max}" means the observed maximum (peak) plasma concentration of a specified compound, such as Compound (I), after administration of a dose of a composition comprising the compound. In an embodiment, the C_{max} is measured after 2 or more doses of the composition. In an embodiment, the C_{max} is measured when the specified compound reaches steady-state.

[00229] "C_{min}" means the observed minimum plasma concentration of a specified compound, such as Compound (I), after administration of a dose of a composition comprising the compound. In an embodiment, the C_{max} is measured after 2 or more doses of the composition. In an embodiment, the C_{max} is measured when the specified compound reaches steady-state.

[00230] "C_{ss}" means the concentration at the steady state.

[00231] "C_{ave}" means the average concentration which is the AUC over time ratio.

[00232] "C_p" means the plasma concentration of a specified compound, such as Compound (I), at any time *T* after administration of a dose of a composition comprising the compound.

[00233] "$C_{p(last)}$" means the last measured C_p, with reference to the time of collection of the last of a series of blood samples for assay for the specified compound.

[00234] "$C_{p(T)}$" means the C_p at the specified time; thus $C_{p(4H)}$ and $C_{p(12H)}$ are the C_p at 4 hours and 24 hours, respectively.

[00235] "H" means hours.

[00236] "PK" is pharmacokinetic(s).

[00237] "Steady-state" means the rate of absorption of a specified compound of interest such as Compound (I) is equal to the rate of elimination of the compound.

[00238] "Tau" means a dosing interval (H). For example, for once daily dosing, tau is 24H,

[00239] T_{max} means the time to maximum (or peak) plasma or serum concentration of a specified therapeutic compound after administration of a single dose of a composition comprising the compound and before administration of a second dose.

[00240] V_{max} means the maximum absorption rate (mg/H).

[00241] "Subject" and "patient" may be used interchangeably herein, and refer to a human of any age.

[00242] "Therapeutically effective amount", as used herein with respect to therapeutic uses of a dosage form comprising Compound (I) or pharmaceutically salt and/or solvate thereof,

means an amount of the free base (Compound (I)) that is sufficient to treat, ameliorate, or prevent a specified disease, disease symptom, disorder or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The effective amount for a particular subject may depend upon the subject's body weight, size, and health; the nature and extent of the condition; and whether additional therapeutics are to be administered to the subject. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[00243] "Treat", "treating", "treatment" and similar terms, as used herein with respect to one or more specified disease symptoms shall include the management and care of a patient for the purpose of improving one or more of the specified symptoms, and include administration of a gastro-resistant, controlled release oral dosage form described herein at a dosing frequency and for a treatment period that are sufficient to prevent the onset of one or more of the symptoms, reduce the frequency, intensity or severity of one or more of the symptoms, delay or avoid the development of additional symptoms, or any combination of these treatment objectives. In an embodiment, the effect of treatment with a dosage form of the present disclosure is assessed by comparing the severity of the subject's symptoms at baseline (e.g., prior to treatment) and after at least one treatment period. In an embodiment, the treatment period is at least one week, at least two weeks, at least four weeks, at least six weeks, at least eight weeks, at least 10 weeks or at least twelve weeks or more. In an embodiment, the symptoms to be treated is at least one negative symptom in a schizophrenic or non-schizophrenic patient, the dosage form comprises 32 mg of Compound (I), the dosing frequency is once daily, and the treatment period is at least eight weeks.

Summary of Gastro-Resistant Controlled Release (CR) Oral Dosage Forms

[00244] In one embodiment, the present disclosure relates to a gastro-resistant, CR oral dosage form comprising between about 4 mg to about 100 mg of Compound (I) or an equivalent amount of a pharmaceutically acceptable salt and/or solvate of Compound (I), wherein the gastro-resistant, CR oral dosage form is selected from the group consisting of a 32 mg CR GR-01 tablet, 32 mg CR GR-02 tablet, a 32 mg CR GR-01/B tablet, a 64 mg CR GR-01/B tablet, a 32 mg CR GR-01/C tablet, and a 64 mg CR GR-01/C tablet.

[00245] In one embodiment, the 32 mg CR GR-01 tablet has the following composition:

Composition	CR GR-01 tablet		Function
	%w/w	mg/tablet	
MIN-101[1]	12.09	38.40	Active ingredient
Hypromellose (Metolose® 90SH 100 SR)	9.45	30.00	Controlled release excipient
Hypromellose (Methocel™ K100M CR)	22.67	72.00	Controlled release excipient
Microcrystalline Cellulose	29.95	95.10	Filler
Lactose Monohydrate	18.89	60.00	Filler
Silica Colloidal Anhydrous	0.47	1.50	Glidant
Magnesium stearate	0.94	3.00	Lubricant
Total (Core Tablet)	94.47	300.00	
Eudragit L30D55	4.72	15.00	Controlled release excipient
Plasacryl HTP20	0.80	2.55	Anti-tacking agent
Total	100.00	317.55	

[1] Salt correction factor of 1.2 applied

NA: Not Applicable

[00246] In one embodiment, the 32 mg CR GR-02 tablet has the following composition:

Composition	CR GR-02 tablet		Function
	%w/w	mg/tablet	
MIN-101[1]	11.98	38.40	Active ingredient
Hypromellose (Methocel™ K15M CR)	9.36	30.00	Controlled release excipient

Hypromellose (Methocel™ K100M CR)	22.46	72.00	Controlled release excipient
Microcrystalline Cellulose	29.67	95.10	Filler
Lactose Monohydrate	18.72	60.00	Filler
Silica Colloidal Anhydrous	0.47	1.50	Glidant
Magnesium stearate	0.94	3.00	Lubricant
Total (Core Tablet)	93.59	300.00	
Eudragit L30D55	4.68	15.00	Controlled release excipient
Plasacryl HTP20	0.80	2.55	Anti-tacking agent
Surelease E-7-19040	0.94	3.00	Controlled release excipient
Total	100.00	320.55	

[1] Salt correction factor of 1.2 applied

NA: Not Applicable

[00247] In one embodiment, the 32 mg CR GR-01/B tablet has the following composition:

Component/Ingredient	**GR-01/B-32mg**	
	mg/tablet	**% (w/w)**
MIN-101[1]	38.40	12.11
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67
Microcrystalline Cellulose	96.60	30.42
Lactose	60.00	18.89
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	1.50	0.47

Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.55	100.00

[1] Salt correction factor of 1.2 applied

[00248] In one embodiment, the 32 mg CR GR-01/C tablet has the following composition:

[00249] Component/Ingredient	**GR-01/C-32mg**	
	mg/tablet	**% (w/w)**
MIN-101[1]	38.40	12.11
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67
Microcrystalline Cellulose	95.10	29.95
Lactose	60.00	18.89
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	3.00	0.94
Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.55	100.00

[00250] In one embodiment, the 64 mg CR GR-01/B tablet has the following composition:

Component/Ingredient	**GR-01/B-64mg**	
	mg/tablet	**% (w/w)**
MIN-101[1]	76.8	24.19
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67
Microcrystalline Cellulose	77.40	24.37
Lactose	40.80	12.85
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	1.50	0.47
Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.55	100.00

[1] Salt correction factor of 1.2 applied

[00251] In one embodiment, the 64 mg CR GR-01/C tablet has the following composition:

Component/Ingredient	GR-01/C-64mg	
	mg/tablet	% (w/w)
MIN-101[1]	76.8	24.19
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67
Microcrystalline Cellulose	75.90	23.91
Lactose	40.80	12.85
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	3.00	0.94
Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.55	100.00

Design and Manufacture of Gastro-Resistant Controlled Release Oral Dosage Forms

[00252] An object of the present disclosure is to provide a gastro-resistant, controlled release oral dosage form comprising between about 4 mg to about 100 mg of Compound (I) or an equivalent amount of a pharmaceutically acceptable salt and/or solvate of Compound (I). The dosage form is formulated to exhibit, upon oral administration to a subject, a specific, desired release profile for Compound (I) which reduces the maximum plasma concentrations of BFB-520 while providing a therapeutically effective amount of Compound (I) during one or more dosing intervals. This desired release profile is achieved in two ways: (a) delay release of Compound (I) until after gastric emptying pushes the dosage form to the small intestine and then (b) provide sustained release of at least about 90%, 95% or 100% of the amount of Compound (I) in the dosage form at a rate that provides a plasma PK profile which comprises a T_{max} for Compound (I) of between about 4 and about 22 hours.

[00253] This *in vivo* release profile for Compound (I) is designed to reduce the subject's plasma levels of BFB-520 below a threshold that is correlated with a greater risk for QT

prolongation. In an embodiment, the threshold is a C_{max} for BFB-520 that is below 5.0 ng/mL, below 4.5 ng/mL, below 4.0 ng/mL, below 3.5 ng/mL, below 3.0 ng/mL, below 2.5 ng/mL, below 2.0 ng/mL, below 1.5 ng/mL, below 1.0 ng/mL, or below 0.5 ng/mL.

[00254] In some embodiments, the plasma PK profile for Compound (I) is further characterized in terms of one or more additional PK parameters, such as C_{max}, $AUC_{(0\text{-}tau)}$, C_{min} and other PK parameters defined above. It will be understood by the skilled person that the values for some of these additional PK parameters will depend, at least in part, on the amount of Compound (I) in the dosage form.

[00255] The values for the T_{max} and other plasma PK parameters produced by a dosage form described herein may exhibit some inter-individual variation within a population of subjects. Thus, in some embodiments, certain plasma PK parameters are expressed as mean values determined for a population of at least 2, 4, 8, 16 or more subjects. In an embodiment, the population consists of healthy volunteers. In an embodiment, each subject in the population has a positive test for an EM genotype. In an embodiment, each subject in the population has a positive test for an EM genotype or an IM genotype. In an embodiment, each subject in the population has a positive test for an IM genotype or a PM genotype. In an embodiment, each subject in the population has a positive test for a PM genotype.

[00256] Compound (I) may be synthesized using standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations, including the use of protective groups, as can be obtained from the relevant scientific literature or from standard reference textbooks in the field. Although not limited to any one or several sources, recognized reference textbooks of organic synthesis include: Smith, M.B.; March, J. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th ed.; John Wiley & Sons: New York, 2001; and Greene, T.W.; Wuts, P.G. M. Protective Groups in Organic Synthesis, 3rd; John Wiley & Sons: New York, 1999. A method for preparing Compound (I) is described in U.S. Patent No. 7,166,617, the contents of which are incorporated herein in their entirety.

[00257] In an embodiment, the drug substance form of Compound (I) used in the dosage form is a dihydrate of a hydrochloride salt of Compound (I), which has the chemical name 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-,

hydrochloride, hydrate (1:1:2), which has a molecular formula of $C_{22}H_{23}FN_2O_2$, HCl, $2H_2O$ and a molecular weight of 438.92. Methods for preparing this Compound (I) drug substance are described in US Patent Nos 7,166,617 and 9,458,130. An amount of this drug substance that is equivalent to a specified amount of free base may be calculated by multiplying the specified amount of Compound (I) by 1.2; thus, 38.4 mg of this drug substance is equivalent to 32.0 mg of Compound (I).

[00258] In an embodiment, the delayed and sustained-release properties of the CR oral dosage form may be provided by encasing a sustained-release composition comprising the desired amount of Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, within an enteric coating.

[00259] Various physical and chemical approaches for designing sustained-release compositions are well known in the art. Any sustained-release composition that is capable of releasing Compound (I) to provide the *in vivo* plasma PK profile described herein may be used to prepare a dosage form of the disclosure. In an embodiment, the sustained-release composition comprises at least one polymeric material that modulates release of Compound (I). Suitable polymeric materials include, but are not limited to, cross-linked polyvinylpyrrolidone, hydroxypropylmethylcellulose, hydroxypropylcellulose, cross-linked sodium carboxymethylcellulose, carboxymethyl starch, starch and derivatives thereof, acrylic and methacrylic acid polymers and copolymers, polyesters, polyanhydrides, polymethylvinylether/anhydride copolymers, potassium methacrylate-divinylbenzene copolymers, polyvinylalcohols, glucan, scleroglucan, mannan, betacyclodextrins and cyclodextrin derivatives containing linear and/or branched polymeric chains. In one embodiment, the polymeric material is a hydroxyproplymethocellulose.

[00260] In an embodiment, a mixture of a low viscosity and a high viscosity hypromellose is used as the controlled release agent in the sustained-release composition. The viscosity properties of suitable hypromelloses may be determined in a 2% by weight solution in water at 20°C as described in USP Hypromellose Monograph, Official December 1, 2016, which is available at http://www.usp.org/usp-nf/official-text/stage-6/hypromellose-2015-11-20.

[00261] The enteric coating, which typically comprises a pH-sensitive polymer, begins to dissolve in an aqueous solution at pH greater than 5.5, and in one embodiment, begins to

dissolve in an aqueous solution at pH greater than 6.0. In one embodiment, the pH-sensitive polymer begins to dissolve in an aqueous solution at pH greater than 6.5. In one embodiment, the pH-sensitive polymer begins to dissolve in an aqueous solution at pH 6.7. In an embodiment, the amounts of Compound (I) released in the stomach from a gastro-resistant CR dosage form administered to subjects in a fed state or a fasted state are about the same (e.g., less than 5%, less than 2% or less than 1% difference).

[00262] The composition and thickness of the enteric coating are typically chosen to substantially maintain its integrity in the stomach, while allowing substantially all of the enteric coating to dissolve after the dosage form leaves the stomach. In an embodiment, substantially all of the enteric coating dissolves within 15 minutes, 30 minutes, 1 hour or 2 hours after the dosage form leaves the stomach.

[00263] The design and preparation of gastro-resistant enteric coatings are well-known in the formulation art. Polyacids having an appropriate pKa range may be used to prepare enteric coatings. Non-limiting examples of suitable enteric coating materials are polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose proprionate phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers, typically formed from methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters. For example, the enteric coating may comprise a copolymer based on methacrylic acid and ethyl acrylate marketed as EUDRAGIT® L 30 D-55 by Evonik Industries AG. In an embodiment, the coating comprises a mixture of (i) EUDRAGIT® L 30 D-55 at 4.5 % to 5.0 %, w/w, or about 4.7% w/w and (ii) PlasACRYL™ HTP20 at 0.80 % w/w.

[00264] In another aspect, the disclosure provides a batch composition and process for manufacturing a gastro-resistant CR oral dosage form described herein. In an embodiment, a batch composition for manufacturing a 32 mg-dosage form comprises the components listed in Table 4 in Example 4 below. In another embodiment, a batch composition for manufacturing a 32 mg-dosage form comprises the components listed in Table 5 in Example 4 below. or Table in

Example 4 below. Examples of processes that are suitable for manufacturing these 32-mg dosage forms are described in flowcharts 1 and 2 of Example 4.

Analytical Methods

[00265] *A. In vitro Dissolution Testing*

[00266] To assess the potential for a proposed gastro-resistant CR oral dosage form comprising Compound (I) to produce the desired in *in vivo* release profile and plasma PK provide for Compound (I), *in vitro* dissolution testing as described in the Examples below may be performed.

[00267] In an embodiment, the dosage form comprises 32 mg and produces cumulative dissolution and dissolution rate profiles that are substantially similar to the target profile, the CR-GR-01 profile or the CR-GR-02 profile shown in Figure 1 and in Tables 6 and 7 below. In an embodiment, the cumulative dissolution amount and dissolution rate at each time point in substantially similar profiles are within +/- 10% of the values for the corresponding time point in the target, CR-GR-01 or CR-GR-02 dissolution profiles shown in Tables 6 and 7.

[00268] *B. Detection of Compound (I) and BFB-520 in Human Plasma*

[00269] To assess whether a gastro-resistant CR oral dosage form comprising Compound (I) produces the desired PK profile for one or both of Compound (I) and BFB-520, plasma concentrations of the compound(s) of interest may be determined at various time points after administration of the dosage form to a single subject, but is typically determined in a group of two or more subjects. In an embodiment, PK profile is determined in a group of at least 8, 12, 16 or 20 subjects. In an embodiment, the group comprises healthy male and female subjects. In an embodiment, the number of subjects in the group is chosen to allow a statistically significant assessment of whether the PK profile produced by a test oral dosage form is a bioequivalent PK profile with respect to the PK profile shown in Figure 1.

[00270] An open-label, randomized, 3-treatment sequence, 3-period study to evaluate the PK profile of Compound (I) and its metabolite BFB-520 after single oral administration of 3 formulations of MIN-101 (2 prototypes of CR gastro-resistant (GR) formulations (GR-01 and GR-02) and 1 comparator MR formulation (MR32)) is summarized in Scheme 1 (MIN-101) and Scheme 2 (BFB-520). Full details of these experiments are found in the Examples section.

[00271] Scheme 1. Summary of MIN-101 PK Study for MR32, GR-01, and GR-02 Formulations.

MR32 MIN101 DATA AND PARAMETERS (from n= 12 subjects cross-over)
CMAX 29,52 ng/ml
AUC 291,55 H.ng/ml TMax 2,4H

GRO1 MIN101 RELATIVE BIOAVAILABILITY VERSUS MR32 (from n= 12 subjects cross-over)
CMAX 19,59 ng/ml F=89,9%
AUC 284,5 H.ng/ml F=101,3% TMax 6,0H

GRO2 MIN101 RELATIVE BIOAVAILABILITY VERSUS MR32 (from n= 13 subjects cross-over)
CMAX 15,43 ng/ml F=54,33%
AUC 253,01 H.ng/ml F=86,9% TMax 15,2 H

PLASMA CONCENTRATIONS RATE OF MIN101 INCREASE (VMax)

	MR32	GR01	GR02
VMax ng/ml/H	26,2	11,9	2,9
RATIO Test / MR32	REF	0,45	0,4

[00272] Scheme 2. Summary of BFB-520 PK Study for MR32, GR-01, and GR-02 Formulations.

MR32 BFB-520 DATA AND PARAMETERS (from n=12 subjects cross-over)
CMAX 1,91 ng/ml
AUC 30,26 H.ng/ml TMax 6,9H

GRO1 BFB-520 RELATIVE BIOAVAILABILITY VERSUS MR32 (from n= 12 subjects cross-over)
CMAX 1,43 ng/ml F=80,48%
AUC 27,48 H.ng/ml F=96,1% TMax 12,5 H

GRO2 BFB-520 RELATIVE BIOAVAILABILITY VERSUS MR32 (from n= 12 subjects cross-over)
CMAX 1,27 ng/ml F=69,48%
AUC 27,53 H.ng/ml F=88,48% TMax 17,5 H

PLASMA CONCENTRATIONS RATE OF BFB-520 INCREASE (VMax)

	MR32	GR01	GR02
VMax ng/ml/H	0,84	0,54	0,2
RATIO Test / MR32	REF	0,64	0,24

[00273] The PK profiles of MIN-101 and its metabolite BFB-520 were predicted for 3 formulations of MIN-101 (2 prototypes of CR gastro-resistant (GR) formulations (GR-01 and GR-02) and 1 comparator MR formulation (MR32)) at 2 doses. (32 mg and 64 mg), based on 4 daily dosings. These studies are summarized in Scheme 3 (32 mg) and Scheme 4 (64 mg). Full details are found in the Examples section.

[00274] Scheme 3. Summary of Predicted Plasma Concentrations of MIN-101 and BFB-520 for MR32, GR-01, and GR-02 Formulations (32 mg).

PREDICTED 32 mg MR32 GR01 AND GR02 PLASMA CONCENTRATIONS AT DAY 4							
		MR32	GR01	GR01	GR02		GR02
MIN101	CMaxSS	27,1	20,9 ng/ml	F=76,9%	15,4	ng/ml	F=56,7%
	AUCSS72-96	292,6	287,6 H.ng/ml	F=98,3%	248,3	H.ng/ml	F=84,9%
	CMinSS	3,32	6,46 ng/ml		7,17	ng/ml	
BFB-520	CMaxSS	1,89	1,46 ng/ml	F=77,2%	1,23	ng/ml	F=64,8%
	AUCSS72-96	29,1	26,3 H.ng/ml	F=90,6%	23,6	H.ng/ml	F=81,4%
	CMinSS	0,5	0,66 ng/ml		0,79	ng/ml	

[00275] Scheme 4. Summary of Predicted Plasma Concentrations of MIN-101 and BFB-520 for MR32, GR-01, and GR-02 Formulations (64 mg).

PREDICTED 64 mg MR32 GR01 AND GR02 PLASMA CONCENTRATIONS AT DAY 4							
		2xMR32	2xGR01	2xGR01	2xGR02		2xGR02
MIN101	CMaxSS	54,28	41,77 ng/ml	F=76,9%	30,77	ng/ml	F=56,7%
	AUCSS72-96	585,2	577,6 H.ng/ml	F=98,7%	498,6	ng/ml	F=85,2%
	CMinSS	6,64	12,93 ng/ml		14,35	ng/ml	
BFB-520	CMaxSS	3,79	2,92 ng/ml	F=77,2%	2,45	ng/ml	F=64,8%
	AUCSS72-96	58,1	52,8 H.ng/ml	F=90,8%	47,4	H.ng/ml	F=81,6%
	CMinSS	0,99	1,32 ng/ml		1,58	ng/ml	

[00276] The PK profiles of the GR-01 formulation in healthy CYP2D6 EM male and female subjects in fed and fasted states are summarized in Scheme 5 (MIN-101) and Scheme 6 (BFB-520). Subjects who completed part 1 of the study (evaluation of the PK profile of MIN-101 and its metabolite BFB-520 in the GR-01, GR-02, and MR32 formulations) returned and received a further single oral dose of GR-01 under fed or fasted conditions to allow the assessment of food effect by comparison of the PK properties to those obtained in part 1 (Examples 9-12). There was a wash-out period of 14 ± 2 days after part 1. Full details of these experiments are found in the Examples section.

[00277] Scheme 5. Summary of MIN-101 PK Study for GR-01 Formulation in Fed and Fasted States.

GRO1 FED MIN101 (from n= 12 subjects cross-over)
CMAX 20,89 ng/ml F=108,97% versus FASTED
AUC 269,19 H.ng/ml F=95,14% versus FASTED
TMax 12,5H

GRO1 FASTED MIN101 (from n= 12 subjects cross-over)
CMAX 19,59 ng/ml
AUC 284,52 H.ng/ml
TMax 6,0 H

[00278] Scheme 6. Summary of BFB-520 PK Study for GR-01 Formulation in Fed and Fasted States.

GRO1 FED BFB-520 (from n= 12 subjects cross-over)
CMAX 1,69 ng/ml F=121,32% versus FASTED
AUC 30,12 H.ng/ml F=111,58% versus FASTED
TMax 18,25 H

GRO1 FASTED BFB-520 (from n= 12 subjects cross-over)
CMAX 1,43 ng/ml
AUC 27,48 H.ng/ml
TMax 12,5 H

[00279] The PK profiles of MIN-101 and its metabolite BFB-520 were predicted in the fed and fasted states for gastro-resistant formulation GR-01 at 2 doses (32 mg and 64 mg), based on 4 daily dosings. These studies are summarized in Scheme 7 (32 mg) and Scheme 8 (64 mg), respectively. Full details are found in the Examples section.

[00280] Scheme 7. Summary of Predicted Plasma Concentrations of MIN-101 and BFB-520 for GR-01 (32 mg) in the Fed and Fasted States.

PREDICTED 32 mg GR01 FED AND FASTED PLASMA CONCENTRATIONS AT DAY 4					
		GR01 FED		GR01 FASTED	
MIN101	CMaxSS	16,7	F=80,0%	20,9	ng/ml
	AUCSS72-96	263,8	F=91,7%	287,6	H.ng/ml
	CMinSS	3,32		6,46	ng/ml
BFB-520	CMaxSS	1,51	F=103,7%	1,46	ng/ml
	AUCSS72-96	29,5	F=109,4%	26, 3	H.ng/ml
	CMinSS	1,03		0,66	ng/ml

[00281] Scheme 8. Summary of Predicted Plasma Concentrations of MIN-101 and BFB-520 for GR-01 (64 mg) in the Fed and Fasted States.

PREDICTED 64mg GR01 FED AND FASTED PLASMA CONCENTRATIONS AT DAY 4					
		GR01 FED		GR01 FASTED	
MIN101	CMaxSS	33,41	F=80,0%	41,77	ng/ml
	AUCSS72-96	527,5	F=91,3%	577,6	H.ng/ml
	CMinSS	16,17		12,93	ng/ml
BFB-520	CMaxSS	3,01	F=103,7%	2,91	ng/ml
	AUCSS72-96	59,0	F=109,1%	54	H.ng/ml
	CMinSS	2,06		1,32	ng/ml

[00282] BFB-520 is believed to be metabolized in part by CYP2D6. In clinical studies of MIN-101, CYP2D6 poor metabolizers have exhibited high plasma levels of BFB-520. Thus, in an embodiment, the C_{max} for BFB-520 is assessed after oral administration of a test dosage form comprising Compound (I) to only subjects who have been assigned an IM CYP2D6 genotype or an EM CYP2D6 genotype using a commercially available genotype test. In an embodiment, all of the subjects have been assigned an EM CYP2D6 genotype.

[00283] Levels of Compound (I) and the metabolite BFB-520 produced in plasma after oral administration of an oral dosage form of the disclosure may be determined by the method described below. It is expected that variations of and improvements to this method could be employed as well.

[00284] Blood samples from subjects are collected on sodium heparin tubes at various time points of interest. A suitable sampling schedule includes the following:

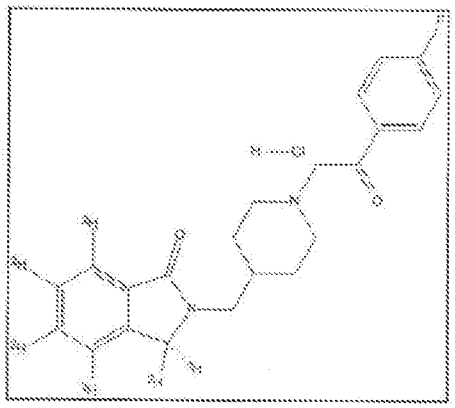
- Day 1 (D1): at pre-dose; 1h; 2h; 3h; 4h; 6h; 8h; 10h; 12h and 16h;
- Day 2 to Day 6 (D2-D6): at pre-dose

- Day 7 (D7): at pre-dose; 1h; 2h; 3h; 4h; 6h; 8h; 10h; 12h; 16; 24h (D8) and 48h (D9).

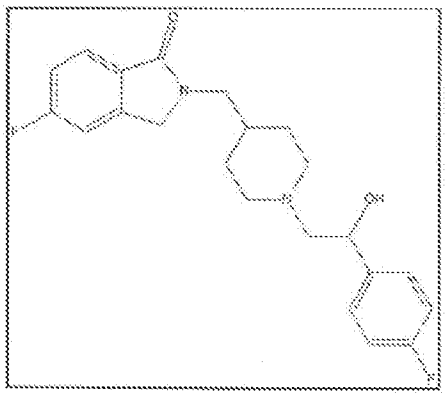
[00285] After blood centrifugation, a desired number of aliquots (typically 2) of each plasma sample are prepared in suitable storage containers (e.g., polypropylene tubes tightly capped to prevent leak and desiccation which could occur during storage). The containers containing the plasma samples are stored at -80°C for up to one month before analysis.

[00286] A GLP validated method to detect and quantify Compound (I) and its metabolites BFB-520 and BFB-999 employs liquid chromatographic (LC) analysis coupled to a mass spectrometry detection (MS/MS) after a liquid/liquid extraction step of Compound (I) and metabolites BFB-520 and BFB-999 from plasma samples.

[00287] The analytical method uses two internal standards (a deuterated analog of MIN-101 (designated herein as [$^2H_6$]-MIN-101 or MIN-101-d6 or CYR-101-d6) and BFB-784 for both BFB-520 and BFB-999), which were submitted to the same analytical procedure as MIN-101, BFB-520 and BFB-999 in plasma samples. MIN-101-d6 and BFB-784 have the structures shown in Formulas IV and V below:



(IV)



(V).

[00288] Chromatograms are processed by default in an automatic mode. Chromatographic peaks of MIN-101, BFB-520, BFB-999 and internal standards (IS) are identified according to their retention times. The recorded response is expressed as an area ratio of MIN-101 to MIN-101-d6, and of BFB-520 or BFB-999 to BFB-784.

[00289] The lower limit of quantification (LLOQ) of this analytical method in plasma is 0.25 ng/mL for MIN-101 and its metabolites BFB-520 and BFB-999.

[00290] Details of the analytical method are described in Example 7 below. It is expected that variations of and improvements to this analytical method could be employed as well.

Treatment Methods

[00291] The gastro-resistant CR oral dosage forms of the present disclosure may be useful for treating diseases or conditions that are susceptible to treatment with Compound (I). As not limiting examples, it is believed that Compound (I) can potentially be used to treat schizophrenic and non-schizophrenic patients with one or more of the following symptoms or conditions: negative symptoms, depressive symptoms, sleep disorders and cognitive impairment.

[00292] In a phase 2b study, MIN-101 at 32 mg and 64 mg doses, demonstrated rapid, statistically significant and clinically meaningful reductions in negative symptoms in patients with schizophrenia. The oral dosage forms used in this Phase 2b study were the 32 mg MR tablet described in Example 1 below and an essentially identical 64 mg MR tablet. Neither of these MR tablets had a GR coating and each produced *in vitro* dissolution and plasma PK profiles that are different than those produced by the gastro-resistant CR oral dosage forms of the present disclosure.

[00293] Negative symptoms generally refer to a reduction in normal functioning, and include five major sub-domains: blunted affect (affective flattening, blunted expression), alogia (poverty of speech), amotivation (loss of volition), anhedonia (reduced ability to experience or anticipate pleasure) and asociality (social withdrawal). While negative symptoms are a well-documented and intensively studied aspect of schizophrenia, this class of symptoms has been identified in patients with other psychiatric and neurological disorders, including, for example, Alzheimer's disease and other dementias, particularly frontotemporal dementia (FTD), autism spectrum disorder (ASD), bipolar disorder (BPD), major depressive disorder (MDD), Parkinson's disease, temporal lobe epilepsy, stroke, and traumatic brain injury (TBI) (see, e.g., Boone et al, J. of Internat. Neuropsycol. Soc., 2003, Vol 9, pages 698-709; Bastiaansen, J. et al., J. Autism Dev. Disord. 2011, Vol 41:1256-1266; Getz, K. et al., Am. J. Psychiatry 2002, Vol 159:644-651; Winograd-Gurvich, C. et al., Brain Res. Bulletin, 2006, Vol. 70:312-321; Galynker et al., Neuropsychiatry Neuropsychol Behav Neurol 2000, Vol 13:171-176; Galynker I, et al., J. Nerv. Ment. Dis 1997, Vol 185:616-621; Chaudhury, S., et al., Indian J. of Neurotrauma 2005, Vol 2:13-21; Ameen, S et al., German J. of Psychiatry 2007). Indeed, as early as 2001, it was

proposed that negative symptoms are common to mental illnesses generally (Herbener and Harrow, Schizophrenia Bulletin 2001, Vol. 27:527-537). Furthermore, reports of several population studies have concluded that between 20-22% of the general population have one or more negative symptoms, and that the majority of subjects with negative symptoms do not exhibit a clinical diagnosed psychiatric disorder (Werbeloff, N. et al., PLoS ONE 2015, Vol 10:e0119852; Barrantes-Vidal, N., et al., Schizophr. Res. 2010, Vol 122:219-225).

[00294] Thus, it is an object of the present disclosure to treat at least one negative symptom in a subject by a method of administering to the subject a gastro-resistant CR dosage form described herein one time per day (QD). In an embodiment, the subject is diagnosed with schizophrenia. In another embodiment, the subject does not have a clinical diagnosis of schizophrenia, i.e., is a non-schizophrenic patient.

[00295] For purposes of the disclosure encompassed herein, the term "negative symptoms" is to be understood as including primary negative symptoms typically associated with schizophrenia, the negative symptoms measured in the PANSS negative symptoms subscale score, the negative factor score based on the pentagonal structure model method, and the negative symptoms measured in the BNSS.

[00296] In an embodiment, the negative symptom is one of the five major sub-domains of negative symptoms: blunted affect, alogia, amotivation, anhedonia and asociality. The core characteristics of each sub-domain are described below.

[00297] Blunted affect (affective flattening, blunted expression) is characterized by reduced intensity and range of emotional expression as manifested via vocal and non-verbal modes of communication including intonation (prosody), facial expression, hand-gestures and body movements.

[00298] Alogia (poverty of speech) is characterized by decreased quantity of speech, reduced spontaneous speech and loss of conversational fluency.

[00299] Amotivation (loss of volition) is characterized by deficits in the initiation and maintenance of goal-directed behaviors like work, study, sport, personal hygiene and daily tasks, especially when requiring and effort (cognitive or physical) and significant organization, as well

as deficits in desire to undertake such activities. This sub-domain is related to apathy and lack of energy.

[00300] Anhedonia (reduced ability to experience or anticipate pleasure) is characterized by the looking forward to a reward, recreational or other pleasurable experience ("wanting") being more markedly and consistently impaired (anticipatory anhedonia) than the appreciation ("liking") of the experience itself (consummatory anhedonia).

[00301] Asociality (social withdrawal) is characterized by diminished interest in, motivation for, and appreciation of social interactions with others, like family and friends, loss of interest in intimate (sexual) relationships independent of any somatic problems, and for a child, may include loss of interest in playing with other children.

[00302] In some embodiments, the dosage form is administered to the subject once a day for a first treatment period of sufficient length to achieve improvement in at least one negative symptom. In an embodiment, the first treatment period is at least 2 weeks, at least 4 weeks, at least 6 weeks, at least 8 weeks, at least 10 weeks or at least 12 weeks. In an embodiment, positive symptoms in a subject treated with the dosage form are stable during the treatment period, i.e., remain at substantially the same level as at baseline. In an embodiment, the level of improvement in negative symptoms is a reduction of at least 3 points on the PANSS five factor (pentagonal structure model) negative symptom factor scores after 12 weeks of treatment. In an embodiment, the subject's negative symptom score continues to improve from 12 weeks to at least about 24, 36 or 48 weeks of treatment. The PANSS pentagonal structure model is described in WHITE L, HARVEY PD, OPLER L, LINDENMAYER J. EMPIRICAL ASSESSMENT OF THE FACTORIAL STRUCTURE OF CLINICAL SYMPTOMS IN SCHIZOPHRENIA. *PSYCHOPATHOLOGY.* 1997;30(5):263-74.

[00303] In some embodiments, if a subject experiences improvement in at least one negative symptom during the first treatment period, then administration of the therapeutically effective dose of Compound (I) is continued for a second treatment period of at least 12 weeks, at least 24 weeks, at least 48 weeks, or until the subject is determined to exhibit functional improvement subsequent to improvement in the negative symptoms. In an embodiment, positive symptoms in a subject treated with the dosage form are stable during at least part of the second treatment period, i.e., remain at substantially the same level as at baseline.

[00304] In some embodiments, the subject has a diagnosis of schizophrenia. In an embodiment, a subject selected for treatment with an oral dosage form of the disclosure has a base-line PANSS negative sub-score greater than or equal to 20. In an embodiment, the selected subject also has baseline scores of less than 4 on the following PANSS items: excitement, hyperactivity, hostility, suspiciousness, uncooperativeness and poor impulse control. In an embodiment, the selected schizophrenic subject has exhibited stable positive symptoms of schizophrenia for at least the previous one, two or three months and has exhibited negative symptoms for at least the previous one, two or three months.

[00305] In some embodiments, the schizophrenic subject treated with a gastro-resistant, CR oral dosage form of the present disclosure has prominent negative symptoms. In an embodiment, a schizophrenic subject is defined as having prominent negative symptoms when the subject has having a score ≥4 (moderate) on at least three subscale items in the PANSS negative symptoms subscale items but not on PANSS positive subscale items. In an embodiment, the subject has both prominent positive and prominent negative symptoms when the subject has scores ≥4 on items for both positive and negative symptom items.

[00306] Up to 75% of schizophrenic patients suffer from cognitive impairment, and the phase 2b study of MIN-101 discussed above showed improvement in cognitive function. Thus, in an aspect, administration of a gastro-resistant CR oral dosage form of the present disclosure to a patient with a diagnosis of schizophrenia is intended to improve cognitive function in the patient.

[00307] In some embodiments, the subject has not been previously treated with an anti-psychotic drug. In other embodiments, the subject has discontinued prior treatment with an anti-psychotic drug due to experiencing one or more of the following: satisfactory reduction in positive symptoms, an inadequate response for negative symptoms, or intolerable side effects.

[00308] A secondary outcome of the phase 2b study of MIN-101 discussed above was patients' performance on the Calgary Depression Scale for Schizophrenia (CDSS) ADDINGTON D, ADDINGTON J, MATICKA-TYNDALE E. ASSESSING DEPRESSION IN SCHIZOPHRENIA: THE CALGARY DEPRESSION SCALE. *BRITISH JOURNAL OF PSYCHIATRY SUPPLEMENT* 1993; (22):39-44. The CDSS has little overlap with positive and negative symptoms and has become the recommended scale to assess the severity of depression in patients with schizophrenia. In the

phase 2b study, the severity of symptoms as measured by the CDSS was reduced following treatment with 32 or 64 mg of MIN-101 compared to placebo. A correlation analysis between baseline treatment effects on negative symptoms and on depression symptoms in this patient cohort demonstrated there was only a small correlation between MIN-101's effects on these two symptom categories. Thus, since the effects of MIN-101 on negative symptoms and depression symptoms in schizophrenia patients were largely independent of each other, MIN-101 has the potential to alleviate one or more depression symptoms in patients who are not schizophrenic.

[00309] Thus, another object of the present disclosure is to treat at least one symptom of depression in a subject in need thereof by a method of administering a gastro-resistant CR dosage form described herein. In an embodiment, the subject has a diagnosis of schizophrenia. In an embodiment, the improvement in depression symptoms in a schizophrenic patient is measured using the CDSS.

[00310] It is another object of the present disclosure to reduce the risk for QT prolongation in a subject treated with Compound (I) by administering to the subject Compound (I) as formulated in a gastro-resistant CR dosage form described herein. In an embodiment, the subject has been identified as having one or more risk factors for drug-induced QT prolongation. In an embodiment, the subject discontinued previous treatment with a compound other than Compound (I) due to experiencing QT prolongation. In an embodiment, the subject discontinued previous treatment with a different dosage form comprising Compound (I) due to experiencing QT prolongation. In an embodiment, the subject has a diagnosis selected from the group consisting of: prominent negative symptoms of schizophrenia, prominent positive and prominent negative symptoms of schizophrenia, major depressive disorder (MDD), a sleep disorder and cognitive impairment.

[00311] In some embodiments of any of the above treatment methods, the gastro-resistant oral dosage form is administered in the morning or evening. In an embodiment, the dosage form is administered at least two hours before eating.

[00312] In some embodiments of any of the above treatment methods, the subject is 12 or more years of age. In some embodiments, the subject is at least 14, 16, 18, or 20 years old. In some embodiments, the subject is less than 50, 45, 40, 35 or 30 years old. In an embodiment, the subject is at least 16 years old and less than any of 40, 35 or 30 years old.

[00313] In some embodiments of any of the above treatment methods, the dosage form may be administered to the subject in combination with another therapeutic agent. In an embodiment, the other therapeutic agent does not inhibit CYP2D6 activity. In an embodiment, the subject is diagnosed with schizophrenia and the other therapeutic agent is an anti-psychotic drug.

[00314] In some embodiments of any of the above treatment methods, the subject may have been assigned an IM genotype or and EM genotype. In an embodiment, the subject has been assigned an EM genotype.

[00315] In some embodiments of any of the above treatment methods, the oral dosage form may comprise 32 mg of Compound (I). In an embodiment, the oral dosage form consists essentially of the components listed in Table 2 or Table 3 below.

EXAMPLES

Example 1: Description of a 32 mg MR tablet used in the Phase 2b Trial of MIN-101.

[00316] The MR 32 mg tablets are supplied as round (diameter 10 mm and R=10) white-coated tablets free from visual defects. Each tablet contains 32 mg of Compound (I). The complete statement of the components and quantitative composition of MR 32mg tablet is given in Table 1 below.

Table 1: Composition of MR 32mg tablet

Composition	MR 32mg tablet		Function
	%w/w	mg/tablet	
MIN-101[1]	12.19	38.40	Active ingredient
Hypromellose (Methocel™ K100LV CR)	9.52	30.00	Controlled release excipient
Hypromellose (Methocel™ K4M CR)	22.86	72.00	Controlled release excipient
Microcrystalline Cellulose (Avicel PH102)	30.19	95.10	Filler
Lactose Monohydrate (Fast Flo 316)	19.05	60.00	Filler

Silica Colloidal Anhydrous (Aerosil 200 Pharma)	0.48	1.50	Glidant
Magnesium stearate (vegetable grade source Hyqual NF)	0.95	3.00	Lubricant
Total (core tablets)	95.23	300.00	
Sepifilm (LP 770 Blanc)	4.76	15	Coating Agent
Total	**100.00**	**315.00**	

[1] Salt correction factor of 1.2 applied

NA: Not Applicable

Example 2: Description of an exemplary 32 mg gastro-resistant CR tablet.

[00317] The CR GR-01 tablets are supplied as round (diameter 10 mm and R=10) tablets, free from visual defects. Each tablet contains 32 mg of Compound (I). The complete statement of the components and quantitative composition of CR GR-01 tablet is given in Table 2.

Table 2: Composition of CR GR-01 tablet

Composition	CR GR-01 tablet		Function
	%w/w	mg/tablet	
MIN-101[1]	12.09	38.40	Active ingredient
Hypromellose (Metolose® 90SH 100 SR)	9.45	30.00	Controlled release excipient
Hypromellose (Methocel™ K100M CR)	22.67	72.00	Controlled release excipient
Microcrystalline Cellulose (Avicel PH102)	29.95	95.10	Filler
Lactose Monohydrate (Fast Flo 316)	18.89	60.00	Filler
Silica Colloidal Anhydrous (Aerosil 200 Pharma)	0.47	1.50	Glidant
Magnesium stearate (vegetable grade source Hyqual NF)	0.94	3.00	Lubricant
Total (Core Tablet)	94.47	300.00	

Eudragit L30D55	4.72	15.00	Controlled release excipient
Plasacryl HTP20	0.80	2.55	Anti-tacking agent
Total	100.00	317.55	

[1] Salt correction factor of 1.2 applied

NA: Not Applicable

Example 3: Description of another exemplary 32 mg gastro-resistant CR tablet.

[00318] The CR GR-02 tablets are supplied as round (diameter 10 mm and R=10) tablets, free from visual defects. Each tablet contains 32 mg of Compound (I). The complete statement of the components and quantitative composition of CR GR-02 tablet is given in Table 3 below.

Table 3: Composition of CR GR-02 tablet

Composition	CR GR-02 tablet		Function
	%w/w	mg/tablet	
MIN-101[1]	11.98	38.40	Active ingredient
Hypromellose (Methocel™ K15M CR)	9.36	30.00	Controlled release excipient
Hypromellose (Methocel™ K100M CR)	22.46	72.00	Controlled release excipient
Microcrystalline Cellulose (Avicel PH102)	29.67	95.10	Filler
Lactose Monohydrate (Fast Flo 316)	18.72	60.00	Filler
Silica Colloidal Anhydrous (Aerosil 200 Pharma)	0.47	1.50	Glidant
Magnesium stearate (vegetable grade source Hyqual NF)	0.94	3.00	Lubricant
Total (Core Tablet)	93.59	300.00	
Eudragit L30D55	4.68	15.00	Controlled release excipient

Plasacryl HTP20	0.80	2.55	Anti-tacking agent
Surelease E-7-19040	0.94	3.00	Controlled release excipient
Total	100.00	320.55	

[1] Salt correction factor of 1.2 applied

NA: Not Applicable

Example 4:. *Batch Formula for CR GR-01 and CR GR-02 tablets.*

[00319] A representative batch size for the CR GR-01 and CR GR-02 tablets are 5,400 tablets. The batch formulas are described in Tables 4 and 5 below.

Table 4: Batch Formula for CR GR-01 tablet

Composition	**kg/ batch**
MIN-101	0.206
Hypromellose Metolose® 90SH 100SR	0.162
Hypromellose Methocel™ K100M CR	0.389
Microcrystalline Cellulose	0.514
Lactose	0.324
Silica Colloidal Anhydrous	0.008
Magnesium stearate	0.016
Eudragit L30D55	0.081
Plasacryl HTP 20	0.014
Total	1.714

NA: Not Applicable

Table 5: Batch Formula for CR GR-02 tablet

Composition	**kg/ batch**
MIN-101	0.207
Hypromellose Methocel™ K15M CR	0.162
Hypromellose Methocel™ K100M CR	0.389
Microcrystalline Cellulose	0.514
Lactose	0.324
Silica Colloidal Anhydrous	0.008
Magnesium stearate	0.016

Eudragit L30D55	0.081
Plasacryl HTP 20	0.014
Surelease E-7-19040	0.016
Total	1.731

Table 5A: Batch Formula for GR-01/B Tablets (representative batch formula size is 150 000 tablets

Composition	**kg/ batch**
MIN-101	5.75
Hypromellose Methocel™ K100 LV CR	4.5
Hypromellose Methocel™ K100M CR	10.80
Microcrystalline Cellulose	14.5
Lactose	9
Silica Colloidal Anhydrous	0.22
Magnesium stearate	0.22
Eudragit L30D55	2.25
Plasacryl HTP 20	0.380
Total	47.63

Example 5: Development of an Optimized *In Vitro* Dissolution Method

[00320] Based on Compound (I) PK profiles obtained with MIN-101 MR 32mg tablets used in clinical studies, an *in vitro/in vivo* correlation (IVIVC) approach was proposed. The IVIVC approach is defined by the FDA as a predictive mathematical model describing the relationship between an *in-vitro* property of the dosage form and an *in-vivo* response. In this context, the model refers to the relationship between the *in vitro* dissolution of the MR 32mg tablet and its *in vivo* response such as Compound (I) plasma concentration. The main objectives of the IVIVC model were to validate the use of a predictive *in-vitro* dissolution method and to select target optimized formulations. If the validity of the IVIVC model is confirmed by clinical results, the *in-vitro* dissolution method could be used as a surrogate method for clinical studies.

[00321] First, after analysis of all PK data for Compound (I) from clinical studies, an *in-vitro* dissolution profile of the MR 32 mg tablet described in Example 1 was defined. This target *in-vitro* dissolution profile was then used to develop an optimized *in-vitro* dissolution method. This method is described in the next Example.

[00322] Secondly, and when the *in-vitro* dissolution method was considered as closed enough to the expectations, the target *in-vitro* dissolution profile of a gastro-resistant CR oral dosage form was defined and used to design the gastro-resistant dosage forms described in Examples 2 and 3. The dissolution profiles for these two GR dosage forms (GR-01 and GR-02) and the MR 32 mg tablet of Example 1, which were generated using the optimized dissolution method, are shown in tables 6 and 7 below.

Table 6: Cumulative *In Vitro* Dissolution Profiles

Time (hours)	Cumulative Dissolution of Compound (I) (mg)			
	Target profile	MR 32mg tablet	GR-01 tablet	GR-02 tablet
0	0	0	0	0
0.5	0	3.2	0	0
1	0	5.0	0	0
2	0	8.4	0	0
2.5	0.2	-	0	0
3	0.9	10.4	2.3	0.1
4	3.2	14.5	5.6	0.9
5	5.2	-	-	2.6
6	7.1	19.4	9.9	4.5
8	11.0	23.1	12.9	8.1
10	14.8	-	-	-
11	-	27	18.2	12.6
13	19.5	28.6	22.0	15.4
14	20.8	-	-	-
15	21.9	-	-	-
16	-	30.1	25.9	18.6
18	25.0	-	-	-
19	-	30.6	28.2	21.1
21	27.6		-	22.8
26	31.6		30.1	24.6

Table 7: *In Vitro* Dissolution Rate Profiles

Time (hours)	Compound (I) Dissolution Rate (mg/hour)			
	Target Profile	MR 32mg tablet	GR-01 tablet	GR-02 tablet
0	0	0	0	0
0.5	0	6.4	0	0
1	0	3.7	0	0
2	0	2.7	0	0
2.5	0.4	-	0	0
3	1.5	2.0	2.3	0.1
4	2.3	4.1[1]	3.3	0.8
5	2.0	2.4[1]	-	1.7
6	1.9	-	2.2	2
8	1.9	1.9	1.5	1.8
10	1.9	-	-	1.5
11	-	1.3	1.8	-
13	1.6	0.8	1.9	1.4
14	1.3	-	-	-
15	1.2	-	-	-
16		0.5	1.3	1.1
18	1.0	-	-	0.9
19		0.2	0.7	0.9
21	0.9		-	0.9
24	0.8		0.4	

[1]not considered

[00323] The CR GR-01 and CR GR-02 tablets and the MR 32 mg tablet, used as a comparator, were tested in a clinical study (MIN-101-C06) to evaluate the plasma PK profile of each dosage form.

Example 6: Analytical method for the assay of MIN-101, BFB-520 and BFB-999 in Human Plasma

PREPARATION OF SOLVENTS AND REAGENTS

All solvents and reagents listed below are recognized as analytical grade or better (relevant for the entire document).

Volumes are indicated as examples, different volumes may be prepared if proportions are kept.

Dilution solvent: 50/50 (v/v) Acetonitrile/water solution
Mix 500 mL of acetonitrile with 500 mL of water.
Storage: 1 month at room temperature.

Buffer: pH 9 Buffer solution
Transfer the content of an ampoule of pH 9 buffer concentrate (Merck, P/N 109889) in a 500 mL volumetric flask.
Fill up *q.s.* 500.0 mL with water.
Storage: 1 month at *ca.* +5°C.

Buffer: 1 M Ammonium acetate buffer
Dissolve 7.7 g of ammonium acetate with 100 mL of water.
Storage: 3 months at *ca.* +5°C.

Mobile phase: 10 mM Ammonium acetate buffer solution
Add 10 mL of 1 M ammonium acetate buffer to 990 mL of water.
Or dissolve 0.77 g of ammonium acetate with 1 L of water.
Degas if necessary (by sonication or by magnetic agitation under vacuum).
Storage: 5 days at room temperature.

Reconstitution solvent: 80/20 (v/v) 10 mM Ammonium acetate buffer/acetonitrile solution
Mix 400 mL of 10 mM ammonium acetate buffer solution with 100 mL of acetonitrile.
Or add 4 mL of 1 M ammonium acetate buffer to 396 mL of water and 100 mL of acetonitrile.
Storage: 5 days at room temperature.

Needle rinsing solvent: 80/20 (v/v) Acetonitrile/water solution
Mix 800 mL of acetonitrile with 200 mL of water.
Degas if necessary (by sonication or by magnetic agitation under vacuum).
Storage: 1 month at room temperature.

Needle rinsing solvent: 65/35 (v/v) Acetonitrile/water solution
Mix 650 mL of acetonitrile with 350 mL of water.
Degas if necessary (by sonication or by magnetic agitation under vacuum).
Storage: 1 month at room temperature.

Column rinsing solvent: 90/10 (v/v) Acetonitrile/water solution
Mix 900 mL of acetonitrile with 100 mL of water.
Degas if necessary (by sonication or by magnetic agitation under vacuum).
Storage: 1 month at room temperature.

SAMPLE PREPARATION AND EXTRACTION PROCEDURE

Control plasma and plasma samples are thawed at room temperature and centrifuged at 1920 g for 5 minutes at +4°C.

- **Preparation of samples**

Blank reagent sample

In a 10 mL polypropylene tube:

1. Transfer 250 µL of water.

Blank and zero samples

In a 10 mL polypropylene tube:

1. Transfer 250 µL of control plasma.

Calibration standards

In a 1.5 mL conic polypropylene tube:

1. Transfer 900 µL of control plasma,
2. Add 100 µL of appropriate WS,
3. Mix on a vortex for 30 seconds,
4. Transfer 250 µL of the preparation into a 10 mL polypropylene tube.

QC samples

In a 1.5 mL conic polypropylene tube:

1. Transfer 900 µL of control plasma,
2. Add 100 µL of appropriate QC-WS,
3. Mix on a vortex for 30 seconds,
4. Transfer 250 µL of the preparation into a 10 mL polypropylene tube.

Specimens

In a 10 mL polypropylene tube:

1. Transfer 250 µL of plasma sample.

20-fold diluted samples [2]

In a 1.5 mL conic polypropylene tube:

1. Transfer 380 µL of control plasma,
2. Add 20 µL of plasma sample to be diluted,
3. Mix on vortex for 30 seconds,
4. Transfer 250 µL of the preparation into a 10 mL polypropylene tube.

- **Extraction procedure**

1. Add 25 µL of dilution solvent (blank reagent sample, blank sample) or 25 µL of IS-WS (other samples),
2. Add 1 mL of pH 9 buffer solution,
3. Mix on a vortex for 10 seconds,
4. Add 4 mL of diethylether,
5. Mix on a reciprocating shaker at slow speed for 20 minutes,
6. Centrifuge at 1920 g for 10 minutes at +4°C,
7. Transfer the tubes at *ca.* -80°C for 15 minutes,
8. Transfer the organic phase (upper phase) into a 5 mL glass tube,
9. Evaporate to dryness under a stream of nitrogen at +30°C,
10. Reconstitute with 200 µL of reconstitution solvent,
11. Mix on a vortex for 30 seconds
12. Centrifuge at 1920 g for 5 minutes at +4°C,
13. Transfer the final extract into a polypropylene vial,
14. Seal the vial with a cap with Teflon/silicone/Teflon septum,
15. Centrifuge at 2500 g for 7 minutes at +4°C,
16. Place the vials in the autosampler until analysis.

Or [4]

13. Transfer the final extract into a 2 mL polypropylene 96-wells collection plate,
14. Seal the plate with a silicone pre-pierced cap mat,
15. Centrifuge at 2500 g for 7 minutes at +4°C,
16. Place the plate in the autosampler until analysis.

ANALYSIS CONDITIONS

- **Chromatographic conditions**

Column and oven

Column	Gemini C18 100 x 4.6 mm, 3.0 µm (Phenomenex)
Filter or guard column	C18 4 x 2 mm (Phenomenex)
Column temperature	+40°C ±5°C
Column rinsing solvent	90/10 (v/v) Acetonitrile/water solution
Column rinsing conditions	60 minutes at 0.6 mL/min

Autosampler

Injection volume	5 µL (to be adapted according to MS sensitivity)
Autosampler temperature	+5°C

Pump

Mobile phase A	10 mM Ammonium acetate buffer solution
Mobile phase B	Acetonitrile

Isocratic mode

Flow rate (mL/min)	Mobile phase A (%)	Mobile phase B (%)
0.6	35	65

Detection

Detection type	MRM
Ionisation type and mode	ESI in positive ionisation mode
Precursor ion	$[M+H]^+$

MRM transitions

Analyte	MRM transition
MIN-101 (CYR-101)	367 > 146
BFB-520	369 > 146
BFB-999	383 > 232
CYR-101-d6	373 > 152
BFB-784	387 > 164

- **LC equipment no. 1**

Description

Equipment	Type
Autosampler	G1367B autosampler and G1330B thermostat (Agilent)
LC pump	G1311A quaternary pump and G1322A degasser (Agilent)
Column oven	G1316A thermostatted column compartment (Agilent)
Detector	$EP10^{+}$ $HSID^{++}$ (Ionics)

System care

Needle rinsing solvent 80/20 (v/v) Acetonitrile/water solution

Needle rinsing programming

Step	Description
1	Wash needle in flush port for 15 seconds
2	Drow def amount from sample, 200 µL/min, 1 mm offset
3	Wash needle in flush port for 15 seconds
4	Inject
5	Remote start pulse, duration 10 x 12.5 msec

Analysis conditions

Injection volume 5 µL

Run time 6.0 min

Retention times (R_t)

Analyte	Rt (min)
MIN-101 (CYR-101)	*ca.* 2.9
BFB-520	*ca.* 2.3
BFB-999	*ca.* 2.4
CYR-101-d6	*ca.* 2.9
BFB-784	*ca.* 2.4

- **LC equipment no. 3** [5]

Description

Equipment	Type
Autosampler	Acquity UPLC Sample Manager FTN (Waters)
LC pump	Acquity UPLC I-Class (Waters)
Columnoven	Acquity UPLC Column Heater (Waters)
Detector	XevoTQ-S (Waters)

System care

Needle rinsing solvent

Exterior (Wash)	80/20 (v/v) Acetonitrile/water solution
Interior (Purge)	65/35 (v/v) Acetonitrile/water solution
Needle rinsing programming	Pre-injection wash: 0 second
	Post-injection wash: 6 seconds

Analysis conditions

Injection volume	0.5 µL
Run time	6.0 min

Retention times (Rt)

Analyte	Rt (min)
MIN-101 (CYR-101)	*ca.* 3.0
BFB-520	*ca.* 2.4
BFB-999	*ca.* 2.4
CYR-101-d6	*ca.* 2.9
BFB-784	*ca.* 2.5

- **LC equipment no. 2** [3]

Description

Equipment	Type
Autosampler	Acquity UPLC (Waters)
LC pump	
Column oven	Acquity UPLC high temperature column heater (Waters)
Detector	API 4000 (AB Sciex)

System care

Needle rinsing solvent

Strong solvent	80/20 (v/v) Acetonitrile/water solution
	2000 µL
Weak solvent	65/35 (v/v) Acetonitrile/water solution
	4000 µL

Analysis conditions

Injection volume	1 µL
Injection mode	Partial loop
Run time	6.0 min

Retention times (R_t)

Analyte	Rt (min)
MIN-101 (CYR-101)	*ca.* 2.9
BFB-520	*ca.* 2.3
BFB-999	*ca.* 2.4
CYR-101-d6	*ca.* 2.9
BFB-784	*ca.* 2.4

DATA PROCESSING AND ACCEPTANCE CRITERIA

- **Data processing** [2]

		MIN-101 (CYR-101)	BFB-520	BFB-999
Calibration range	LLOQ (ng/mL)	0.2500	0.2500	0.2500
	ULOQ (ng/mL)	200.0	50.00	50.00
Response		MIN-101 peak area / CYR-101-d6 peak area	BFB-520 peak area / BFB-784 peak area	BFB-999 peak area / BFB-784 peak area
Regression model		$1/X^2$ weighted simple linear regression	$1/X^2$ weighted simple linear regression	$1/X^2$ weighted simple linear regression

Example 7: Synopsis of Protocol MIN-101C06

Name of Sponsor/Company: Minerva Neurosciences, Inc.
Name of Investigational Product: MIN-101
Study Title: A Phase 1, Open-Label, Randomized, 3-Treatment Sequence, 3-Period, Single-Dose, Crossover Study in CYP2D6 Extensive Metaboliser Healthy Subjects to Compare the Pharmacokinetic Properties of 2 Gastro-Resistant and 1 Comparator Modified Release Formulations of MIN-101 and its Metabolites Followed by Food Effect Testing of the Selected Gastro-Resistant Controlled Release Formulation
Objectives: **Primary:** Part 1: PK Evaluation • To evaluate the pharmacokinetic (PK) profiles of MIN-101 and its main metabolites (BFB-520 and BFB-999) following administration of 2 Gastro-Resistant and 1 Comparator Modified Release (MR) formulations of MIN-101 in healthy cytochrome P450 (CYP) 2D6 Extensive Metaboliser (EM) male and female subjects • To Select 1 gastro-resistant MR formulation for use in fed state. Part 2: Food effect • To evaluate the effect of food (given as a high fat, high calorie meal) on the bioavailability of MIN-101 and its main metabolites when the selected gastro-resistant MR formulation is administered as a single dose of 32 mg to healthy CYP2D6 EM male and female subjects. **Secondary:** Part 1: PK Evaluation • To provide additional information on the safety and tolerability of single doses of MIN-101 in healthy CYP2D6 EM male and female subjects. • To evaluate the relationship between plasma levels of MIN-101 and its main metabolites on electrocardiogram (ECG) parameters including QT / QTcF • Part 2: Food effect • To evaluate the safety and tolerability of the selected MR formulation in healthy CYP2D6 EM male and female subjects in fed as compared to fasted state.

Methodology:

This is a single-center, 2-part, phase 1 study.

Part 1: PK Evaluation

Part 1 is an open-label, randomised, 3-treatment sequence, 3-period study to evaluate the PK profile of MIN-101 and its metabolites (BFB-520 and BFB-999) after single oral administration of 3 formulations of MIN-101 (2 prototypes of CR gastro-resistant (GR) formulations and 1comparator MR formulation). Each subject will receive a single dose of each of the formulations over the 3 periods. There will be a washout of 14 ± 2 days between the three periods.

In total, 16 healthy CYP2D6 EM male or female subjects (with an ideal equal gender split, but a minimum of 6 of each sex) will be dosed to ensure data in 12 evaluable subjects. To be evaluable, subjects must have received all 3 formulations and have sufficient data for the primary objective of Part 1 of the study. Subjects must provide written informed consent to participate in the study before evaluations are performed or any laboratory samples are collected. Subjects will be evaluated for study eligibility during the screening period. After written informed consent is obtained, a complete medical history will be documented. A complete physical examination will be conducted, including measurement of vital signs, ECG (triplicate), body weight, and height. Hematology, clinical chemistry and urinalysis will be performed for all subjects. All subjects must be willing to use an acceptable double-barrier method of birth control with their partners from Screening through 90 days after the last dose.

Part 2: Food effect

Subjects who completed part 1 of the study will return and receive a further single oral dose of one of the selected GR prototype under fed conditions to allow the assessment of food effect by comparison of the PK properties to those obtained in Part 1. Part 2 will commence after a review of the PK and safety data to decide which GR formulation will be used. There will be a wash-out period of 14 ± 2 days after part 1 has been completed.

The end-of-study or early withdrawal assessments will be performed 5-9 days after the last received dose.

Number of Subjects (planned):

In total, 16 healthy CYP2D6 EM male or female subjects (with an ideal equal gender split, but a minimum of 6 of each sex) will be dosed to ensure data in 12 evaluable subjects.

Subjects who are withdrawn for non-IMP related adverse events (AEs) will be replaced as required to ensure 12 evaluable subjects for Part 1 and for Part 2, at the end of the clinical study. Subjects withdrawn due to an IMP–related AE will not be replaced.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria

Subjects must satisfy all of the following inclusion criteria during screening to be enrolled in the study:

1. Confirmed CYP 2D6 extensive metaboliser genotype defined as a subject that has at least one functional allele (*1, or *2) but has no non-functional allele, meaning any combination of *1 and *2, and a decreased function allele (*10, *17 or *41) is allowed via documented testing
2. Subject has given voluntary written informed consent before performance of any study related procedure
3. Must be 18 to 45 years of age, inclusive
4. Subject must be a healthy male or female as indicated by the following:
   - Clinical chemistries, haematology, and urinalysis tests must be within normal, allowable limits (if out of range, and with the exception of potassium, magnesium, and calcium, must be considered clinically significant to be exclusionary) and performed within 21 days of receiving first dose of study drug
   - Body mass index of between 18 and 30 kg/m^2, inclusive
   - Normal vital signs after 5 minutes resting in supine position:
     - 95 mm Hg < systolic blood pressure < 140 mm Hg
     - 50 mm Hg < diastolic blood pressure < 90 mm Hg
     - 50bpm < heart rate < 90 bpm
     - Normal 12-lead ECG defined as: P ≤120 ms, 120 ms < PR < 210 ms, QRS < 120 ms, QTc (Fridericia) ≤ 430 msec for males and ≤ 440 msec for females (incomplete right bundle branch block can be accepted)
5. Agree to abstain from all medication (except for allowed birth control defined in inclusion criteria 6), including non-prescription and prescription medication (including vitamins and natural or herbal remedies, e.g. St. John's Wort) for 21 days before the first dose with IMP on period 1 until discharged from the study (end of post study medical following period 4)
6. Subject agrees to use the following methods of birth control:

   Female subjects of child bearing potential must be willing to use two methods of contraception throughout and up to 30 days after completion of the study. One of which must be a highly effective method defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

   The following highly effective contraception methods acceptable for this study are:

   - Surgical sterilization (i.e., bilateral tubal ligation/salpingectomy, hysterectomy for female subjects or partners; vasectomy for male subjects or partners)
   - Placement of an intrauterine device or intrauterine system
   - Hormonal contraception (implantable, patch, injectable)

   PLEASE NOTE: Oral hormonal contraceptives are not permitted in this study.

   - True sexual abstinence when this is in line with the preferred and usual lifestyle of the subject, periodic abstinence (e.g. calendar ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of the trial and withdrawal are NOT acceptable methods of contraception)

The following acceptable methods can be used as a second form of contraception during the study:

- Barrier methods for female subjects include either their partner's use of a condom or the subject's use of an occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam, gel, film, cream, or suppository

Female subjects who are post-menopausal (defined as spontaneous amenorrhea for at least 1 year or spontaneous amenorrhea for at least 6 months confirmed by Follicle stimulating hormone [FSH] result of ≥40 IU/mL) are eligible for this study.

Male subjects

Male subjects who have been sterilised or have partners of non-childbearing potential (including homosexual men) are required to use one barrier method of contraception. This is to prevent unintended exposure of the partner to the study drug via seminal fluid (for male subjects, this must be a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps].

Male subjects who have partners of childbearing potential must be willing to use one barrier method of contraception with their partners throughout the study (a condom or their partner's use of an occlusive cap [diaphragm or cervical/vault caps]). Their partners must also be using a highly effective method of birth control defined as one in which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as sterilisation, implants, injectables, combined oral contraceptives, and intrauterine devices for up to 90 days after completion of the study. Subjects must agree to inform the Investigator if their partner becomes pregnant during this time.

7. Must be willing and able to communicate and participate in the whole study.
8. Willing to eat all the food supplied throughout the study

Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

1. A history of clinically significant gastrointestinal disease (especially peptic ulcerations, gastrointestinal bleeding, ulcerative colitis, Crohn's disease or Irritable Bowel Syndrome); renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic or psychiatric disease (especially those with a past history of clinically significant depression, suicidal ideation or suicide attempts), or cardiovascular disease, or any other condition which, in the opinion of the principle investigator, would jeopardize the safety of the subject or impact the validity of the study results
2. Acute diarrhea or constipation in the 7 days before the predicted first study day. If screening occurs >7 days before first study day, this criterion will be determined on first study day. Diarrhea is defined as the passage of liquid feces and/or a stool frequency of > 3 times per day. Constipation will be defined as a failure to move the bowels more frequently than every other day
3. Subject has donated blood within 90 days or plasma within 30 days of study dosing
4. Regular alcohol consumption in males > 21 units per week and females > 14 units per week (1 Unit = ½ pint beer, 25 mL of 40% spirit or a 125 mL glass of wine)
5. Subject has a borderline or long QTc Fridericia interval as defined by screening readings of >430 msec for males and >440 for females or a personal or familial history of long QT syndrome
6. Subject has participated in a clinical trial within 90 days prior to study initiation
7. Females who are pregnant or breast feeding
8. Subject has used any prescription medication or over-the-counter (OTC) medication, including vitamin supplements, within 21 days prior to day -1
9. Subject has been treated with any known P450 2D6 or 3A4 enzymes altering drugs (e.g., beta blockers, antidepressants, antipsychotics, certain antibiotics such as erythromycin, ketoconazole, rifampicin, trimethoprim or clarithromycin, benzodiazepine such as alprazolam or midazolam, antihistamines such as chlorpheniramine, calcium channel blockers such as amlodipine or diltiazem, or PDE5 inhibitors) within 30 days prior to the study
10. Subject has smoked or used nicotine products within 2 months prior to or during the study
11. Subject has sought advice from or been referred to a GP or counsellor for abuse or misuse of alcohol, non-medical drugs, medicinal drugs or other substance abuse, *e.g.* solvents
12. Subject has a positive blood screen for HIV, Hepatitis B surface antigen (HBsAg), and Hepatitis C Antibody
13. Any current or previous use of drugs such as opiates, cocaine, ecstasy, or intravenous amphetamines and/or a positive urine screen for alcohol or drugs of abuse. Subjects who admit to occasional past use of cannabis will not be excluded as long as they have a negative drugs-of-abuse test and have been abstinent from cannabis use for at least 3 months
14. Subject has a current uncontrolled inter-current illness (i.e., active infection) or has had a clinically significant illness within the last 30 days prior to Day -1
15. Subject has had major surgery within 28 days of study entry, or 12 months prior to study for gastrointestinal surgery.
16. Failure to satisfy the investigator of fitness to participate for any other reason.

Test Product, Dosage, and Route of Administration:

Part 1:

After fasting for 10 hours overnight, on the morning of dosing days, study drug will be administered with 240 mL of noncarbonated water. Subjects will have their first meal at lunch time. Subjects will receive a single oral administration of each of the following regimens in a randomized manner, separated by a **14±2** days washout period:

Regimen A: 32 mg MIN-101 of the current modified-release formulation (comparator) identified as MR-32 formulation administered in the fasted state

Regimen B: 32 mg MIN-101 of Gastro-resistant CR Formulation identified as GR-01: administered in the fasted state

Regimen C:32 mg MIN-101 of Gastro-resistant CR Formulation identified as GR-02: administered in the fasted state

Part 2:

In Part 2, subjects will receive 1 oral dose of the selected gastro-resistant CR formulation (GR-01 or GR-02) in the fed state.

After fasting for 10 hours overnight, on the morning of Day 1, subjects will be given a high-fat, high-calorie breakfast before study drug administration. Subjects will consume the meal over a 25-minute period or less. After completing the meal, and 30 minutes after the start of the meal, study drug will be administered.

All study drugs will be administered orally with 240 mL of noncarbonated water. Water will be allowed as desired except for 1 hour before and 1 hour after drug administration.

Reference Therapy, Dosage and Mode of Administration:

Not Applicable. 32mg MIN-101 of the current modified release formulation to be used as a comparator.

Duration of Subject Participation/Duration of Study/Duration of Treatment:

Selection:

Up to 21 days prior to first dose period 1

Institutionalization:

From morning of Day -1 up to Day 4 for 4 separate periods

Washout Period:

14±2 days from previous period dosing

End-of-study visit:

7 (± 2 days) days after the last dose

Total study length (including a screening period of 21 days):

Up to 78 Days.

EVALUATION CRITERIA

Pharmacokinetics:

Plasma will be stored at -80°C until analysis. Plasma samples will be analyzed for MIN-101 and its metabolites BFB-520 and BFB-999 using a validated LC-MS/MS method.

Blood samples for MIN-101 will be collected at time 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 48, 60, and 72 hours post-dose on Day 1 of all periods. The following key plasma PK parameters will be calculated using non-compartmental methods: C_{max}, T_{max}, T_{lag}, partial AUC (e.g., AUC_{12}, AUC_{24}), AUC_{last}, AUC_{∞}, and $t_{1/2}$. Additional PK parameters may be included if deemed appropriate.

ECG to be detailed as there will be PK/PD assessment

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from Baseline values (the pre-dose ECG will be used as Baseline) to allow detection of clinically relevant changes in individuals.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc interval corrected for heart rate using QTcF. QTcF values will be tabulated for their absolute values and also tabulated relative to Baseline measurements in order to detect individual QTcF changes.

Descriptive statistics of QTcF intervals and changes from Baseline will be summarised at each scheduled time point. The percent of subjects with QTc interval > 450 milliseconds, > 480 milliseconds, or ≥ 500 milliseconds will be summarised as will the percent of subjects with QTcF interval increases from Baseline of 30 to 59 milliseconds or ≥ 60 milliseconds.

Important abnormalities in ECG waveform that are changes from the Baseline readings will be reported (e.g., changes in T-wave morphology or the occurrence of U-waves).

Safety and Tolerability:

The incidence of adverse events and clinically significant abnormal laboratory, vital signs and ECGs values will be recorded based upon Investigator observation and subject reporting.

STATISTICAL CONSIDERATIONS

Sample size: The sample size for this study is based upon both quantitative and qualitative consideration. In previous single dose experience with EM subjects, the inter-subject coefficient of variance (CV) for plasma AUC and C_{max} for MIN-101 reference formulation is estimated to be about 30% and 50%, respectively. Therefore, the selected sample size of 12 to 16 completers should be sufficient to address the objectives of this study and to detect the occurrence of rare adverse events should such event are likely due to treatment with MIN-101. Every effort will be made to have an equal number of males and females enrolled.

Pharmacokinetics: Pharmacokinetic parameters will be summarized by mean, standard deviation, standard error of the mean, coefficient of variation, minimum, median, and maximum, as appropriate, for each formulation and between the selected MR formulation for each food condition. The 90% confidence intervals for the ratio of mean log-transformed plasma partial AUC, AUC_{last}, and AUC_{∞} and C_{max} will be constructed using the estimated least squares means and intra-subject variance from a mixed effects model.

Additional analysis will be performed if deemed necessary including the relationship between plasma levels of MIN-101 and its main metabolites and changes in QTcF intervals.

Safety: Safety and tolerability of MIN-117 will be based upon the review of individual values and summary statistics. Incidence of treatment-emergent adverse events will be tabulated by counts and percentages. Abnormalities in clinical laboratory, vital signs, and ECG will be based on pre-defined normal ranges and will be tabulated by dose group showing subject counts and percentages.

[00324] Examples 8-11 detail an open-label, randomized, 3-treatment sequence, 3-period study to evaluate the PK profile of MIN-101 and its metabolite BFB-520 after single oral administration of 3 formulations of MIN-101 (2 prototypes of CR gastro-resistant (GR) formulations (GR-01 and GR-02) and 1 comparator MR formulation (MR32)). Each subject received a single dose of each of the formulations over the 3 periods. There was a washout of 14 ± 2 days between the three periods.

[00325] In the Examples, various tables are shown which include the plasma concentrations time profile of various compounds, including, for example, 1H-Isoindol-1-one, 2-[[1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, i.e., Compound (I). In these Tables, the use of the "MIN-101" or "MIN101" is intended to refer to the free base, i.e., Compound (I).

Example 8: *In Vivo* Pharmacokinetic Analysis of MIN-101 in CR GR-01 Tablets, CR GR-02 Tablets, and MR 32 mg Capsules (MR32) (tau = 72 h)

[00326] **MR32** - 12 subjects (cross-over)

[00327] Geo Mean C_{max}: 28.34 ng/mL

[00328] Median T_{max}: 2.00 H

$AUC_{(0\text{-}tau)}$: 291.55 ng·H/mL

Table 8. MR32 Mean MIN-101 Plasma Concentrations and Parameters

MR32	MR32 MIN-101 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00
0,5	6,56	7,42	6,46	113,08
1	19,68	7,24	5,44	36,77
1,5	23,96	7,68	6,33	32,04
2	24,16	7,89	5,97	32,64
2,5	24,68	6,47	5,19	26,24
3	22,06	5,41	4,71	24,54
3,5	20,34	5,38	4,21	26,46
4	19,45	5,61	4,92	28,83
5	21,54	10,08	7,17	46,80
6	15,19	6,89	4,91	45,33
7	11,89	5,89	3,82	49,52
8	10,36	4,69	3,39	45,27
10	12,46	5,94	4,95	47,65
12	12,56	5,64	4,41	44,58
14	10,33	4,68	3,96	47,05
16	7,74	3,14	2,64	40,56
20	4,12	2,26	1,85	54,83
24	3,11	1,62	1,48	52,21
28	2,39	2,24	1,38	93,57
32	1,45	1,42	0,96	97,56
36	0,96	1,15	0,65	119,73
48	0,20	0,35	0,27	176,68
60	0,03	0,12	0,06	346,41
72	0,04	0,13	0,07	346,41
CMax ng/ml	29,52	9,00	6,70	30,48
Tmax H	2,42	1,33	0,99	54,98
AUC0-t H.ng/ml	291,55	66,12	53,61	22,68

[00329] See Figure 4.

[00330] **GR-01** - 12 subjects (cross-over)

[00331] Geo Mean C_{max}: 18.82 ng/mL

[00332] Median T_{max}: 4.50 H

$AUC_{(0\text{-}tau)}$: 284.52 ng·H/mL

Relative Bioavailability versus MR32: F% C_{max}: 69.9%, F% $AUC_{(0\text{-}tau)}$: 101.3%

Table 9. GR-01 Individual MIN-101 Plasma Concentrations and Parameters

GR01	GR01 MEAN MIN-101 PLASMA CONCENTRATIONS (ng/ml) and AUC0-t (H.ng/ml)											
Hours	1-MIN-101	2-MIN-101	3-MIN-101	5-MIN-101	6-MIN-101	7-MIN-101	8-MIN-101	9-MIN-101	10-MIN-101	11-MIN-101	12-MIN-101	13-MIN-101
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	4,22	0,00	0,00	0,00
1,5	0,00	0,00	6,26	0,00	0,00	0,00	0,38	0,00	0,42	0,00	0,00	7,98
2	3,83	5,42	10,86	2,50	0,00	0,00	13,23	0,00	8,71	16,03	0,48	8,14
2,5	15,95	13,82	11,87	12,14	0,00	3,45	12,42	3,00	12,78	24,17	23,30	7,62
3	17,85	17,81	11,10	13,86	0,39	12,78	11,08	24,02	12,98	26,58	28,00	10,13
3,5	15,58	21,53	10,87	12,31	6,52	10,89	10,94	28,19	13,66	25,78	24,01	12,18
4	20,60	19,03	9,23	11,96	15,23	9,53	8,04	22,91	17,64	24,78	22,59	11,30
5	17,05	17,24	6,66	14,68	15,63	8,44	14,90	17,95	12,92	24,45	12,86	12,69
6	15,26	14,41	6,89	13,16	13,39	6,06	12,36	11,72	7,62	19,24	5,64	10,42
7	9,61	11,29	6,28	12,62	10,60	4,71	11,51	12,95	5,70	17,63	9,72	9,08
8	7,46	7,20	5,66	11,86	10,51	3,61	8,19	16,53	13,39	14,16	5,62	5,52
10	4,30	5,10	12,66	11,88	6,19	2,71	18,08	17,00	18,05	6,68	13,19	10,59
12	9,45	5,69	10,24	20,15	7,24	3,05	12,22	13,92	16,31	11,15	13,39	12,47
14	13,11	10,14	12,01	17,73	7,12	3,52	12,65	12,02	14,42	11,67	20,32	9,36
16	10,98	9,35	12,59	16,88	6,40	3,18	7,19	11,25	13,43	13,29	19,44	9,02
20	5,54	3,88	4,69	8,36	4,95	2,56	2,44	7,99	6,52	9,78	5,92	3,23
24	5,57	1,94	3,21	6,73	5,31	2,38	2,90	12,21	3,90	10,97	3,63	7,08
28	4,31	1,64	3,18	2,55	3,91	2,35	1,47	7,67	3,78	10,31	0,54	5,80
32	3,50	1,56	2,73	1,16	3,55	5,90	0,66	3,59	2,79	7,59	0,67	3,46
36	2,37	1,05	1,34	0,54	2,14	12,25	0,00	1,06	0,56	3,73	0,37	3,60
48	1,33	0,73	0,28	0,00	2,04	2,55	0,00	0,00	0,00	0,56	0,00	1,76
60	0,00	0,48	0,00	0,00	1,33	1,33	0,00	0,00	0,00	0,00	0,00	0,45
72	0,00	0,69	0,00	0,00	0,41	0,44	0,00	0,00	0,00	0,00	0,00	0,27
CMax ng/ml	20,6	21,5	12,7	20,2	15,6	12,8	18,1	28,2	18,1	26,7	28,0	12,7
Tmax H	4,0	3,5	10,0	12,0	5,0	3,0	10,0	3,5	10,0	3,0	3,0	5,0
AUC0-t H.ng/ml	281,6	219,3	230,1	309,7	262,8	257,0	213,8	357,2	289,7	430,4	279,0	283,6
F AUC	84,0	93,6	98,8	172,8	92,0	112,6	80,0	92,5	75,8	143,9	76,0	92,5
F Cmax	85,3	72,9	48,6	110,5	54,2	69,1	74,4	68,4	37,7	118,9	75,9	45,7

Table 10. GR-01 Mean MIN-101 Plasma Concentrations and Parameters

GR01	GR01 MIN-101 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00
1	0,35	1,22	0,65	346,41
1,5	1,25	2,77	1,95	220,78
2	5,75	5,57	4,67	96,91
2,5	11,71	7,46	5,46	63,69
3	15,54	7,84	6,08	50,45
3,5	16,04	7,01	5,89	43,68
4	15,99	6,08	5,27	38,00
5	14,62	4,60	3,26	31,47
6	11,35	4,17	3,35	36,70
7	10,33	3,58	2,64	34,63
8	9,39	3,93	3,25	41,81
10	10,69	5,39	4,42	50,45
12	11,26	4,66	3,48	41,34
14	11,76	4,67	3,33	39,73
16	10,58	4,87	3,96	46,01
20	5,49	2,33	1,85	42,48
24	5,57	3,30	2,58	59,31
28	3,96	2,80	2,04	70,67
32	3,10	2,06	1,50	66,68
36	2,42	3,33	2,05	137,58
48	0,77	0,92	0,77	119,51
60	0,30	0,51	0,40	171,48
72	0,15	0,24	0,20	159,83
CMax ng/ml	19,59	5,74	4,61	29,30
Tmax H	6,00	3,43	3,00	57,19
AUC0-t H.ng/ml	284,52	60,83	41,49	21,38
F AUC	101,30	29,16	20,90	28,79
F Cmax	69,90	23,92	17,04	34,22

[00333] See Figure 5.

[00334] **GR-02** - 12 subjects (cross-over)

[00335] Geo Mean C_{max}: 15.43 ng/mL

[00336] Median T_{max}: 14.00 H

$AUC_{(0\text{-}tau)}$: 253.01 ng·H/mL

Relative Bioavailability versus MR32: F% C_{max}: 54.33%, F% $AUC_{(0\text{-}tau)}$: 86.9%

Table 11. GR-02 Individual MIN-101 Plasma Concentrations and Parameters

GP02	GR02 MEAN MIN-101PLASMA CONCENTRATIONS (ng/ml) and AUCo-t (H.ng/ml)												
Hours	1-MIN-101	2-MIN-101	3-MIN-101	4-MIN-101	5-MIN-101	7-MIN-101	8-MIN-101	9-MIN-101	10-MIN-101	11-MIN-101	12-MIN-101	13-MIN-101	14-MIN-101
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	2,03
2	0,00	0,00	0,41	0,00	0,70	0,00	0,00	0,00	0,00	0,00	0,00	0,86	6,86
2,5	2,13	0,00	1,87	0,00	1,17	1,09	0,00	1,24	2,48	1,02	0,00	2,79	11,87
3	4,71	0,41	2,66	0,00	2,98	1,52	0,68	2,55	3,87	5,06	4,14	3,81	11,48
3,5	5,35	1,16	3,08	0,35	2,16	2,14	1,06	3,14	5,27	11,72	7,24	3,02	14,23
4	6,70	2,20	3,06	1,17	2,19	2,25	1,21	3,45	6,24	12,69	8,58	3,45	12,39
5	8,93	6,06	3,40	2,00	10,46	2,87	2,49	4,07	7,52	14,53	7,76	8,84	11,87
6	7,60	6,38	2,61	2,92	10,83	3,27	1,94	4,24	6,94	11,33	5,09	8,09	8,75
7	5,96	5,09	3,56	5,26	7,32	3,16	2,06	4,52	4,85	10,76	5,23	9,19	8,67
8	5,11	4,28	2,89	5,14	5,40	3,30	2,58	5,76	5,02	6,39	11,43	8,95	10,08
10	4,90	3,27	3,92	5,82	12,63	4,26	3,26	9,25	5,39	10,25	12,96	11,15	15,14
12	15,08	2,81	6,31	9,24	20,26	3,27	6,31	8,07	21,50	17,68	13,85	16,18	25,88
14	11,62	7,94	7,57	10,68	18,73	3,42	3,77	10,19	11,15	16,50	15,37	9,66	28,85
16	9,87	5,79	11,46	7,68	15,69	8,22	2,81	10,94	9,53	9,32	19,54	7,85	19,75
20	10,06	8,27	6,62	3,77	9,34	5,15	6,94	7,56	4,26	8,94	9,83	4,84	6,44
24	9,29	4,59	5,07	5,95	6,89	12,96	6,64	10,97	6,98	7,46	12,76	13,32	3,97
28	9,23	3,21	4,04	4,43	1,54	13,20	6,48	10,56	10,72	6,28	10,95	7,05	3,54
32	8,21	4,06	2,61	3,36	0,44	6,48	0,00	7,92	9,55	3,03	4,75	4,50	1,38
36	4,24	2,75	1,59	2,12	0,00	2,87	0,00	4,57	4,94	1,66	2,03	3,42	0,40
48	1,72	0,63	0,58	0,56	0,00	0,43	0,00	0,91	0,00	0,55	0,29	0,54	0,00
60	0,00	1,34	0,41	0,00	0,00	0,00	0,00	0,65	0,00	0,00	0,00	0,31	0,00
72	0,00	0,28	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
CMax ng/ml	15,1	7,9	11,5	10,7	20,3	13,2	6,3	11,0	21,5	17,7	19,5	16,2	29,9
Tmax H	12,0	14,0	16,0	14,0	12,0	28,0	12,0	24,0	12,0	12,0	16,0	12,0	14,0
AUC0-t H.ng/ml	315,5	190,9	183,2	182,0	247,4	233,2	52,0	306,3	275,7	300,5	367,4	298,9	338,9
F AUC	95,4	61,5	78,5	101,5	98,5	102,2	15,8	75,9	73,2	100,5	97,3	57,5	116,3
F Cmax	47,5	26,9	44,0	55,6	70,3	71,4	26,0	25,5	46,0	77,5	53,7	58,3	101,1

Table 12. GR-02 Mean MIN-101 Plasma Concentrations and Parameters

GR02	GR02 MIN-101 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00
1,5	0,16	0,59	0,31	375,28
2	0,68	1,95	1,04	286,76
2,5	1,98	3,29	1,89	166,30
3	3,22	3,03	1,90	94,21
3,5	4,69	4,39	3,38	93,69
4	5,20	4,14	3,38	79,73
5	7,05	3,94	3,24	55,85
6	6,16	3,20	2,68	51,99
7	5,86	2,63	2,09	44,82
8	5,95	2,84	2,19	47,70
10	7,86	4,27	3,79	54,29
12	12,81	7,69	6,62	60,04
14	12,06	7,28	5,35	60,38
16	10,63	5,24	3,98	49,25
20	6,23	2,37	1,75	37,95
24	7,72	4,01	3,23	52,01
28	6,49	4,15	3,47	63,88
32	4,36	2,90	2,24	66,52
36	2,35	1,62	1,26	69,09
48	0,50	0,34	0,29	66,40
60	0,21	0,41	0,30	197,87
72	0,02	0,08	0,04	375,28
CMax ng/ml	15,43	6,70	5,37	43,38
Tmax H	15,23	5,20	3,67	34,12
AUC0-t H.ng/ml	253,01	65,28	65,81	33,71
F AUC	86,94	24,39	16,36	26,05
F Cmax	54,33	23,09	17,99	42,50

[00337] See Figure 6.

Table 13. Comparison of MR32, GR-01, and GR-02 MIN-101 Plasma Concentrations.

MR32 GR01 and GR02 Mean MIN-101 Plasma Concentrations (ng/ml)			
Hours	MR32-Mean	GR01-Mean	GR02-Mean
0	0,00	0,00	0,00
0,25	0,00	0,00	0,00
0,5	6,56	0,00	0,00
1	19,68	0,35	0,00
1,5	23,96	1,25	0,16
2	24,16	5,75	0,68
2,5	24,66	11,71	1,98
3	22,06	15,54	3,22
3,5	20,34	16,04	4,69
4	19,45	15,99	5,20
5	21,54	14,62	7,05
6	15,19	11,35	6,16
7	11,89	10,33	5,86
8	10,36	9,39	5,95
10	12,46	10,69	7,86
12	12,66	11,26	12,81
14	10,33	11,76	12,06
16	7,74	10,56	10,63
20	4,12	5,49	6,23
24	3,11	5,57	7,72
28	2,39	3,96	6,49
32	1,45	3,10	4,36
36	0,96	2,42	2,35
48	0,20	0,77	0,50
60	0,03	0,30	0,21
72	0,04	0,15	0,02
Max ng/ml	29,5	19,6	15,4
Tmax H	2,4	6,0	15,2
AUC0-t H.ng/ml	291,6	284,5	253,01
F AUC	REF	101,3	86,94
F Cmax	REF	69,9	54,33

[00338] See Figure 7.

Table 14. Comparison of MR32, GR-01, and GR-02 MIN-101 Plasma Concentrations – Rates of Increase and Decrease.

MR32 and GR01 Mean MIN101 Plasma Conc. Rates of Increase and Decrease (ng/ml)/H			
Hours	MR32-RATE	GR01-RATE	GR02-RATE
0	0,00	0,00	0,00
0,25	0,00	0,00	0,00
0,5	26,25	0,00	0,00
1	26,24	0,70	0,00
1,5	8,56	1,80	0,31
2	0,39	9,00	1,05
2,5	1,03	11,92	2,60
3	0,00	7,66	2,48
3,5	0,00	1,00	2,94
4	0,00	0,00	1,02
5	2,09	0,00	1,85
6	0,00	0,00	0,00
7	0,00	0,00	0,00
8	0,00	0,00	0,09
10	1,05	0,65	0,96
12	0,10	0,29	2,48
14	0,00	0,25	0,00
16	0,00	0,00	0,00
20	0,00	0,00	0,00
24	0,00	0,02	0,37
28	0,00	0,00	0,00
32	0,00	0,00	0,00
36	0,00	0,00	0,00
VMax (ng/ml)/H	26,2	11,9	2,9
Time of VMax	0,50	2,50	3,50
TEST/MR32	REF	0,45	0,11

[00339] During each time interval (dt) the plasma concentration (C_p) of MIN-101 increases or decreases. From t=0 to T_{max}, the rate of increase $V_{max} = d(C_p)/dt$. After the V_{max}, the rates are decreasing. See Figure 8.

Example 9: *In Vivo* Pharmacokinetic Analysis of BFB-520 in CR GR-01 Tablets, CR GR-02 Tablets, and MR 32 mg Capsules (MR32) (tau = 72 h)

[00340] **MR32** - 12 subjects (cross-over)

[00341] Geo Mean C_{max}: 1.77 ng/mL

[00342] Median T_{max}: 6.00 H

$AUC_{(0\text{-}tau)}$: 30.26 ng·H/mL

Table 15. MR32 Individual BFB-520 Plasma Concentrations and Parameters

MR32	MR32 BFB-520 PLASMA CONCENTRATIONS (ng/ml) and AUCo-t (H.ng/ml)											
Hours	1-BFB-520	2-BFB-520	3-BFB-520	5-BFB-520	6-BFB-520	7-BFB-520	8-BFB-520	9-BFB-520	10-BFB-520	11-BFB-520	12-BFB-520	13-BFB-520
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,56	0,54	0,00	0,30	0,53	0,32	0,28	1,01	0,00	0,70	0,56	0,26
1,5	1,20	0,85	0,68	0,36	0,72	0,61	0,76	1,25	0,42	1,23	1,10	0,50
2	1,24	0,95	0,89	0,62	0,92	0,89	0,89	2,42	0,80	1,41	1,23	0,80
2,5	1,41	0,75	0,97	0,89	1,18	0,88	0,84	2,16	1,19	1,69	1,76	0,79
3	1,37	0,84	0,99	1,18	1,56	1,12	1,10	3,33	1,56	1,93	1,63	0,74
3,5	1,72	1,03	0,81	1,25	1,44	1,20	1,28	2,91	1,57	1,81	1,94	0,84
4	2,03	0,95	0,98	1,38	1,65	1,21	1,28	2,30	1,66	1,77	2,27	0,95
5	1,91	1,10	1,09	0,90	1,64	1,10	1,07	2,65	2,97	2,09	1,61	1,03
6	1,81	1,09	0,83	0,88	1,76	0,96	1,05	2,23	3,13	1,94	1,73	1,10
7	1,91	0,95	0,90	0,90	1,40	0,94	0,89	2,25	2,91	2,10	1,16	1,01
8	1,69	0,92	0,71	0,79	1,80	1,01	1,19	2,63	3,13	1,93	1,42	1,08
10	1,27	1,05	1,09	0,62	1,69	0,73	1,73	1,97	2,76	2,49	1,44	1,01
12	0,73	1,20	0,56	0,84	1,39	0,56	1,42	1,07	2,12	2,63	1,26	0,71
14	0,88	1,06	0,62	1,07	1,30	0,75	1,46	2,63	2,36	2,74	1,37	0,55
16	0,95	0,86	0,54	0,66	0,85	0,58	1,23	1,79	1,53	1,65	1,03	0,51
20	1,42	0,68	0,48	0,58	0,51	0,86	0,70	1,20	0,97	1,49	0,95	0,41
24	0,85	0,39	0,35	0,00	0,35	0,77	0,47	0,67	0,70	0,58	0,53	0,36
28	0,59	0,00	0,31	0,00	0,30	0,44	0,00	0,45	0,46	0,37	0,33	0,51
32	0,40	0,00	0,00	0,00	0,00	0,35	0,00	0,00	0,28	0,00	0,00	0,31
36	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,51
48	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
60	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
72	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Max ng/ml	2,0	1,2	1,1	1,4	1,8	1,2	1,7	3,3	3,1	2,7	2,3	1,1
Tmax H	4,0	12,0	10,0	4,0	8,0	4,0	10,0	3,0	6,0	14,0	4,0	6,0
AUC0-t H.ng/ml	34,7	20,1	16,7	15,3	27,2	22,6	24,9	44,9	47,2	46,7	34,5	28,5

Table 16. MR32 Mean BFB-520 Plasma Concentrations and Parameters

MR32	MR32 BFB-520 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00			
0,25	0,00			
0,5	0,00			
1	0,42	0,29	0,23	68,42
1,5	0,81	0,33	0,28	41,40
2	1,04	0,51	0,36	48,77
2,5	1,21	0,45	0,36	37,60
3	1,46	0,68	0,46	46,84
3,5	1,49	0,58	0,43	38,99
4	1,56	0,48	0,40	31,20
5	1,59	0,67	0,54	42,36
6	1,55	0,69	0,55	44,45
7	1,44	0,68	0,57	47,23
8	1,51	0,75	0,57	49,53
10	1,48	0,66	0,53	44,91
12	1,21	0,63	0,46	52,49
14	1,40	0,77	0,60	54,91
16	1,01	0,44	0,36	43,42
20	0,85	0,34	0,27	40,36
24	0,50	0,22	0,18	44,39
28	0,35	0,26	0,19	75,95
32	0,15	0,26	0,21	168,74
36	0,05	0,18	0,09	346,41
48	0,00			
60	0,00			
72	0,00			
Max ng/ml	1,91	0,80	0,65	41,65
Tmax H	6,92	3,65	3,06	52,84
AUC0-t H.ng/ml	30,26	11,35	9,43	37,51

[00343] See Figure 9.

[00344] **GR-01** - 12 subjects (cross-over)

[00345] Geo Mean C_{max}: 1.77 ng/mL

[00346] Median T_{max}: 6.00 H

$AUC_{(0\text{-}tau)}$: 27.48 ng·H/mL

Relative Bioavailability versus MR32: F% C_{max}: 80.48%, F% $AUC_{(0\text{-}tau)}$: 96.1%

Table 17. GR-01 Individual BFB-520 Plasma Concentrations and Parameters

GR01	GR01 BFB-520 PLASMA CONCENTRATIONS (ng/ml) and AUCo-t (H.ng/ml)											
Hours	1-BFB-520	2-BFB-520	3-BFB-520	5-BFB-520	6-BFB-520	7-BFB-520	8-BFB-520	9-BFB-520	10-BFB-520	11-BFB-520	12-BFB-520	13-BFB-520
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2	0,00	0,00	0,26	0,00	0,00	0,00	0,00	0,00	0,00	0,28	0,00	0,00
2,5	0,00	0,58	0,43	0,00	0,00	0,00	0,30	0,00	0,46	0,60	0,29	0,00
3	0,42	0,71	0,45	0,44	0,00	0,29	0,60	0,60	0,63	0,88	0,53	0,38
3,5	0,54	1,00	0,50	0,47	0,00	0,38	0,67	1,28	0,74	1,00	0,88	0,43
4	0,84	1,04	0,48	0,63	0,35	0,38	0,45	1,41	1,08	1,29	0,72	0,51
5	1,01	0,98	0,39	0,72	0,62	0,51	0,75	1,56	1,13	1,45	0,98	0,61
6	1,07	1,07	0,43	0,78	0,83	0,54	0,85	1,47	0,85	1,19	0,72	0,64
7	1,20	1,28	0,37	0,92	0,93	0,51	0,88	1,47	0,71	1,47	0,74	0,80
8	1,17	1,07	0,44	1,10	1,03	0,68	0,76	1,80	1,37	1,63	1,06	0,74
10	0,68	0,96	0,68	1,23	0,77	0,33	1,28	1,72	1,84	1,32	1,37	0,98
12	0,65	0,77	0,65	1,30	0,66	0,32	0,91	1,40	1,74	0,78	2,26	1,08
14	1,00	0,87	0,72	1,73	0,74	0,43	1,24	1,54	1,82	1,11	1,11	1,05
16	1,00	0,71	0,83	1,80	0,51	0,43	1,09	1,45	1,80	1,24	1,11	0,95
20	0,69	0,70	0,63	1,56	0,67	0,40	0,71	1,73	1,13	1,44	1,17	0,68
24	0,57	0,31	0,43	0,85	0,50	0,00	0,39	1,31	0,57	1,05	0,99	0,58
28	0,72	0,26	0,50	0,58	0,59	0,00	0,28	1,15	0,92	1,27	0,85	0,58
32	0,33	0,00	0,28	0,30	0,48	0,43	0,00	0,67	0,62	0,68	0,28	0,43
36	0,29	0,00	0,00	0,00	0,38	1,10	0,00	0,26	0,00	0,51	0,00	0,42
48	0,00	0,00	0,00	0,00	0,00	0,33	0,00	0,00	0,00	0,00	0,00	0,00
60	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
72	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Max ng/ml	1,2	1,3	0,8	1,8	1,0	1,1	1,3	1,8	1,8	1,6	2,3	1,1
Tmax H	7,0	7,0	16,0	16,0	8,0	36,0	10,0	8,0	10,0	8,0	12,0	12,0
AUC0-t H.ng/ml	23,5	18,6	16,1	31,3	19,7	19,0	18,5	43,8	36,1	49,6	33,7	27,9
F AUC	67,7	92,5	96,3	204,6	72,3	82,9	79,2	97,6	76,5	86,9	97,7	98,0
F Cmax	58,0	107,4	75,8	131,0	58,6	90,8	73,6	54,0	58,8	59,7	86,8	97,5

Table 18. GR-01 Mean BFB-520 Plasma Concentrations and Parameters

GR01	GR01 BFB-520 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00			
0,25	0,00			
0,5	0,00			
1	0,00			
1,5	0,00			
2	0,04	0,10	0,07	233,68
2,5	0,22	0,25	0,22	112,01
3	0,49	0,23	0,17	45,99
3,5	0,65	0,35	0,27	53,37
4	0,77	0,36	0,31	47,35
5	0,89	0,36	0,29	40,77
6	0,87	0,29	0,22	33,50
7	0,94	0,35	0,28	37,58
8	1,07	0,39	0,29	36,81
10	1,10	0,45	0,36	40,79
12	1,04	0,55	0,43	53,43
14	1,11	0,42	0,31	37,58
16	1,08	0,45	0,34	41,52
20	0,96	0,43	0,38	45,29
24	0,63	0,36	0,28	57,32
28	0,63	0,36	0,26	57,90
32	0,37	0,23	0,18	60,48
36	0,25	0,33	0,25	133,52
48	0,03	0,09	0,05	346,41
60	0,00			
72	0,00			
Max ng/ml	1,43	0,43	0,37	30,06
Tmax H	12,50	8,04	5,08	64,32
AUC0-t H.ng/ml	27,48	9,46	8,07	34,41
F AUC	96,10	35,77	18,95	37,22
F Cmax	80,48	24,60	20,65	30,56

[00347] See Figure 10.

[00348] **GR-02** - 12 subjects (cross-over)

[00349] Geo Mean C_{max}: 1.13 ng/mL

[00350] Median T_{max}: 16.00 H

$AUC_{(0\text{-}tau)}$: 27.53 ng·H/mL

Relative Bioavailability versus MR32: F% C_{max}: 69.48%, F% $AUC_{(0\text{-}tau)}$: 88.46%

Table 19. GR-02 Individual BFB-520 Plasma Concentrations and Parameters

GR02	GR02 BFB-520 PLASMA CONCENTRATIONS (ng/ml) and AUC0-t (H.ng/ml)												
Hours	1-BFB-520	2-BFB-520	3-BFB-520	4-BFB-520	5-BFB-520	7-BFB-520	8-BFB-520	9-BFB-520	10-BFB-520	11-BFB-520	12-BFB-520	13-BFB-520	14-BFB-520
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,44
3	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,26	0,00	0,00	0,66
3,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,62	0,00	0,00	0,76
4	0,38	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,97	0,27	0,00	1,08
5	0,35	0,00	0,00	0,00	0,32	0,00	0,00	0,27	0,27	1,37	0,35	0,35	0,75
6	0,53	0,38	0,00	0,00	0,49	0,00	0,00	0,28	0,42	1,47	0,38	0,45	0,75
7	0,54	0,29	0,00	0,00	0,41	0,29	0,00	0,27	0,39	1,64	0,49	0,58	0,79
8	0,47	0,32	0,00	0,25	0,57	0,25	0,00	0,51	0,42	1,85	0,57	0,69	0,79
10	0,47	0,35	0,25	0,36	0,62	0,34	0,00	0,74	0,51	1,62	1,12	1,07	1,14
12	0,58	0,00	0,41	0,52	0,94	0,35	0,35	0,74	1,28	2,26	0,80	1,09	1,58
14	1,00	0,33	0,51	0,66	1,28	0,36	0,41	0,88	1,28	2,45	1,28	1,16	2,25
16	1,31	0,38	0,56	0,62	1,46	0,52	0,37	1,26	1,22	2,36	1,37	1,03	2,31
20	1,08	0,64	0,75	0,59	1,25	0,75	0,26	1,43	0,71	2,42	1,64	0,80	1,38
24	0,81	0,44	0,55	0,49	0,75	0,55	0,00	0,58	0,61	1,75	1,39	0,59	0,84
28	0,67	0,47	0,56	0,56	0,48	1,22	0,00	1,00	0,53	1,74	1,04	0,67	0,59
32	0,52	0,34	0,21	0,32	0,00	1,14	0,00	1,03	1,21	0,70	0,59	0,61	0,33
36	0,47	0,32	0,00	0,00	0,00	0,68	0,00	0,55	0,64	0,41	0,32	0,46	0,00
48	0,27	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
60	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
72	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Max ng/ml	1,1	0,6	0,8	0,7	1,4	1,2	0,4	1,4	1,3	2,4	1,6	1,2	2,3
Tmax H	20,0	20,0	20,0	14,0	16,0	28,0	14,0	20,0	12,0	14,0	20,0	14,0	16,0
AUC0-t H.ng/ml	30,0	11,5	12,3	12,5	21,8	23,8	6,1	31,9	31,4	61,4	38,8	32,9	43,5
F AUC	86,6	57,0	73,3	81,9	80,3	105,2	24,6	71,1	66,6	131,5	112,6	115,5	142,7
F Cmax	53,1	53,3	72,2	45,2	79,8	100,6	23,9	42,9	41,0	89,3	72,3	104,8	120,8

Table 20. GR-02 Mean BFB-520 Plasma Concentrations and Parameters

GR02	GR01 BFB-520 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00			
0,25	0,00			
0,5	0,00			
1	0,00			
1,5	0,00			
2	0,00			
2,5	0,03	0,13	0,07	375,28
3	0,07	0,20	0,13	280,02
3,5	0,11	0,27	0,19	254,72
4	0,21	0,40	0,29	191,24
5	0,31	0,40	0,27	130,19
6	0,39	0,42	0,28	106,04
7	0,44	0,45	0,30	102,76
8	0,52	0,49	0,31	94,19
10	0,68	0,51	0,41	75,52
12	0,90	0,68	0,51	75,73
14	1,07	0,70	0,53	65,30
16	1,11	0,69	0,54	61,68
20	1,06	0,59	0,47	55,93
24	0,77	0,45	0,31	59,06
28	0,80	0,45	0,34	55,61
32	0,57	0,41	0,33	71,69
36	0,30	0,28	0,24	92,16
48	0,02	0,00		
60	0,00			
72	0,00			
Max ng/ml	1,27	0,63	0,47	49,77
Tmax H	17,54	4,46	3,56	25,42
AUC0-t H.ng/ml	27,53	15,99	12,65	58,08
F AUC	88,46	33,92	27,56	38,35
F Cmax	69,48	29,58	24,00	42,56

[00351] See Figure 11.

Table 21. Comparison of MR32, GR-01, and GR-02 BFB-520 Plasma Concentrations.

MR32 GR01 and GR02 Mean BFB-520 Plasma Concentrations (ng/ml)			
Hours	MR32-Mean	GR01-Mean	GR02-Mean
0	0,00	0,00	0,00
0,25	0,00	0,00	0,00
0,5	0,00	0,00	0,00
1	0,42	0,00	0,00
1,5	0,81	0,00	0,00
2	1,04	0,04	0,00
2,5	1,21	0,22	0,03
3	1,46	0,49	0,07
3,5	1,49	0,65	0,11
4	1,55	0,77	0,21
5	1,59	0,69	0,31
6	1,55	0,67	0,39
7	1,44	0,94	0,44
8	1,51	1,07	0,52
10	1,48	1,10	0,68
12	1,21	1,04	0,90
14	1,40	1,11	1,07
16	1,01	1,08	1,11
20	0,85	0,96	1,06
24	0,50	0,63	0,77
28	0,35	0,63	0,80
32	0,15	0,37	0,57
36	0,05	0,25	0,30
48	0,00	0,03	0,02
60	0,00	0,00	0,00
72	0,00	0,00	0,00
CMax ng/ml	1,9	1,4	1,27
Tmax H	6,9	12,5	17,5
AUC0-8 H.ng/ml	9,7	4,5	1,66
AUC0-12 H.ng/ml	15,4	8,8	4,4
AUC0-t H.ng/ml	30,3	27,5	27,5
F AUC	REF	96,1	88,5
F Cmax	REF	80,5	69,5

[00352] See Figure 12.

Table 22. Comparison of MR32, GR-01, and GR-02 BFB-520 Plasma Concentrations – Rates of Increase and Decrease.

MR32 GR01 and GR02 Mean BFB-520 Plasma Conc. Rates of Increase and Decrease (ng/ml)/H			
Hours	MR32-RATE	GR01-RATE	GR02-RATE
0	0,00	0,00	0,00
0,25	0,00	0,00	0,00
0,5	0,00	0,00	0,00
1	0,84	0,00	0,00
1,5	0,77	0,00	0,00
2	0,46	0,09	0,00
2,5	0,34	0,35	0,07
3	0,49	0,54	0,07
3,5	0,07	0,31	0,07
4	0,11	0,24	0,20
5	0,04	0,13	0,10
6	0,00	0,00	0,08
7	0,00	0,07	0,04
8	0,07	0,13	0,08
10	0,00	0,01	0,08
12	0,00	0,00	0,11
14	0,10	0,04	0,09
16	0,00	0,00	0,02
20	0,00	0,00	0,00
24	0,00	0,00	0,00
28	0,00	0,00	0,01
32	0,00	0,00	0,00
36	0,00	0,00	0,00
VMax (ng/ml)/H	0,84	0,54	0,20
Time of VMax	1,00	3,00	4,00
TEST/MR32	REF	0,64	0,24

[00353] During each time interval (dt) the plasma concentration (C_p) of BFB-520 increases or decreases. From t=0 to T_{max}, the rate of increase $V_{max} = d(C_p)/dt$. After the V_{max}, the rates are decreasing. See Figure 13.

Example 10: Predicted Plasma Concentrations of MIN-101 and BFB-520 at Steady State in MR32 and GR-01 Tablets (32 and 64 mg)

Table 23. Predicted Plasma Concentrations of MIN-101 at Steady State in MR32 and GR-01, 32 mg Tablets

MR32 and GR01 Mean MIN-101 at Steady-State Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR01 SS
72	3,32	6,45
72,5	9,68	6,20
73	22,62	6,30
73,5	25,74	6,96
74	26,78	11,23
74,5	27,14	16,97
75	24,39	20,59
75,5	22,54	20,89
76	21,96	20,58
77	23,38	18,91
78	16,83	15,30
79	13,34	13,96
80	11,89	12,95
82	13,49	13,53
84	13,66	14,02
86	10,97	13,80
88	8,24	12,32
92	4,44	6,75
96	3,32	6,46
CMaxSS ng/ml	27,1	20,9
CMinSS	3,32	6,46
TmaxSS H	2,50	3,5
AUC72-96 H.ng/ml	292,6	287,6
F AUC	REF	98,3
F Cmax	REF	76,9

[00354] See Figure 14.

Table 24. Predicted Plasma Concentrations of BFB-520 at Steady State in MR32 and GR-01, 32 mg Tablets

MR32 and GR01 BFB-520 at Steady-State Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR01 SS
72	0,50	0,66
72,5	0,44	0,63
73	0,81	0,60
73,5	1,15	0,57
74	1,35	0,58
74,5	1,48	0,72
75	1,78	0,97
75,5	1,71	1,10
76	1,89	1,42
77	1,74	1,27
78	1,66	1,21
79	1,54	1,24
80	1,68	1,46
82	1,53	1,31
84	1,26	1,29
86	1,41	1,25
88	1,03	1,19
92	0,85	1,03
96	0,50	0,66
CMaxSS ng/ml	1,89	1,46
CMinSS	0,50	0,66
TmaxSS H	4,00	8,00
AUC72-96 H.ng/ml	29,1	26,3
F AUC	REF	90,6
F Cmax	REF	77,2

[00355] See Figure 15.

Table 25. Predicted Plasma Concentrations of MIN-101 at Steady State in MR32 and GR-01, 64 mg Tablets

MR32 and GR01 64 mg at Steady-State MIN101 Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR01 SS
72	6,64	12,90
72,5	19,36	12,49
73	45,24	12,60
73,5	53,47	13,93
74	53,55	22,45
74,5	54,28	33,94
75	48,77	41,18
75,5	45,07	41,77
76	43,93	41,17
77	46,76	37,82
78	33,65	30,60
79	26,69	27,92
80	23,78	25,90
82	26,97	27,06
84	27,31	26,05
86	21,94	27,61
88	16,49	24,64
92	8,89	13,49
96	6,64	12,93
CMaxSS ng/ml	54,28	41,77
CMinSS	6,64	12,93
TmaxSS H	2,50	3,50
AUC72-96 H.ng/ml	585,2	577,6
F AUC	REF	98,7
F Cmax	REF	76,9

[00356] See Figure 16.

Table 26. Predicted Plasma Concentrations of BFB-520 at Steady State in MR32 and GR-01, 64 mg Tablets

MR32 and GR01 64 mg at Steady-State BFB-520 Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR01 SS
72	0,99	1,32
72,5	0,88	1,27
73	1,63	1,20
73,5	2,31	1,13
74	2,68	1,15
74,5	2,96	1,45
75	3,40	1,93
75,5	3,41	2,19
76	3,79	2,84
77	3,46	2,54
78	3,33	2,41
79	3,07	2,48
80	3,32	2,82
82	3,05	2,62
84	2,51	2,57
86	2,83	2,49
88	2,06	2,37
92	1,70	2,05
96	0,99	1,32
CMaxSS ng/ml	3,79	2,92
CMinSS	0,99	1,32
TmaxSS H	4,00	8,00
AUC72-96 H.ng/ml	58,1	52,8
F AUC	REF	90,8
F Cmax	REF	77,2

[00357] See Figure 17.

Example 11: Predicted Plasma Concentrations of MIN-101 and BFB-520 at Steady State in MR32 and GR-02 Tablets (32 and 64 mg)

Table 27. Predicted Plasma Concentrations of MIN-101 at Steady State in MR32 and GR-02, 32 mg Tablets

MR32 and GR02 Mean MIN-101 at Steady-State Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR02 SS
72	3,32	8,26
72,5	9,68	7,68
73	22,62	7,46
73,5	26,74	7,23
74	26,78	7,37
74,5	27,14	8,32
75	24,39	9,22
75,5	22,54	10,37
76	21,96	12,08
77	23,38	11,87
78	16,83	10,48
79	13,34	9,74
80	11,89	10,56
82	13,49	10,86
84	13,66	15,38
86	10,87	13,87
88	8,24	12,09
92	4,44	7,17
96	3,32	8,27
CMaxSS ng/ml	27,1	15,4
CMinSS	3,32	7,17
TmaxSS H	2,50	12
AUC72-96 H.ng/ml	292,6	248,3
F AUC	REF	84,9
F Cmax	REF	56,7

[00358] See Figure 18.

Table 28. Predicted Plasma Concentrations of BFB-520 at Steady State in MR32 and GR-02, 32 mg Tablets

MR32 and GR02 BFB-520 at Steady-State Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR02 SS
72	0,50	0,79
72,5	0,44	0,76
73	0,81	0,72
73,5	1,15	0,67
74	1,35	0,63
74,5	1,48	0,63
75	1,70	0,63
75,5	1,71	0,63
76	1,89	1,04
77	1,74	0,75
78	1,66	0,78
79	1,54	0,78
80	1,66	1,10
82	1,53	0,92
84	1,26	1,20
86	1,41	1,22
88	1,03	1,23
92	0,85	1,13
96	0,50	0,79
CMaxSS ng/ml	1,89	1,23
CMinSS	0,50	0,79
TmaxSS H	4,00	16,00
AUC72-96 H.ng/ml	29,1	23,6
F AUC	REF	81,4
F Cmax	REF	64,8

[00359] See Figure 19.

Table 29. Predicted Plasma Concentrations of MIN-101 at Steady State in MR32 and GR-02, 64 mg Tablets

MR32 and GR02 64 mg at Steady-State MIN101 Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR02 SS
72	6,64	16,53
72,5	19,36	15,77
73	45,24	14,83
73,5	53,47	14,45
74	53,55	14,75
74,5	54,28	16,64
75	48,77	18,44
75,5	45,07	20,74
76	43,93	24,16
77	46,76	23,75
78	33,65	20,98
79	26,89	19,49
80	23,78	21,12
82	26,97	21,32
84	27,31	30,77
86	21,94	27,73
88	16,49	24,18
92	8,89	14,35
96	6,64	16,53
CMaxSS ng/ml	54,28	30,77
CMinSS	6,64	14,35
TmaxSS H	2,50	12,00
AUC72-96 H.ng/ml	585,2	498,6
F AUC	REF	85,2
F Cmax	REF	56,7

[00360] See Figure 20.

Table 30. Predicted Plasma Concentrations of BFB-520 at Steady State in MR32 and GR-02, 64 mg Tablets

MR32 and GR02 64 mg at Steady-State BFB-520 Plasma Concentrations (ng/ml)		
HOURS	MR32SS	GR02 SS
72	6,89	1,58
72,5	6,88	1,52
73	1,83	1,43
73,5	2,31	1,35
74	2,69	1,27
74,5	2,96	1,26
75	3,40	1,26
75,5	3,41	1,27
76	3,79	2,07
77	3,48	1,50
78	3,33	1,57
79	3,07	1,57
80	3,32	2,20
82	3,05	1,83
84	2,51	2,40
86	2,83	2,44
88	2,85	2,45
92	1,70	2,25
96	6,89	1,58
CMaxSS ng/ml	3,79	2,45
CMinSS	0,89	1,58
TmaxSS H	4,00	16,00
AUC72-96 H.ng/ml	58,1	47,4
F AUC	REF	81,6
F Cmax	REF	64,8

[00361] See Figure 21.

[00362] Examples 12-15 detail an evaluation of the PK profile of the GR-01 formulation in healthy CYP2D6 EM male and female subjects in fed and fasted states (or predictions thereof). Subjects who completed part 1 of the study (evaluation of the PK profile of MIN-101 and its metabolite BFB-520 in the GR-01, GR-02, and MR32 formulations) returned and received a further single oral dose of GR-01 under fed or fasted conditions to allow the assessment of food

effect by comparison of the PK properties to those obtained in part 1 (Examples 9-12). There was a wash-out period of 14 ± 2 days after part 1.

Example 12: *In Vivo* Pharmacokinetic Analysis of MIN-101 in CR GR-01 Tablets in Subjects in Fed versus Fasted States. (tau = 72 h)

[00363] Fed State - 12 subjects (cross-over)

[00364] Geo Mean C_{max}: 19.70 ng/mL

[00365] T_{max}: 12.00 H

$AUC_{(0\text{-}tau)}$: 269.19 ng·H/mL

Table 31. CR GR-01 Individual MIN-101 Plasma Concentrations and Parameters (Fed State)

GR01	GR01 FED MIN-101 PLASMA CONCENTRATIONS (ng/ml) and AUC0-t (H.ng/ml)											
Hours	1-MIN-101	2-MIN-101	3-MIN-101	5-MIN-101	6-MIN-101	7-MIN-101	8-MIN-101	9-MIN-101	10-MIN-101	11-MIN-101	12-MIN-101	13-MIN-101
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2,5	0,00	0,00	5,78	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
3	0,00	0,00	13,16	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	6,11
3,5	0,00	0,00	11,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	7,53
4	0,00	0,00	14,38	0,00	0,00	0,29	0,00	0,00	0,00	0,00	0,00	6,83
5	0,00	0,00	14,05	23,92	0,00	12,75	0,00	0,00	0,53	0,00	0,00	6,94
6	0,00	18,46	13,78	13,78	0,00	16,81	0,00	0,00	23,85	0,00	0,00	5,14
7	0,00	18,53	12,69	10,82	0,00	11,65	0,00	0,00	18,16	15,83	0,00	5,15
8	0,00	12,77	9,35	9,89	0,00	10,58	0,00	0,00	17,78	14,65	0,00	4,24
10	3,52	7,72	5,89	11,62	0,00	7,97	0,00	23,19	14,86	13,23	0,00	6,85
12	35,98	6,41	9,71	6,41	19,91	13,62	0,00	8,39	14,32	12,38	24,84	12,40
14	12,33	3,95	7,26	2,84	11,75	13,61	0,00	5,32	18,35	17,47	12,74	8,83
16	14,86	9,72	16,04	1,55	8,72	6,89	0,00	8,38	26,47	12,39	7,56	6,04
20	7,18	4,51	4,79	0,52	6,56	9,42	4,24	5,28	11,74	11,61	14,80	4,23
24	5,79	2,72	5,62	0,00	12,81	5,57	10,84	30,78	9,83	16,33	26,27	6,75
28	7,17	2,40	4,48	0,00	18,56	5,28	5,81	18,53	5,52	7,62	21,35	4,34
32	6,56	2,19	2,84	0,00	10,82	3,49	2,32	10,28	3,47	3,44	14,17	3,32
36	5,97	1,15	1,81	0,00	6,36	2,19	0,82	3,61	1,88	1,65	9,78	2,42
48	1,66	0,36	0,80	0,00	1,57	0,67	0,00	0,83	0,58	0,47	0,64	0,59
60	0,00	0,00	0,35	0,00	0,83	0,31	0,00	0,00	0,21	0,00	0,00	0,36
72	0,00	0,00	0,00	0,00	0,36	0,00	0,00	0,00	0,00	0,00	0,00	0,00
CMax ng/ml	36,0	18,9	14,4	23,9	19,9	16,8	10,8	30,8	23,8	17,5	26,3	12,4
Tmax H	12,0	7,5	4,0	5,0	12,0	6,0	24,0	24,0	5,0	14,0	24,0	12,0
AUC0-t H.ng/ml	385,6	177,2	241,3	188,5	347,8	272,9	92,2	367,3	359,7	303,5	444,8	210,2
F AUC	198,3	80,6	184,8	35,0	132,3	186,2	43,1	102,8	124,2	79,5	159,4	74,1
F Cmax	174,7	87,9	133,8	114,2	127,4	131,5	65,8	109,1	132,2	65,5	93,8	87,7

Table 32. CR GR-01 Mean MIN-101 Plasma Concentrations and Parameters (Fed State)

GR01	GR01 FED MIN-101 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00			
0,25	0,00			
0,5	0,00			
1	0,00			
1,5	0,00			
2	0,00			
2,5	0,57	1,96	1,04	346,41
3	1,44	3,53	2,40	245,26
3,5	1,55	3,69	2,59	238,14
4	1,79	4,42	2,94	246,80
5	4,77	7,77	6,27	162,90
6	7,74	9,01	8,00	116,41
7	7,77	7,71	6,91	99,30
8	6,36	6,59	5,65	103,62
10	7,58	6,94	5,20	91,54
12	13,70	9,54	6,71	69,63
14	9,38	5,54	4,66	59,09
16	8,88	5,51	3,85	62,03
20	7,04	3,93	3,13	55,89
24	10,71	9,09	6,31	84,89
28	8,26	6,76	5,27	81,78
32	5,22	4,30	3,50	82,42
36	2,83	2,17	1,79	76,52
48	0,71	0,52	0,39	73,23
60	0,16	0,22	0,18	133,11
72	0,03	0,09	0,05	346,41
CMax ng/ml	26,89	7,48	5,91	35,83
Tmax H	12,50	7,65	6,00	61,16
AUC0-t H.ng/ml	269,19	107,53	86,11	39,95
F AUC	95,14	36,15	28,68	38,00
F Cmax	106,97	31,40	23,32	28,81

[00366] See Figure 22

[00367] Fasted State - 12 subjects (cross-over)

[00368] Geo Mean C_{max}: 18.82 ng/mL

[00369] Median T_{max}: 4.50 H

$AUC_{(0\text{-}tau)}$: 284.52 ng·H/mL

Table 33. CR GR-01 Individual MIN-101 Plasma Concentrations and Parameters (Fasted State)

GR01	GR01 FASTED MEAN MIN-101 PLASMA CONCENTRATIONS (ng/ml) and AUC0-t (H.ng/ml)											
Hours	1-MIN-101	2-MIN-101	3-MIN-101	5-MIN-101	6-MIN-101	7-MIN-101	8-MIN-101	9-MIN-101	10-MIN-101	11-MIN-101	12-MIN-101	13-MIN-101
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	4,22	0,00	0,00	0,00
1,5	0,00	0,00	0,28	0,00	0,00	0,00	0,36	0,00	0,42	0,00	0,00	7,98
2	3,83	5,42	10,56	2,50	0,00	0,00	13,21	0,00	8,71	16,03	0,48	8,14
2,5	15,95	12,82	11,87	12,14	0,00	3,45	12,42	3,00	12,78	24,17	23,30	7,82
3	17,65	17,61	11,40	13,88	8,38	12,78	11,06	24,02	12,38	26,88	26,00	10,43
3,5	16,56	21,53	10,97	12,31	9,52	16,39	10,94	28,49	13,69	25,78	24,01	12,16
4	20,60	19,93	8,23	11,86	15,23	9,53	8,94	22,31	17,64	24,78	22,59	11,39
5	17,05	17,24	6,66	14,68	15,83	8,44	14,00	17,35	12,82	24,46	12,80	12,69
6	15,26	14,41	6,86	13,19	13,39	6,06	12,36	13,72	7,62	19,24	5,64	10,42
7	9,61	11,39	6,28	12,62	10,80	4,74	11,51	13,36	5,70	17,63	5,72	9,68
8	7,46	7,20	5,58	11,88	10,51	3,61	9,18	10,53	13,39	14,16	5,92	8,62
10	4,30	5,10	12,68	11,69	6,19	2,73	18,08	17,98	18,85	8,98	13,16	10,59
12	9,45	5,59	10,24	20,15	7,24	3,65	12,22	13,92	16,34	11,15	13,39	12,47
14	13,15	10,14	12,01	17,73	7,12	3,52	12,65	12,92	14,42	11,67	26,32	8,28
16	10,58	6,35	12,59	16,88	6,40	3,18	7,48	11,25	13,43	13,28	16,44	8,93
20	5,54	3,88	4,89	8,38	4,95	2,65	2,44	7,98	8,52	9,78	5,92	3,23
24	5,57	1,84	3,21	6,73	3,31	2,38	2,86	12,21	3,86	18,97	3,43	7,68
28	4,31	1,84	3,18	2,65	3,61	2,35	1,47	7,67	3,75	18,31	3,54	5,68
32	3,50	1,56	2,73	1,15	3,55	5,60	0,66	3,58	2,75	7,59	3,47	3,48
36	2,37	1,06	1,34	6,54	2,14	12,25	0,00	1,68	8,56	3,73	3,37	3,68
48	1,33	0,73	0,29	6,00	2,04	2,55	0,00	0,00	0,00	0,58	0,00	1,78
60	0,00	0,48	0,00	6,00	1,53	1,53	0,00	0,00	0,00	0,00	0,00	0,45
72	0,00	0,00	0,00	6,00	0,44	0,44	0,00	0,00	0,00	0,00	0,00	0,27
CMax ng/ml	20,6	21,5	12,7	26,2	15,6	12,8	18,1	28,2	18,1	26,7	26,6	12,7
Tmax H	4,0	3,5	10,0	12,0	5,0	3,0	10,0	3,5	10,0	3,0	3,0	5,0
AUC0-t H.ng/ml	281,6	248,3	338,1	306,7	262,8	257,0	213,6	367,2	288,7	439,8	279,0	282,5

Table 34. CR GR-01 Mean MIN-101 Plasma Concentrations and Parameters (Fasted State)

GR01	GR01 FASTED MIN-101 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00
1	0,35	1,22	0,55	346,41
1,5	1,25	2,77	1,95	220,78
2	5,75	5,57	4,67	96,91
2,5	11,71	7,46	5,46	63,69
3	15,54	7,84	6,08	50,45
3,5	16,04	7,01	5,89	43,68
4	15,99	6,08	5,27	38,00
5	14,62	4,60	3,26	31,47
6	11,35	4,17	3,35	36,70
7	10,33	3,58	2,64	34,63
8	9,39	3,93	3,25	41,81
10	10,69	5,39	4,42	50,45
12	11,26	4,66	3,48	41,34
14	11,76	4,67	3,33	39,73
16	10,58	4,87	3,96	46,01
20	5,49	2,33	1,85	42,48
24	5,57	3,30	2,58	59,31
28	3,96	2,80	2,04	70,67
32	3,10	2,06	1,50	66,68
36	2,42	3,33	2,05	137,50
48	0,77	0,92	0,77	119,51
60	0,30	0,51	0,40	171,48
72	0,15	0,24	0,20	159,83
CMax ng/ml	19,59	5,74	4,61	29,30
Tmax H	6,00	3,43	3,00	57,19
AUC0-t H.ng/ml	284,52	60,83	41,49	21,38

[00370] See Figure 23

Table 35. CR GR-01 Mean MIN-101 Plasma Concentrations and Parameters (Fed versus Fasted State)

GR01 FOOD EFFECT Mean MIN-101 MIN101 Plasma Concentrations (ng/ml)		
Hours	GR01 FED	GR01 FASTED
0	0,00	0,00
0,25	0,00	0,00
0,5	0,00	0,00
1	0,00	0,35
1,5	0,00	1,25
2	0,00	5,75
2,5	0,57	11,71
3	1,44	15,54
3,5	1,55	16,04
4	1,79	15,89
5	4,77	14,62
6	7,74	11,35
7	7,77	10,33
8	6,36	9,39
10	7,58	10,89
12	13,70	11,26
14	9,38	11,76
16	8,88	10,58
20	7,04	5,49
24	10,71	5,57
28	8,26	3,96
32	5,22	3,10
36	2,83	2,42
48	0,71	0,77
60	0,16	0,30
72	0,03	0,15
Max ng/ml	20,9	19,6
Tmax H	12,5	6,0
AUC0-t H.ng/ml	269,2	284,5
F AUC	95,14	REF
F Cmax	108,97	REF

[00371] Relative bioavailability of MIN-101 in GR-01 formulation in fed versus fasted states:

F% C_{max}: 108.97%

F% $AUC_{(0\text{-tau})}$: 95.14%

[00372] See Figure 24

Example 13: *In Vivo* Pharmacokinetic Analysis of BFB-520 in CR GR-01 Tablets in Subjects in Fed versus Fasted States. (tau = 72 h)

[00373] Fed State - 12 subjects (cross-over)

[00374] Geo Mean C_{max}: 1.54 ng/mL

[00375] Median T_{max}: 18.00 H

$AUC_{(0\text{-tau})}$: 30.12 ng·H/mL

Table 36. CR GR-01 Individual BFB-520 Plasma Concentrations and Parameters (Fed State)

GR01	GR01 FED BFB-520 PLASMA CONCENTRATIONS (ng/ml) and AUC0-t (H.ng/ml)											
Hours	1-BFB-520	2-BFB-520	3-BFB-520	5-BFB-520	6-BFB-520	7-BFB-520	8-BFB-520	9-BFB-520	10-BFB-520	11-BFB-520	12-BFB-520	13-BFB-520
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
3	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
3,5	0,00	0,00	0,33	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
4	0,00	0,00	0,48	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,27
5	0,00	0,00	0,64	0,46	0,00	0,82	0,00	0,00	0,00	0,00	0,00	0,32
6	0,00	0,46	0,78	0,61	0,00	1,19	0,00	0,00	0,00	0,00	0,00	0,34
7	0,00	0,00	1,08	0,64	0,00	1,28	0,00	0,00	1,19	1,00	0,00	0,38
8	0,00	1,06	0,83	0,00	0,00	1,53	0,00	0,00	1,54	1,77	0,00	0,42
10	0,00	1,06	0,70	1,07	0,00	1,44	0,00	0,51	1,57	1,74	0,00	0,37
12	1,45	0,52	0,68	0,78	0,79	1,82	0,00	1,14	1,59	1,64	1,08	0,37
14	1,56	0,46	0,62	0,52	0,97	2,26	0,00	1,51	2,06	2,53	1,38	0,83
16	1,61	0,79	0,78	0,38	0,87	1,89	0,00	1,28	2,13	2,28	0,95	0,85
20	0,87	0,85	0,64	0,00	1,15	2,15	0,00	1,43	2,36	2,86	0,83	0,72
24	0,85	0,58	0,48	0,00	1,02	1,15	0,00	2,95	1,08	1,88	1,25	0,41
28	1,14	0,48	0,63	0,00	1,75	1,13	0,01	2,48	1,42	1,93	1,86	0,56
32	0,89	0,38	0,32	0,00	1,31	0,58	0,43	2,35	0,74	0,95	1,36	0,43
36	0,00	0,00	0,00	0,00	0,96	0,58	0,00	0,95	0,38	0,50	0,78	0,34
48	0,00	0,00	0,00	0,00	0,26	0,00	0,00	0,00	0,00	0,00	0,00	0,00
60	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
72	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Max ng/ml	1,6	1,1	1,1	1,1	1,8	2,2	0,8	2,9	2,4	2,7	1,9	0,9
Tmax H	14,0	18,0	7,0	16,0	28,0	14,0	28,0	24,0	26,0	20,0	28,0	16,0
AUC0-t H.ng/ml	24,4	17,5	15,6	8,2	34,9	43,7	6,8	49,2	45,8	55,5	34,4	22,9
F AUC	184,2	94,2	112,0	26,4	177,5	239,2	34,5	112,5	126,5	137,5	102,1	82,0
F Cmax	138,3	84,3	132,8	56,3	179,4	198,5	93,4	163,8	128,4	162,6	82,5	79,1

Table 37. CR GR-01 Mean BFB-520 Plasma Concentrations and Parameters (Fed State)

GR01	GR01 FED BFB-520 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00			
0,25	0,00			
0,5	0,00			
1	0,00	0,00	0,00	#DIV/0!
1,5	0,00	0,00	0,00	#DIV/0!
2	0,00	0,00	0,00	#DIV/0!
2,5	0,00	0,00	0,00	#DIV/0!
3	0,00	0,00	0,00	#DIV/0!
3,5	0,03	0,09	0,05	346,41
4	0,06	0,15	0,10	244,57
5	0,19	0,30	0,25	159,98
6	0,35	0,43	0,36	120,06
7	0,54	0,53	0,48	98,36
8	0,67	0,69	0,60	102,84
10	0,73	0,65	0,54	88,68
12	1,01	0,53	0,43	52,69
14	1,22	0,78	0,65	64,14
16	1,08	0,67	0,50	61,50
20	1,14	0,86	0,68	75,79
24	1,01	0,78	0,54	77,24
28	1,18	0,72	0,59	61,16
32	0,83	0,63	0,46	75,80
36	0,42	0,36	0,31	85,11
48	0,02			
60	0,00			
72	0,00			
Max ng/ml	1,69	0,73	0,61	43,32
Tmax H	16,25	7,56	6,42	41,41
AUC0-t H.ng/ml	30,12	16,26	13,82	53,98
F AUC	111,58	55,50	37,75	49,74
F Cmax	121,32	46,86	39,66	38,63

[00376] See Figure 25

[00377] Fasted State - 12 subjects (cross-over)

[00378] Geo Mean C_{max}: 1.32 ng/mL

[00379] Median T_{max}: 12.5 H

$AUC_{(0\text{-}tau)}$: 27.48 ng·H/mL

Table 38. CR GR-01 Individual BFB-520 Plasma Concentrations and Parameters (Fasted State)

GR01	GR01 FASTED BFB-520 PLASMA CONCENTRATIONS (ng/ml) and AUC 0-t (H.ng/ml)											
Hours	1-BFB-520	2-BFB-520	3-BFB-520	5-BFB-520	6-BFB-520	7-BFB-520	8-BFB-520	9-BFB-520	10-BFB-520	11-BFB-520	12-BFB-520	13-BFB-520
0	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,25	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
1,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
2,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
3	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
3,5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
4	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
5	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
6	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
7	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
8	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
10	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
12	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
14	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
16	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
20	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
24	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
28	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
32	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
36	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
48	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
60	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
72	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Max ng/ml	1,2	1,3	0,8	1,8	1,8	1,1	1,3	1,8	1,8	1,6	2,3	1,1
Tmax H	7,5	7,5	16,0	16,0	8,0	36,0	10,0	8,0	10,0	8,0	12,0	12,0
AUC0-t H.ng/ml	23,5	18,6	16,1	34,3	18,7	19,6	19,6	43,8	38,1	45,8	33,7	27,9

Table 39. CR GR-01 Mean BFB-520 Plasma Concentrations and Parameters (Fasted State)

GR01	GR01 BFB-520 PLASMA CONCENTRATIONS and AUCo-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00			
0,25	0,00			
0,5	0,00			
1	0,00			
1,5	0,00			
2	0,04	0,10	0,07	233,68
2,5	0,22	0,25	0,22	112,01
3	0,49	0,23	0,17	45,99
3,5	0,65	0,35	0,27	53,37
4	0,77	0,36	0,31	47,35
5	0,89	0,36	0,29	40,77
6	0,87	0,29	0,22	33,50
7	0,94	0,35	0,28	37,58
8	1,07	0,39	0,29	36,81
10	1,10	0,45	0,36	40,79
12	1,04	0,55	0,43	53,43
14	1,11	0,42	0,31	37,58
16	1,08	0,45	0,34	41,52
20	0,96	0,43	0,38	45,29
24	0,63	0,36	0,28	57,32
28	0,63	0,36	0,26	57,90
32	0,37	0,23	0,18	60,48
36	0,25	0,33	0,25	133,52
48	0,03	0,09	0,05	346,41
60	0,00			
72	0,00			
Max ng/ml	1,43	0,43	0,37	30,06
Tmax H	12,50	8,04	5,08	64,32
AUC0-t H.ng/ml	27,48	9,46	8,07	34,41
F AUC	96,10	35,77	18,95	37,22
F Cmax	88,48	24,60	20,65	30,56

[00380] See Figure 26

Table 40. CR GR-01 Mean BFB-520 Plasma Concentrations and Parameters (Fed versus Fasted State)

GR01	GR01 BFB-520 PLASMA CONCENTRATIONS and AUC0-t			
Hours	MEAN	Sd	Sm	CV%
0	0,00			
0,25	0,00			
0,5	0,00			
1	0,00			
1,5	0,00			
2	0,04	0,10	0,07	233,68
2,5	0,22	0,25	0,22	112,01
3	0,49	0,23	0,17	45,99
3,5	0,65	0,35	0,27	53,37
4	0,77	0,36	0,31	47,35
5	0,89	0,36	0,29	40,77
6	0,87	0,29	0,22	33,50
7	0,94	0,35	0,28	37,58
8	1,07	0,39	0,29	36,81
10	1,10	0,45	0,36	40,79
12	1,04	0,55	0,43	53,43
14	1,11	0,42	0,31	37,58
16	1,08	0,45	0,34	41,52
20	0,96	0,43	0,38	45,29
24	0,63	0,36	0,28	57,32
28	0,63	0,36	0,26	57,90
32	0,37	0,23	0,18	60,48
36	0,25	0,33	0,25	133,52
48	0,03	0,09	0,05	346,41
60	0,00			
72	0,00			
Max ng/ml	1,43	0,43	0,37	30,06
Tmax H	12,50	8,04	5,08	64,32
AUC0-t H.ng/ml	27,48	9,46	8,07	34,41
F AUC	96,10	35,77	18,95	37,22
F Cmax	80,48	24,60	20,65	30,56

[00381] Relative bioavailability of BFB-520 in GR-01 formulation in fed versus fasted states:

F% C_{max}: 121.32%

F% $AUC_{(0\text{-}tau)}$: 111.58%

[00382] See Figure 27

Example 14: Predicted Food Effect on Plasma Concentrations of MIN-101 and BFB-520 at Steady State in GR-01 Tablets (32 mg)

[00383] Determination of elimination slopes from the mean plasma concentrations time curves before numerical computations.

[00384] MIN-101

Fed State: K_e = 0.119/H

Fasted State: K_e = 0.082/H

[00385] BFB-520:

Fed State: from 14 H to 28 H during the flip flop phase K_e = 0.014/H; post absorption K_e = 0.233/H

Fasted State: from 14 H to 28 H during the flip flop phase K_e = 0.005545/H; post absorption K_e = 0.1586/H

Table 41. Predicted Plasma Concentrations of MIN-101 at Steady State in GR-01, 32 mg Tablets (Fed and Fasted states)

GR01 32mg FED and FASTED MIN-101 at Steady-State MIN101 Plasma Concentrations (ng/ml)		
HOURS	GR01 FED SS	GR01 FASTED SS
72	11,45	6,45
72,5	10,70	6,20
73	10,09	6,30
73,5	9,50	6,96
74	8,95	11,23
74,5	9,00	16,97
75	9,39	20,59
75,5	9,04	20,89
76	10,46	20,58
77	11,04	18,91
78	13,30	15,30
79	12,71	13,96
80	11,83	12,95
82	11,04	13,53
84	16,70	14,02
86	11,53	13,80
88	10,57	12,32
92	8,09	6,75
96	11,45	6,46
CMaxSS ng/ml	16,7	20,9
CMinSS	8,09	6,46
TmaxSS H	12,00	3,5
AUC72-96 H.ng/ml	263,8	287,6
F AUC	91,7	REF
F Cmax	80,0	REF

[00386] See Figure 28.

Table 42. Predicted Plasma Concentrations of BFB-520 at Steady State in GR-01, 32 mg Tablets (Fed and Fasted states)

GR01 32mg FED and FASTED BFB-520 at Steady-State BFB-520 Plasma Concentrations (ng/ml)		
HOURS	GR01 FED SS	GR01 FASTED SS
72	1,03	0,66
72,5	1,02	0,64
73	1,01	0,62
73,5	1,00	0,60
74	0,99	0,63
74,5	0,99	0,79
75	0,98	1,04
75,5	1,00	1,18
76	1,25	1,41
77	1,13	1,38
78	1,29	1,33
79	1,46	1,38
80	1,51	1,45
82	1,26	1,37
84	1,43	1,29
86	1,43	1,26
88	1,21	1,19
92	1,19	1,02
96	1,03	0,66
CMaxSS ng/ml	1,51	1,45
CMinSS	1,03	0,66
TmaxSS H	8,00	8,00
AUC72-96 H.ng/ml	29,5	27,0
F AUC	109,4	REF
F Cmax	103,7	REF

[00387] See Figure 29.

Example 15: Predicted Food Effect on Plasma Concentrations of MIN-101 and BFB-520 at Steady State in GR-01 Tablets (64 mg)

[00388] Determination of elimination slopes from the mean plasma concentrations time curves before numerical computations.

[00389] MIN-101

Fed State: $K_e = 0.119/H$

Fasted State: $K_e = 0.082/H$

[00390] BFB-520:

Fed State: from 14 H to 28 H during the flip flop phase $K_e = 0.014/H$; post absorption $K_e = 0.233/H$

Fasted State: from 14 H to 28 H during the flip flop phase $K_e = 0.005545/H$; post absorption $K_e = 0.1586/H$

Table 43. Predicted Plasma Concentrations of MIN-101 at Steady State in GR-01, 64 mg Tablets (Fed and Fasted states)

GR01 64mg FED and FASTED MIN-101 at Steady-State MIN101 Plasma Concentrations (ng/ml)		
HOURS	GR01 FED SS	GR01 FASTED SS
72	22,91	12,90
72,5	21,41	12,40
73	20,17	12,60
73,5	19,01	13,93
74	17,91	22,46
74,5	18,00	33,94
75	18,78	41,18
75,5	18,08	41,77
76	20,92	41,17
77	22,08	37,82
78	26,60	30,60
79	25,42	27,92
80	23,65	25,90
82	22,08	27,06
84	33,41	28,05
86	23,05	27,61
88	21,14	24,64
92	16,17	13,49
96	22,91	12,93
CMaxSS ng/ml	33,41	41,77
CMinSS	16,17	12,93
TmaxSS H	12,00	3,50
AUC72-96 H.ng/ml	527,5	577,6
F AUC	91,3	REF
F Cmax	80,0	REF

[00391] See Figure 30.

Table 44. Predicted Plasma Concentrations of BFB-520 at Steady State in GR-01, 64 mg Tablets (Fed and Fasted states)

GR01 64mg FED and FASTED BFB-520 at Steady-State BFB-520 Plasma Concentrations (ng/ml)		
HOURS	GR01 FED SS	GR01 FASTED SS
72	2,06	1,32
72,5	2,04	1,28
73	2,02	1,24
73,5	2,00	1,21
74	1,99	1,26
74,5	1,97	1,58
75	1,95	2,09
75,5	1,99	2,37
76	2,50	2,82
77	2,27	2,77
78	2,57	2,66
79	2,92	2,76
80	3,01	2,91
82	2,51	2,75
84	2,87	2,57
86	2,86	2,52
88	2,42	2,37
92	2,38	2,03
96	2,06	1,32
CMaxSS ng/ml	3,01	2,91
CMinSS	2,06	1,32
TmaxSS H	8,00	8,00
AUC72-96 H.ng/ml	59,0	54,1
F AUC	109,1	REF
F Cmax	103,7	REF

[00392] See Figure 31.

Example 16: Description of 32 mg gastro-resistant CR tablet (GR01/B-32 mg)

[00393] The CR GR-01/B tablets are supplied as round (diameter 10 mm and R=10) tablets, free from visual defects. Each tablet contains 32 mg of Compound (I). The complete statement of the components and quantitative composition of CR GR-01/B tablet is given in Table 45.

Table 45: Composition of CR GR-01/B 32mg tablet

Component/Ingredient	GR-01/B-32mg	
	mg/tablet	% (w/w)
MIN-101[1]	38.40	12.09
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67
Microcrystalline Cellulose	96.67	30.42
Lactose	60.00	18.89
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	1.50	0.47
Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.62	100.00

[1] Salt correction factor of 1.2 applied Example 17: Description of 64 mg gastro-resistant CR tablet (GR-01/B-64 mg)

[00394] The CR GR-01/B tablets are supplied as round (diameter 10 mm and R=10) tablets, free from visual defects. Each tablet contains 64 mg of Compound (I). The complete statement of the components and quantitative composition of CR GR-01/B tablet is given in Table 46.

Table 46: Composition of CR GR-01/B 64mg tablet

Component/Ingredient	GR-01/B-64mg	
	mg/tablet	% (w/w)
MIN-101[1]	76. 8	24.14
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose	72.00	22.67

(Methocel™ K100M CR)		
Microcrystalline Cellulose	77.40	24.37
Lactose	40.80	12.85
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	1.50	0.47
Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.55	100.00

[1] Salt correction factor of 1.2 applied

Example 18: Comparison of GR-01 32 mg Tablet, GR-01/B 32 mg Tablet, and GR-01/B 64 mg Tablet

Table 47:Tablet Composition : GR01 vs GR01/B

Component/Ingredient	GR01-32mg		GR01/B-32mg		GR01/B-64mg	
	mg/tablet	% (w/w)	mg/tablet	% (w/w)	mg/tablet	% (w/w)
MIN-101[1]	38.40	12.09	38.40	12.09	76.8	24.14
Hypromellose (Metolose® 90SH 100 SR)	30.00	9.45				
Hypromellose (METHOCEL™ K100LV CR)			30.00	9.45	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67	72.00	22.67	72.00	22.67
Microcrystalline Cellulose	95.10	29.95	96.60	30.42	77.40	24.37
Lactose	60.00	18.89	60.00	18.89	40.80	12.85
Silica Colloidal Anhydrous	1.50	0.47	1.50	0.47	1.50	0.47
Magnesium stearate	3.00	0.94	1.50	0.47	1.50	0.47
Eudragit L30D55	15.0	4.72	15.0	4.72	15.0	4.72
Plasacryl HTP20	2.55	0.80	2.55	0.80	2.55	0.80
Total	317.55	5.53	317.55	100.00	317.55	100.00

[1] Salt correction factor of 1.2 applied

Example 19: Stability Data Experiments: Comparison of GR-01 and GR-01/B 32 mg Tablets

[00395] "Impurity A," "2-isomer," and "PMIC" refer to impurities from the manufacturing process for MIN-101.

Table 48: Stability data at 25 °C/60% RH

Product Name: MIN-101 **Strength:** 32mg **Storage Condition:** 25 ºC/60% RH			Product Manufacturer: Amatsi Aquitaine API Manufacturer: PCAS Container Closure: TEKNIFLEX® VPOA 10200 and aluminum blister packs			
Test	Stability Interval (Months)					
	Initial	**1**	**3**	**6**	**9**	**12**
	GR01 tablets					
Related Sub. (%)						
Impurity A	<LOQ	0.02	0.03	0.04	0.03	<LOQ
2-isomer	<LOQ	<LOQ	<LOQ	0.02	<LOQ	<LOQ
PMIC	0.08	0.13	0.18	0.20	0.24	0.26
Unspecified imp.	<0.1% each	<0.1% each	RRT0.67 : 0.11	RRT0.67 : 0.12	RRT 0.67 : 0.12	RRT 0.67 : 0.15
Total impurities	0.15	0.29	0.46	0.51	0.52	0.59
	GR01/B tablets					
Related Sub. (%)						
Impurity A	ND	ND	ND	ND		
2-isomer	0.07	0.07	0.07	0.07		
PMIC	0.09	0.11	0.15	0.16		
Unspecified imp.	<0.1% each	<0.1% each	<0.1% each	<0.1% each		
Total impurities	0.26	0.29	0.37	0.38		

Table 49: Stability data at 40°C/75% RH

Product Name: MIN-101 **Strength:** 32mg **Storage Condition:** 40°C/75% RH		Product Manufacturer: Amatsi Aquitaine API Manufacturer: PCAS Container Closure: TEKNIFLEX® VPOA 10200 and aluminum blister packs		
Test	Stability Interval (Months)			
	Initial	**1**	**3**	**6**
	GR01 tablets			
Related Sub. (%)				
Impurity A	<LOQ	0.04	0.06	0.08
2-isomer	<LOQ	<LOQ	<LOQ	<LOQ
PMIC	0.08	0.27	0.44	0.77
Unspecified imp.	<0.1% each	RRT0.67 = 0.12	RRT0.67 : 0.18	RRT0.67 : 0.24
Total impurities	0.15	0.57	0.94	1.46
	GR01/B tablets			
Related Sub. (%)				
Impurity A	ND	ND	ND	ND
2-isomer	0.07	0.07	0.07	0.06
PMIC	0.09	0.23	0.34	0.52
Unspecified imp.	<0.1% each	<0.1% each	RRT 0.67 : 0.11	RRT 0.67 : 0.15
Total impurities	0.26	0.51	0.71	1.00

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Example 20: In Vitro Dissolution Specifications for GR-01/B Tablets

Table 50: Specifications for GR-01/B tablets

Test	Method	Acceptance Criteria
Dissolution (%) 2 hours 4 hours 8 hours 16 hours	HPLC	Report results (±10%) 0.0 % 24.1% 59.2% 88.6%

Example 21: Description of 32 mg gastro-resistant CR tablet (GR-01/C-32 mg)

[00396] The CR GR-01/C tablets are supplied as round (diameter 10 mm and R=10) tablets, free from visual defects. Each tablet contains 32 mg of Compound (I). The complete statement of the components and quantitative composition of CR GR-01/C tablet is given in Table 51.

Table 51: Composition of CR GR-01/C 32mg tablet

Component/Ingredient	GR-01/C-32mg	
	mg/tablet	% (w/w)
MIN-101[1]	38.40	12.11
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67
Microcrystalline Cellulose	95.10	29.95
Lactose	60.00	18.89
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	3.00	0.94
Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.55	100.00

Example 22: Description of 64 mg gastro-resistant CR tablet (GR-01/C-64 mg)

[00397] The CR GR-01/C tablets are supplied as round (diameter 10 mm and R=10) tablets, free from visual defects. Each tablet contains 64 mg of Compound (I). The complete statement of the components and quantitative composition of CR GR-01/C tablet is given in Table 53.

Table 53: Composition of CR GR-01/C 64mg tablet

Component/Ingredient	GR-01/C-64mg	
	mg/tablet	% (w/w)
MIN-101[1]	76.8	24.19
Hypromellose (METHOCEL™ K100LV CR)	30.00	9.45
Hypromellose (Methocel™ K100M CR)	72.00	22.67
Microcrystalline Cellulose	75.90	23.91
Lactose	40.80	12.85
Silica Colloidal Anhydrous	1.50	0.47
Magnesium stearate	3.00	0.94
Eudragit L30D55	15.0	4.72
Plasacryl HTP20	2.55	0.80
Total	317.55	100.00

EQUIVALENTS AND INCORPORATION BY REFERENCE

[00398] The dosage forms, compositions and methods of the disclosure have been described herein by reference to certain preferred embodiments. However, as particular variations thereon will become apparent to those skilled in the art, based on the disclosure set forth herein, the disclosure is not to be considered as limited thereto.

[00399] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure

belongs. In the specification and claims, the singular forms also include the plural unless the context clearly dictates otherwise.

[00400] It is to be understood that at least some of the descriptions of the disclosure have been simplified to focus on elements that are relevant for a clear understanding of the disclosure, while eliminating, for purposes of clarity, other elements that those of ordinary skill in the art will appreciate may also comprise a portion of the disclosure. However, because such elements are well known in the art, and because they do not necessarily facilitate a better understanding of the disclosure, a description of such elements is not provided herein.

[00401] Further, to the extent that a method does not rely on the particular order of steps set forth herein, the particular order of the steps recited in a claim should not be construed as a limitation on that claim.

[00402] All patents, patent applications, references and publications cited herein are fully and completely incorporated by reference as if set forth in their entirety. Such documents are not admitted to be prior art to the present disclosure.

What is claimed is:

1. A gastro-resistant, controlled release dosage form comprising:

i. about 4 mg to about 100 mg of Compound (I), or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof; and

ii. at least one controlled release agent.

2. The gastro-resistant, controlled release dosage form of claim 1, wherein the dosage form produces, upon oral administration to the subject, a plasma pharmacokinetic profile for Compound (I) which comprises a T_{max} between about 1, 1.5, 2, 2.5, 3, 3.5, or 4 hours and about 22 hours.

3. The gastro-resistant, controlled release dosage form of claim 1, wherein the amount of Compound (I) is 4 mg to 8 mg, 8 mg to 16 mg, 16 mg to 32 mg, 32 mg to 40 mg, 40 mg to 64 mg, 64 mg to 80 mg, or 80 mg to 100 mg.

4. The gastro-resistant, controlled release dosage form of claim 1, wherein the amount of Compound (I) is 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, or 100 mg.

5. The gastro-resistant, controlled release dosage form of claim 1, wherein the amount of Compound (I) is 4 mg, 8 mg, 16 mg, 24 mg, 32 mg, 40 mg, 64 mg, 80 mg, 96 mg, or 100 mg.

6. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 32 mg, or an equivalent amount of a pharmaceutically

acceptable salt and/or solvate thereof, and the AUC_{0-4H} of Compound (I) is less than about 68 h*ng/mL.

7. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 32 mg, or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the C_{max} of Compound (I) is less than about 16 ng/mL, 17 ng/mL, 18 ng/mL, 19 ng/mL, 20 ng/mL, 21 ng/mL, 22 ng/mL, or 23 ng/mL.

8. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 32 mg, or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the AUC_{0-24hr} of Compound (I) is between about 75 h*ng/mL to about 350 h*ng/mL or between about 100 h*ng/mL to about 300 h*ng/mL.

9. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 32 mg, or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma pharmacokinetic profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 3.0 ng/mL, below 2.5 ng/mL, below 2.0 ng/mL, below 1.5 ng/mL or below 1.0 ng/mL.

10. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 64 mg, or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the AUC_{0-4H} of Compound (I) is less than about 50, 60, 70, 80, 90, 100, 110, 120, or 130 h*ng/mL.

11. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 64 mg, or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the C_{max} of Compound (I) is less than about 36 ng/mL or less than about 25 ng/mL.

12. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 64 mg, or an equivalent amount of a pharmaceutically

acceptable salt and/or solvate thereof, and the $AUC_{0\text{-}24hr}$ of Compound (I) is between about 200 h*ng/mL to about 600 h*ng/mL.

13. The gastro-resistant, controlled release dosage form of any one of claims 1-5, wherein the amount of Compound (I) is about 64 mg, or an equivalent amount of a pharmaceutically acceptable salt and/or solvate thereof, and the plasma pharmacokinetic profile for the BFB-520 metabolite of Compound (I) comprises a C_{max} that is below 4.0 ng/mL, below 3.5 ng/mL, below 3.0 ng/mL, or below 2.5 ng/mL.

14. The gastro-resistant, controlled release dosage form of any one of the previous claims, wherein the dosage form is a tablet which comprises a core tablet and an enteric coating.

15. The gastro-resistant, controlled release dosage form of claim 14, wherein the core tablet of the dosage form comprises Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof and a controlled release agent.

16. The gastro-resistant, controlled release dosage form of claim 15, wherein the core tablet further comprises a filler, a glidant, and a lubricant.

17. The gastro-resistant, controlled release dosage form of claim 14, wherein the core tablet of the dosage form comprises Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, a controlled release agent, a filler, a glidant, and a lubricant.

18. The gastro-resistant, controlled release dosage form of any one of claims 15-17, wherein the controlled release agent in the core tablet comprises one or more hypromelloses.

19. The gastro-resistant, controlled release dosage form of any one of claims 15-18, wherein the controlled release agent in the core tablet comprises a mixture of (i) a low viscosity hypromellose with a viscosity of between about 15 millipascal-seconds (mPa·s) to about 100 mPa·s and (ii) a high viscosity hypromellose with a viscosity of about 100,000 mPa·s, wherein each of the low and high viscosity hypromelloses is a controlled release or sustained-release

grade and is further characterized by a methoxy content of 19.0% to 24.0% and a hydroxypropoxy content of 4.0% to 12.0%.

20. The gastro-resistant, controlled release dosage form of claim 16 or 17, wherein the glidant in the core tablet is silica colloidal anhydrous.

21. The gastro-resistant, controlled release dosage form of claim 16 or 17, wherein the lubricant in the core tablet is magnesium stearate.

22. The gastro-resistant, controlled release dosage form of claim 14, wherein the enteric coating of the dosage form comprises at least one polymeric controlled release agent with a dissolution property of greater than pH 5.5, 6.0 or 6.5, and an anti-tacking agent.

23. The gastro-resistant, controlled release dosage form of claim 22, wherein the enteric coating of the dosage form further comprises a plasticizer.

24. The gastro-resistant, controlled release dosage form of claim 22 or 23, wherein the polymeric controlled release agent comprises Eudragit L30D55.

25. The gastro-resistant, controlled release dosage form of claim 22 or 23, wherein the anti-tacking agent is Plasacryl HTP20.

26. A gastro-resistant, controlled release dosage form comprising:

about 7 to about 17% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Metolose® 90SH K15M 100 SR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 25 to about 35% w/w microcrystalline cellulose;

about 13 to about 23% w/w lactose monohydrate

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% magnesium stearate;

about 1 to about 10% w/w Eudragit L30D55; and

about 0.5 to about 5% w/w Plasacryl HTP20.

27. The gastro-resistant, controlled release dosage form of claim 26, comprising:

about 12 % w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Metolose® 90SH K15M 100 SR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate

about 0.5% w/w silica colloidal anhydrous;

about 1 % magnesium stearate;

about 5 % w/w Eudragit L30D55; and

about 1 % w/w Plasacryl HTP20.

28. A gastro-resistant, controlled release dosage form comprising:

about 7 to about 17% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Methocel™ K15M CR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 25 to about 35% w/w microcrystalline cellulose;

about 13 to about 23% w/w lactose monohydrate;

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% w/w magnesium stearate;

about 1 to about 10% Eudragit L30D55;

about 0.5 to about 5% w/w Plasacryl HTP20; and

about 0.5 to about 5% w/w Surelease E-7-19040.

29. A gastro-resistant, controlled release dosage form of claim 28, comprising:

about 12% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Methocel™ K15M CR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate;

about 0.5 % w/w silica colloidal anhydrous;

about 1 % w/w magnesium stearate;

about 5 % w/w Eudragit L30D55;

about 1 % w/w Plasacryl HTP20; and

about 1 % w/w Surelease E-7-19040.

30. A gastro-resistant, controlled release dosage form comprising:

about 7 to about 17% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Methocel™ K100LV CR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 25 to about 35% w/w microcrystalline cellulose;

about 13 to about 23% w/w lactose monohydrate

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% magnesium stearate;

about 1 to about 10% w/w Eudragit L30D55; and

about 0.5 to about 5% w/w Plasacryl HTP20.

31. The gastro-resistant, controlled release dosage form of claim 30, comprising:

about 12% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Methocel™ K100LV CR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate;

about 0.5 % w/w silica colloidal anhydrous;

about 0.5 % w/w magnesium stearate;

about 5 % w/w Eudragit L30D55; and

about 1 % w/w Plasacryl HTP20.

32. The gastro-resistant, controlled release dosage form of claim 30, comprising:

about 12% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9 % w/w hypromellose (Methocel™ K100LV CR);

about 23 % w/w hypromellose (Methocel™ K100M CR);

about 30 % w/w microcrystalline cellulose;

about 19 % w/w lactose monohydrate;

about 0.5 % w/w silica colloidal anhydrous;

about 1 % w/w magnesium stearate;

about 5 % w/w Eudragit L30D55; and

about 1 % w/w Plasacryl HTP20.

33. A gastro-resistant, controlled release dosage form comprising:

about 19 to about 29% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 4 to about 14% w/w hypromellose (Methocel™ K100LV CR);

about 17 to about 27% w/w hypromellose (Methocel™ K100M CR);

about 19 to about 29% w/w microcrystalline cellulose;

about 8 to about 18% w/w lactose monohydrate

about 0.1 to about 4% w/w silica colloidal anhydrous;

about 0.1 to about 4% magnesium stearate;

about 1 to about 10% w/w Eudragit L30D55; and

about 0.5 to about 5% w/w Plasacryl HTP20.

34. The gastro-resistant, controlled release dosage form of claim 33, comprising:

about 24% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;

about 9% w/w hypromellose (Methocel™ K100LV CR);

about 23% w/w hypromellose (Methocel™ K100M CR);
about 24% w/w microcrystalline cellulose;
about 13% w/w lactose monohydrate;
about 0.5% w/w silica colloidal anhydrous;
about 0.5% w/w magnesium stearate;
about 5% w/w Eudragit L30D55; and
about 1% w/w Plasacryl HTP20.

35. The gastro-resistant, controlled release dosage form of claim 33, comprising:
about 24% w/w Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof;
about 9% w/w hypromellose (Methocel™ K100LV CR);
about 23% w/w hypromellose (Methocel™ K100M CR);
about 24% w/w microcrystalline cellulose;
about 13% w/w lactose monohydrate;
about 0.5% w/w silica colloidal anhydrous;
about 1% w/w magnesium stearate;
about 5% w/w Eudragit L30D55; and
about 1% w/w Plasacryl HTP20.

36. A method of reducing a risk of QT prolongation when treating a subject with Compound (I), or a pharmaceutically acceptable salt and/or solvate thereof, the method comprising oral administration to the subject of a gastro-resistant, controlled release dosage form of any one of claims 1-35.

37. A method of treating negative symptoms in a subject comprising an oral administration to the subject of a gastro-resistant, controlled release dosage form of any one of claims 1-35, wherein the subject has a diagnosis of schizophrenia.

38. The method according to claim 36 or 37 wherein the gastro-resistant, controlled release dosage form is administered once daily.

39. The method of claim 37 or 38, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype.

40. The method of any one of claims 36-39, wherein the subject is in fed state prior to oral administration of the dosage form.

41. The method of any one of claims 36-39, wherein the subject is in fasted state prior to oral administration of the dosage form.

42. A gastro-resistant, controlled release dosage form of any one of claims 1-35 for use in reducing a risk of QT prolongation.

43. A gastro-resistant, controlled release dosage form of any one of claims 1-35 for use in treating negative symptoms in a subject, wherein the subject has a diagnosis of schizophrenia.

44. A gastro-resistant, controlled release dosage form for use according to claim 42 or 43, wherein the gastro-resistant, controlled release dosage form is administered once daily.

45. A gastro-resistant, controlled release dosage form for use according to claim 43 or 44, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype.

46. A gastro-resistant, controlled release dosage form for use according to any one of claims 42-45, wherein the subject is in fed state prior to oral administration of the dosage form.

47. A gastro-resistant, controlled release dosage form for use according to claim 42-45, wherein the subject is in fasted state prior to oral administration of the dosage form.

48. Use of a gastro-resistant, controlled release dosage form of any one of claims 1-35 in the manufacture of medicament for reducing a risk of QT prolongation.

49. Use of a gastro-resistant, controlled release dosage form of any one of claims 1-35 in the manufacture of medicament for the treatment of negative symptoms in a subject, wherein the subject has a diagnosis of schizophrenia.

50. The use of claim 48 or 49, wherein the gastro-resistant, controlled release dosage form is administered once daily.

51. The use of claim 49 or 50, wherein the subject having a diagnosis of schizophrenia has a CYP2D6 EM genotype.

52. The use of any one of claims 48-51, wherein the subject is in fed state prior to oral administration of the dosage form.

53. The use of any one of claims 48-51, wherein the subject is in fasted state prior to oral administration of the dosage form.

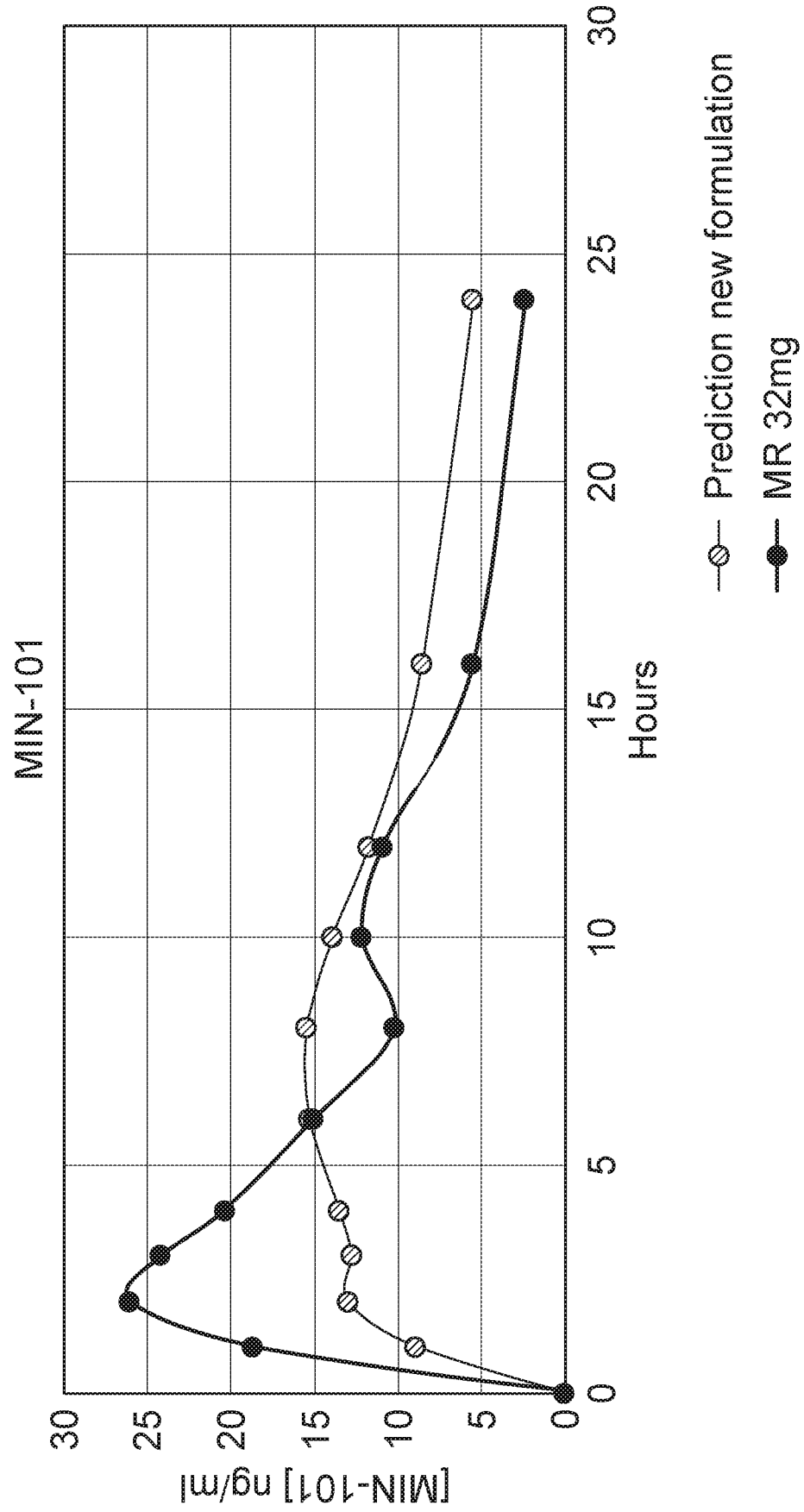
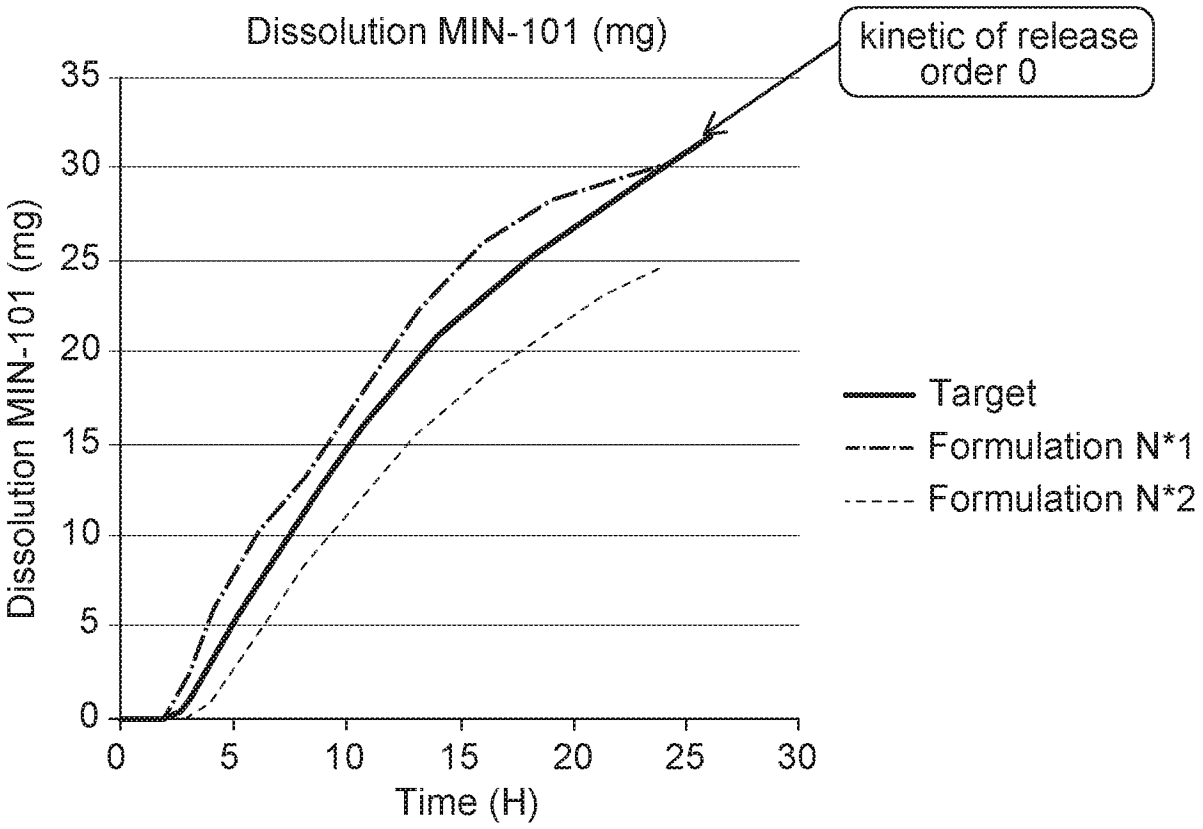
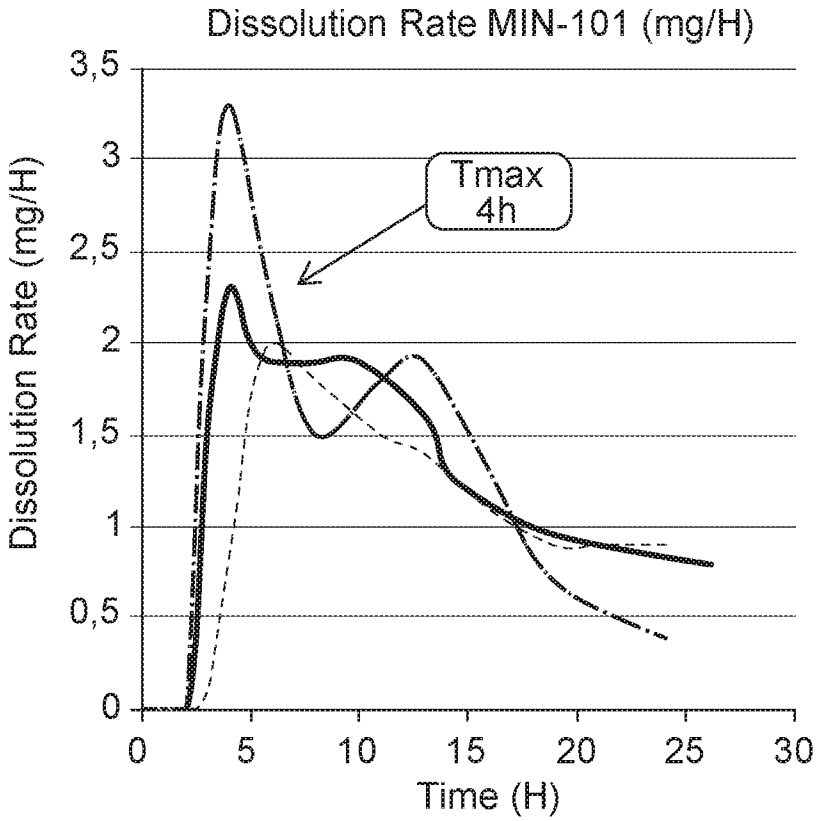

MIN-101
[MIN-101] ng/ml
0
5
10
15
20
25
30
Hours
0
5
10
15
20
25
30
Prediction new formulation
MR 32mg

FIGURE 1

FIGURE 2


Dissolution MIN-101 (mg)
kinetic of release order 0
Dissolution MIN-101 (mg)
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Time (H)
Target
Formulation N*1
Formulation N*2


Dissolution Rate MIN-101 (mg/H)
Tmax 4h
Dissolution Rate (mg/H)
3,5
3
2,5
2
1,5
1
0,5
0
0
5
10
15
20
25
30
Time (H)

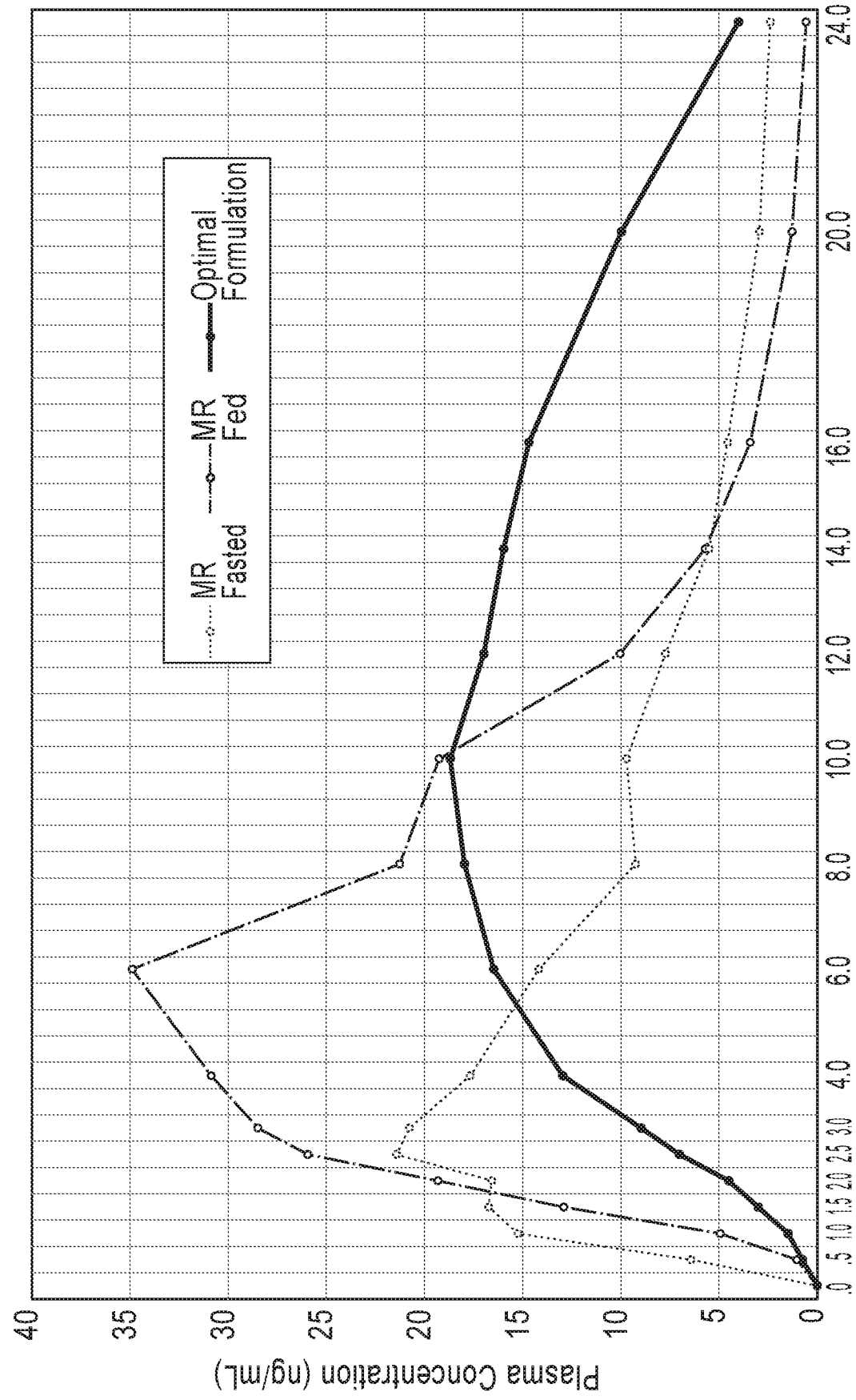

Plasma Concentration (ng/mL)
0
5
10
15
20
25
30
35
40
0
.5
1.0
1.5
2.0
2.5
3.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
20.0
24.0
Optimal Formulation
MR Fed
MR Fasted

FIGURE 3

FIGURE 4

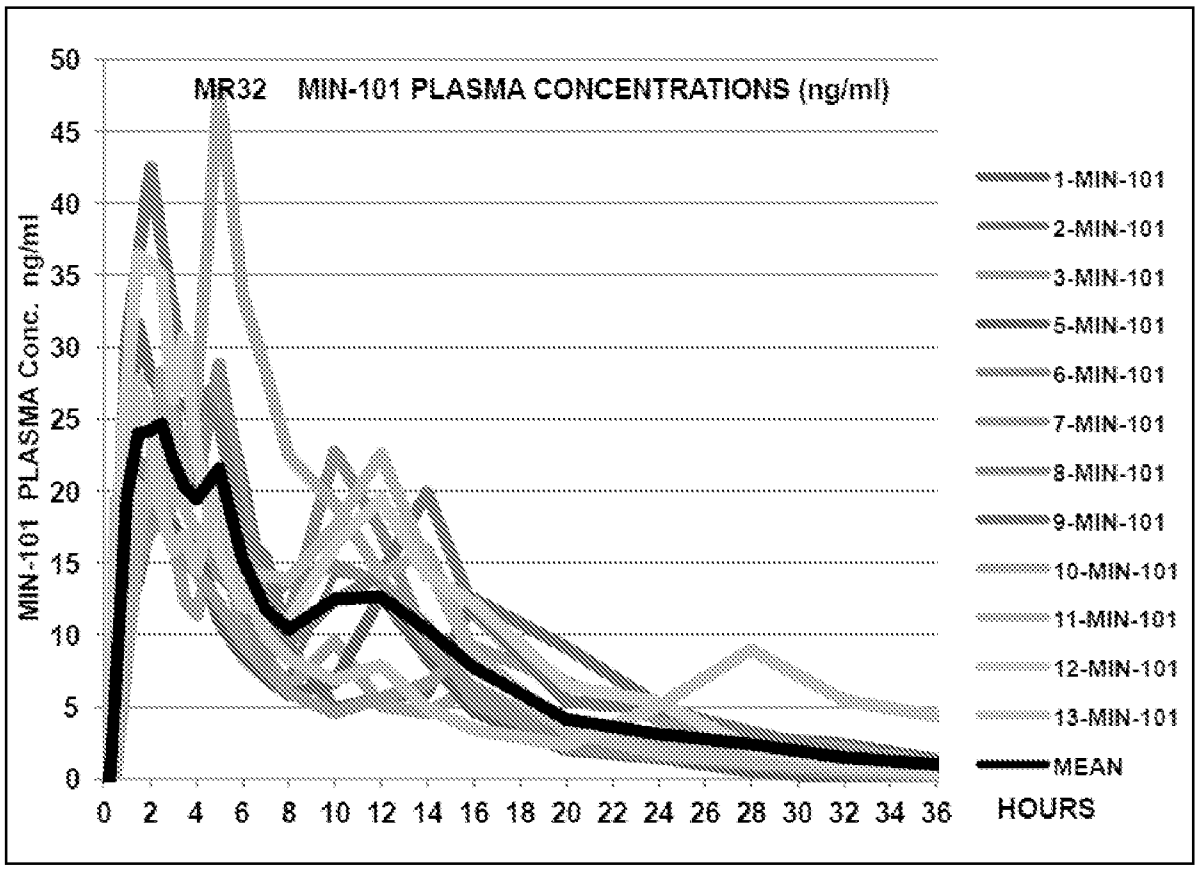

MR32 MIN-101 PLASMA CONCENTRATIONS (ng/ml)
MIN-101 PLASMA Conc. ng/ml
50
45
40
35
30
25
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
HOURS
1-MIN-101
2-MIN-101
3-MIN-101
5-MIN-101
6-MIN-101
7-MIN-101
8-MIN-101
9-MIN-101
10-MIN-101
11-MIN-101
12-MIN-101
13-MIN-101
MEAN

FIGURE 5

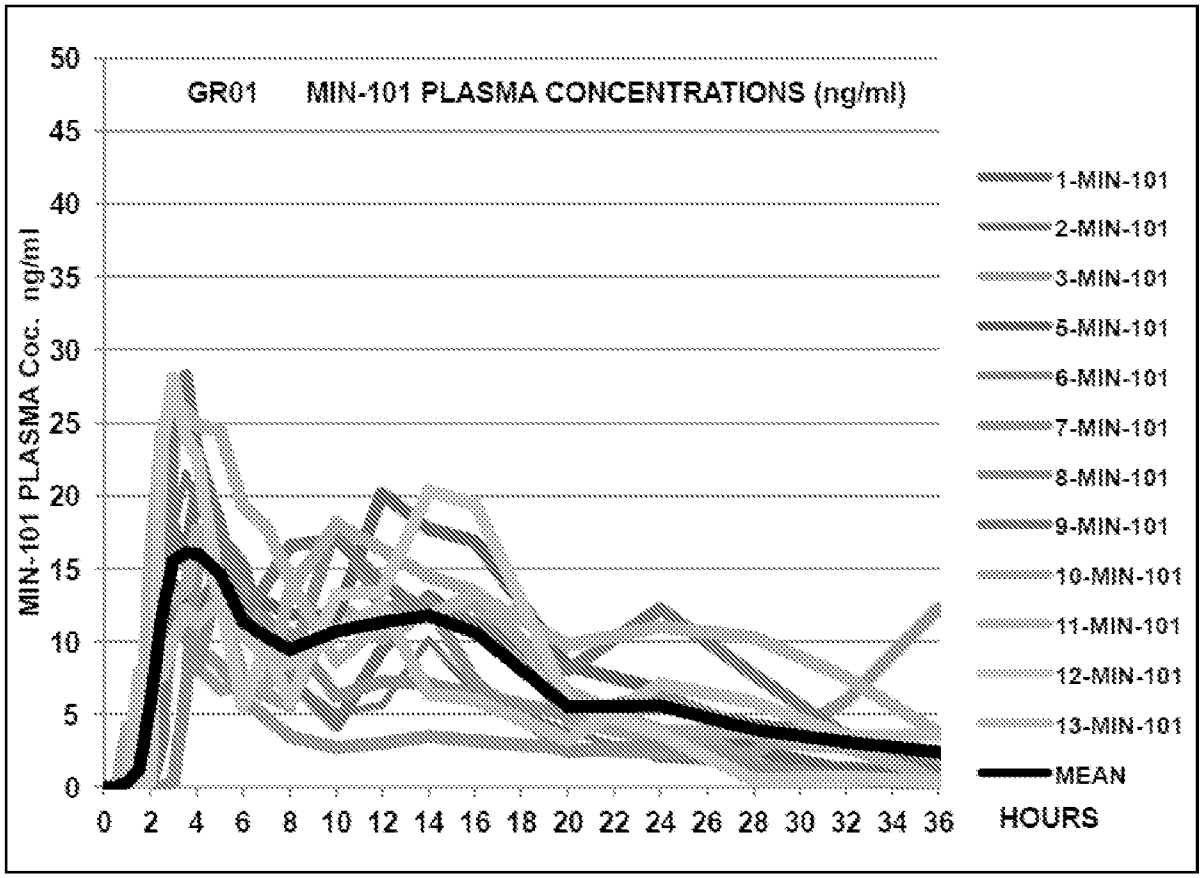

GR01 MIN-101 PLASMA CONCENTRATIONS (ng/ml)
MIN-101 PLASMA Conc. ng/ml
50
45
40
35
30
25
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
HOURS
1-MIN-101
2-MIN-101
3-MIN-101
5-MIN-101
6-MIN-101
7-MIN-101
8-MIN-101
9-MIN-101
10-MIN-101
11-MIN-101
12-MIN-101
13-MIN-101
MEAN

FIGURE 6

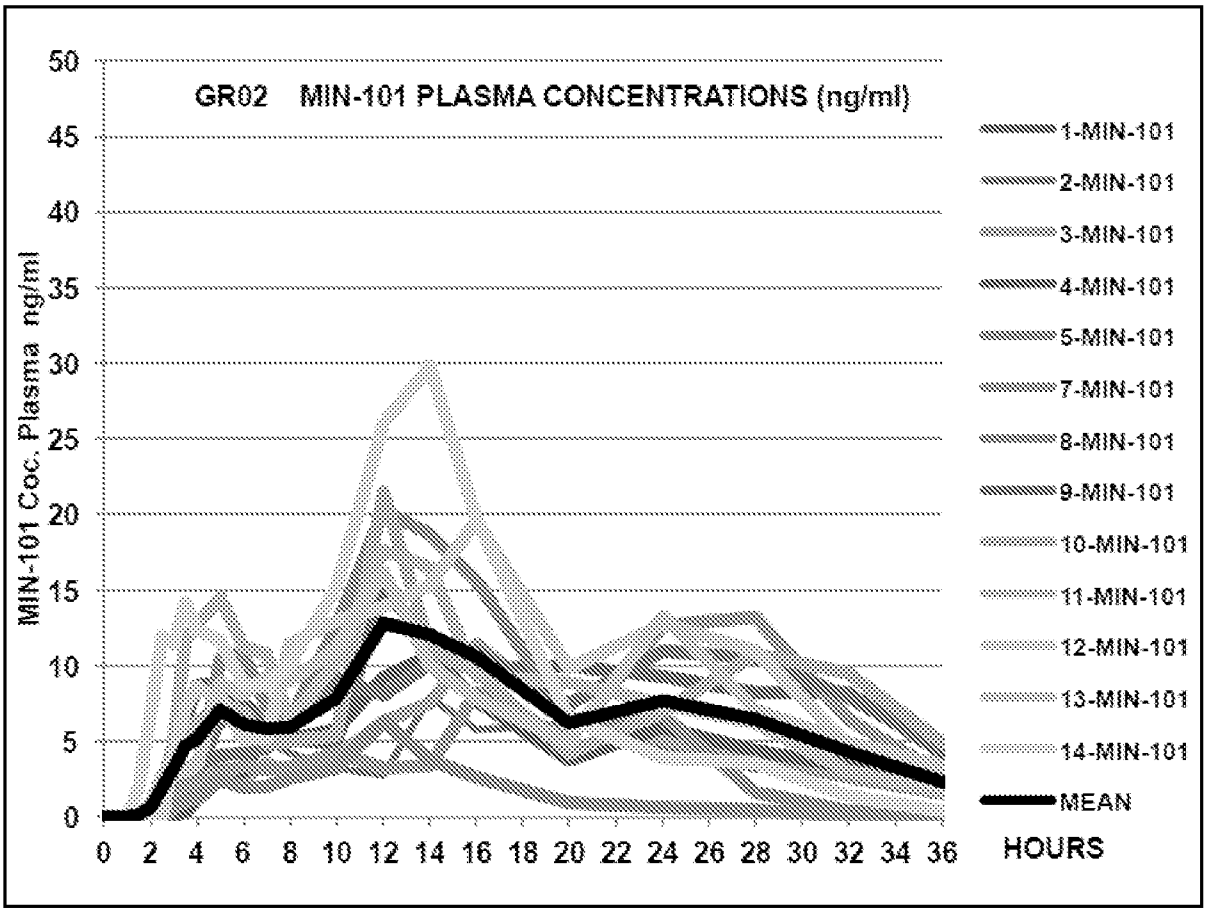

GR02 MIN-101 PLASMA CONCENTRATIONS (ng/ml)
MIN-101 Coc. Plasma ng/ml
50
45
40
35
30
25
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
HOURS
1-MIN-101
2-MIN-101
3-MIN-101
4-MIN-101
5-MIN-101
7-MIN-101
8-MIN-101
9-MIN-101
10-MIN-101
11-MIN-101
12-MIN-101
13-MIN-101
14-MIN-101
MEAN

FIGURE 7

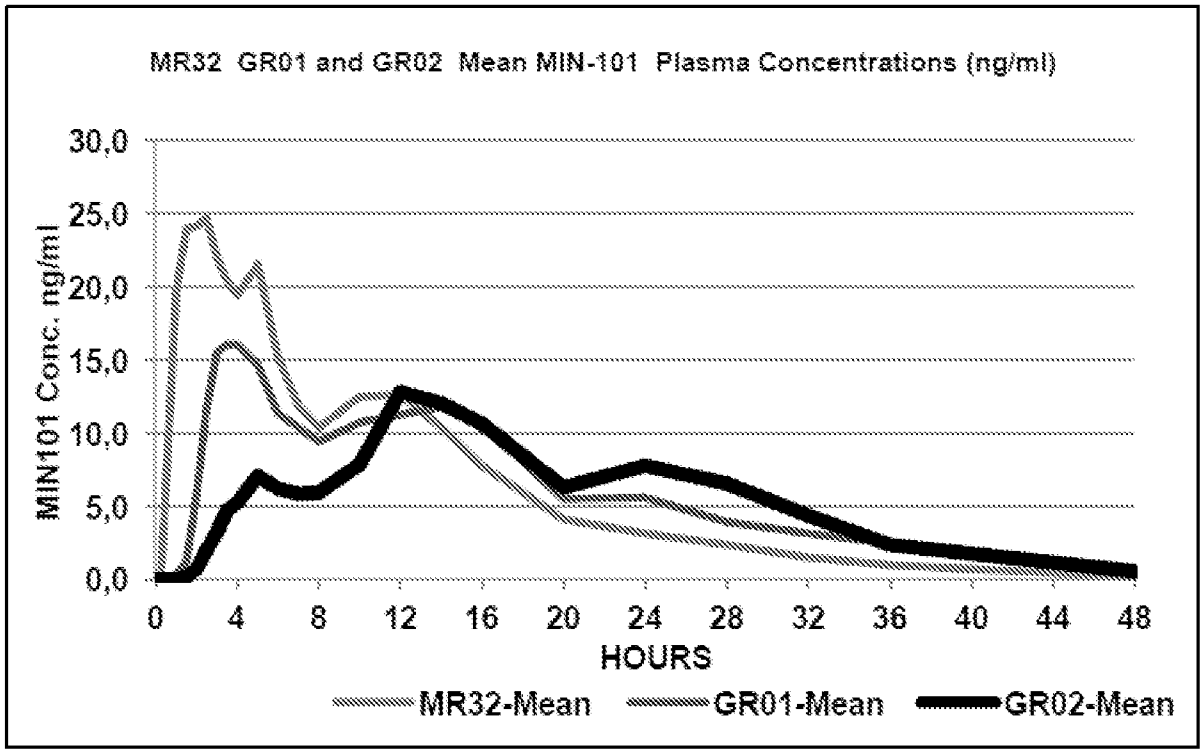

MR32 GR01 and GR02 Mean MIN-101 Plasma Concentrations (ng/ml)
MIN101 Conc. ng/ml
30,0
25,0
20,0
15,0
10,0
5,0
0,0
0
4
8
12
16
20
24
28
32
36
40
44
48
HOURS
MR32-Mean
GR01-Mean
GR02-Mean

FIGURE 8

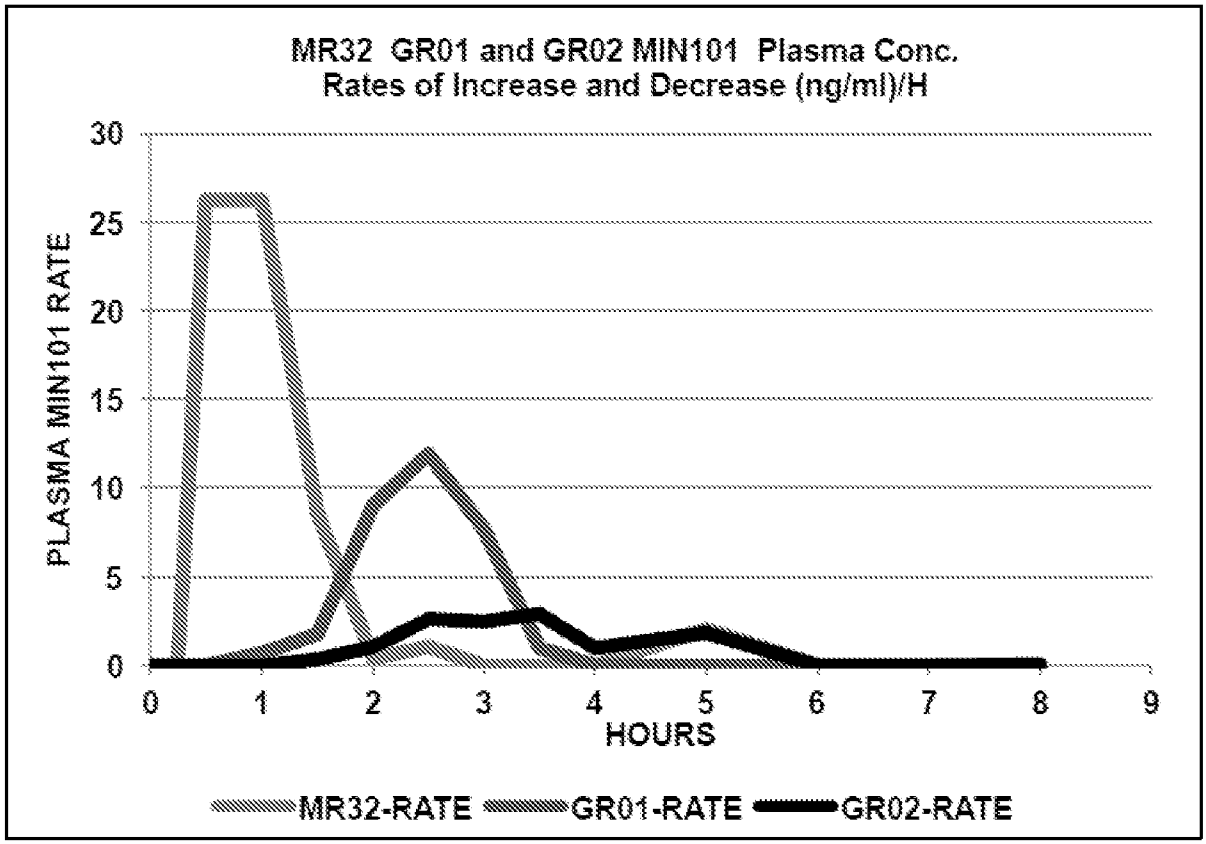

MR32 GR01 and GR02 MIN101 Plasma Conc.
Rates of Increase and Decrease (ng/ml)/H
PLASMA MIN101 RATE
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
9
HOURS
MR32-RATE
GR01-RATE
GR02-RATE

FIGURE 9

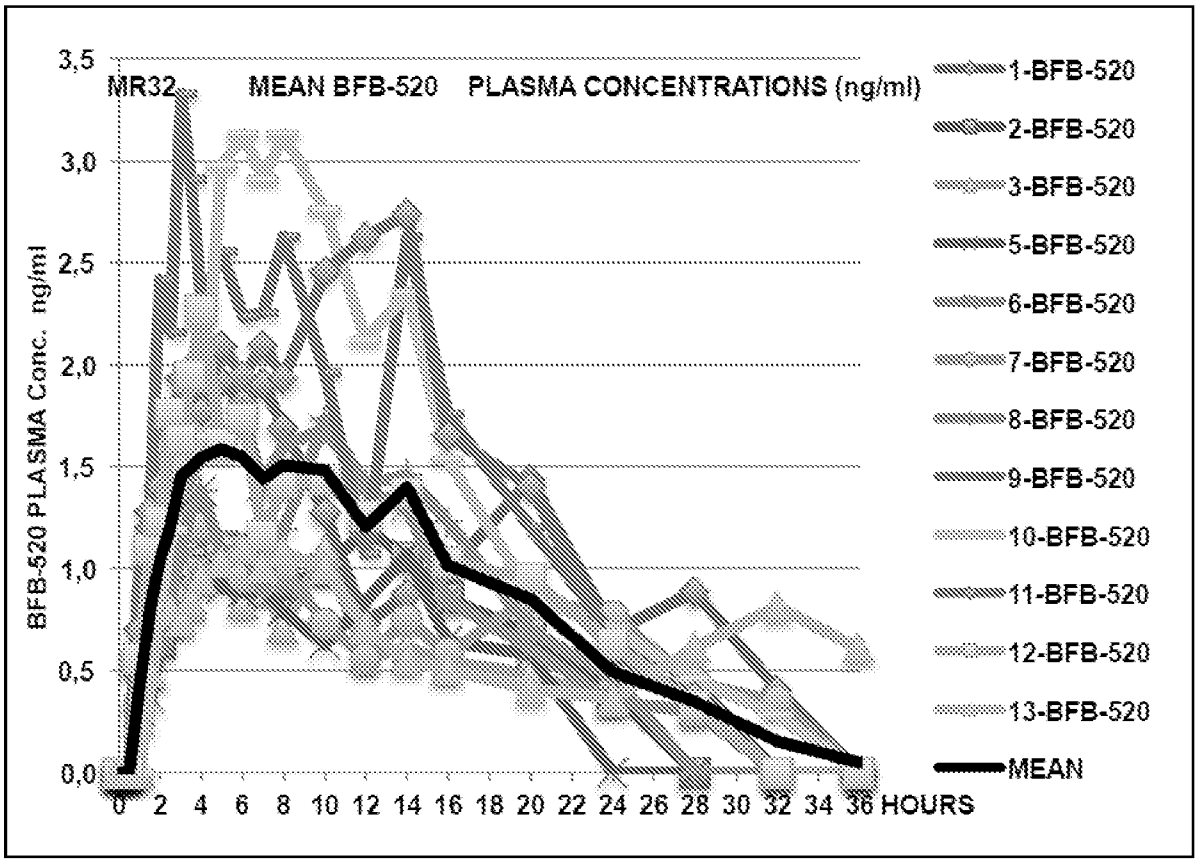

MR32 MEAN BFB-520 PLASMA CONCENTRATIONS (ng/ml)
BFB-520 PLASMA Conc. ng/ml
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 HOURS
1-BFB-520
2-BFB-520
3-BFB-520
5-BFB-520
6-BFB-520
7-BFB-520
8-BFB-520
9-BFB-520
10-BFB-520
11-BFB-520
12-BFB-520
13-BFB-520
MEAN

FIGURE 10

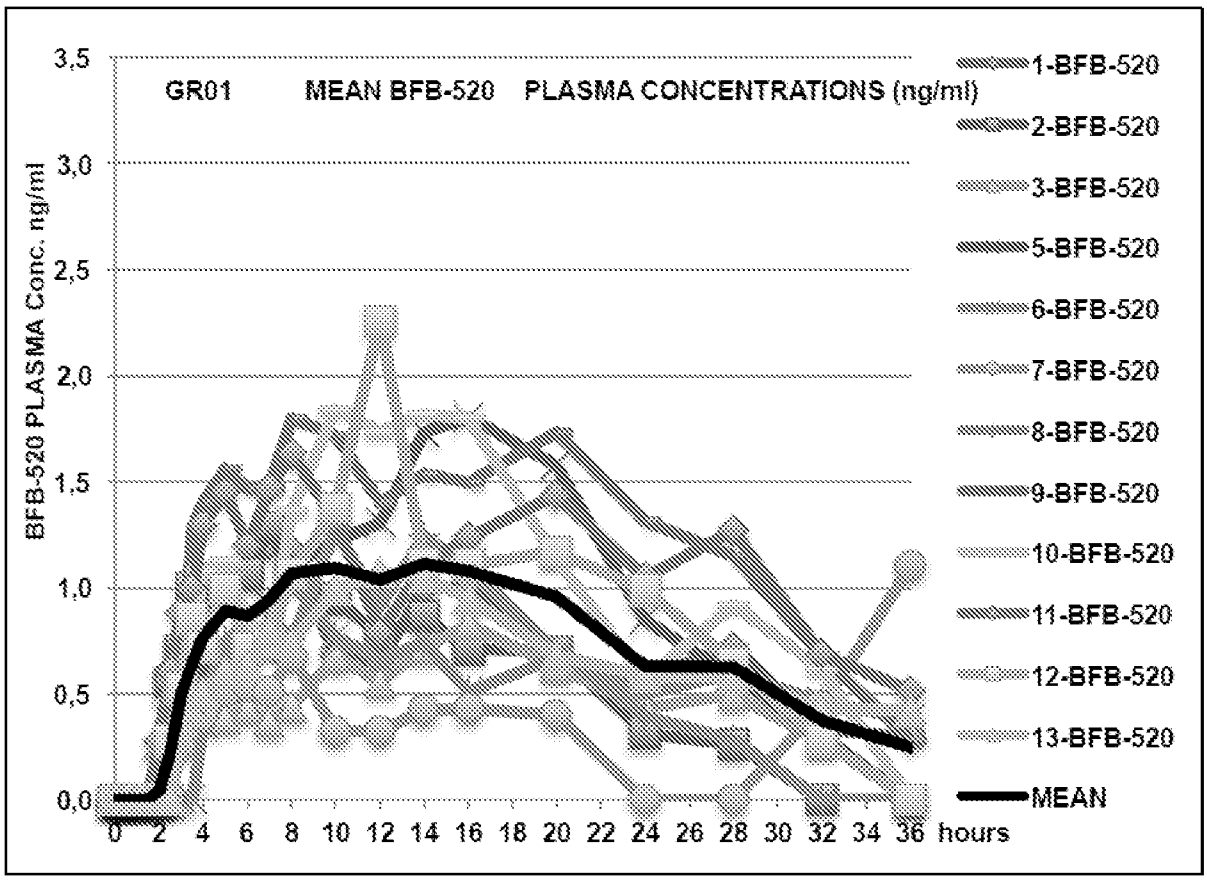

GR01 MEAN BFB-520 PLASMA CONCENTRATIONS (ng/ml)
BFB-520 PLASMA Conc. ng/ml
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 hours
1-BFB-520
2-BFB-520
3-BFB-520
5-BFB-520
6-BFB-520
7-BFB-520
8-BFB-520
9-BFB-520
10-BFB-520
11-BFB-520
12-BFB-520
13-BFB-520
MEAN

FIGURE 11

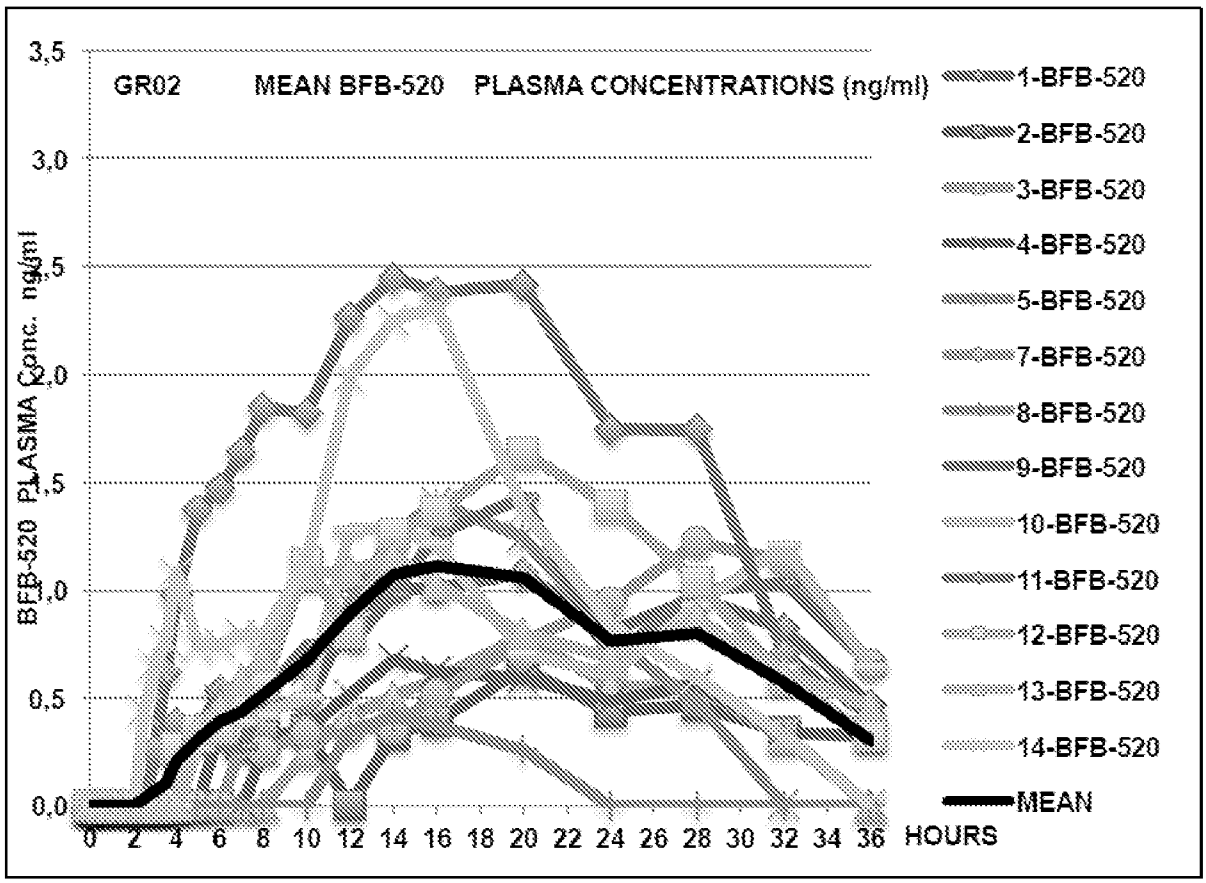

GR02 MEAN BFB-520 PLASMA CONCENTRATIONS (ng/ml)
BFB-520 PLASMA Conc. ng/ml
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 HOURS
1-BFB-520
2-BFB-520
3-BFB-520
4-BFB-520
5-BFB-520
7-BFB-520
8-BFB-520
9-BFB-520
10-BFB-520
11-BFB-520
12-BFB-520
13-BFB-520
14-BFB-520
MEAN

FIGURE 12

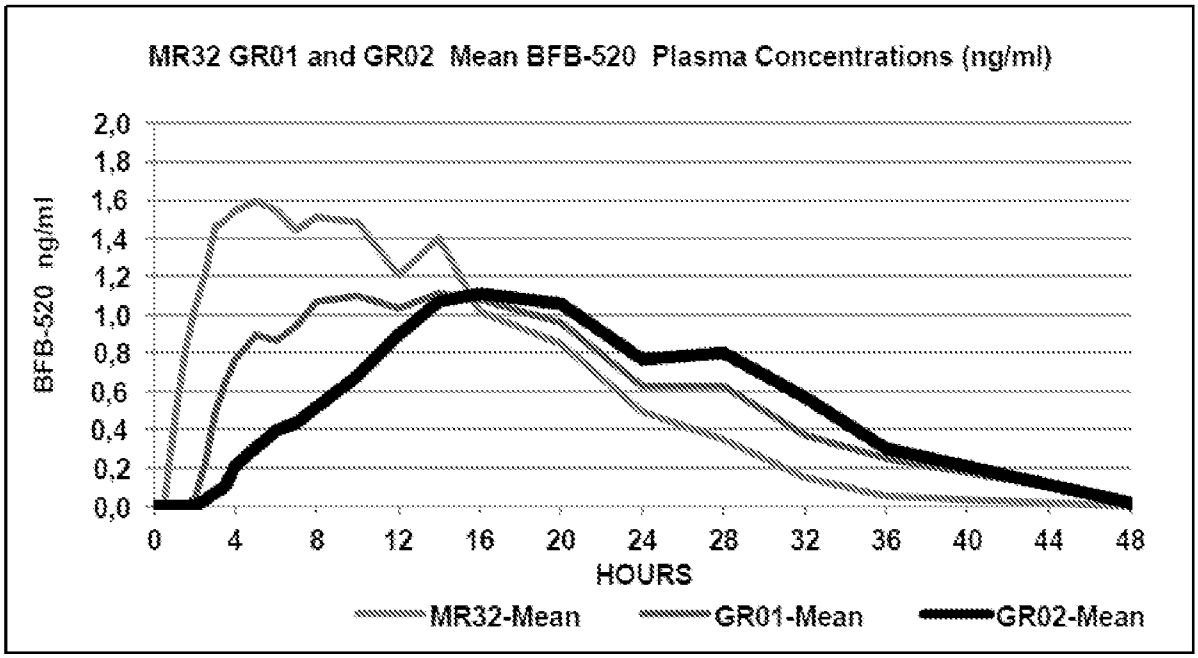

MR32 GR01 and GR02 Mean BFB-520 Plasma Concentrations (ng/ml)
BFB-520 ng/ml
2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
0
4
8
12
16
20
24
28
32
36
40
44
48
HOURS
MR32-Mean
GR01-Mean
GR02-Mean

FIGURE 13

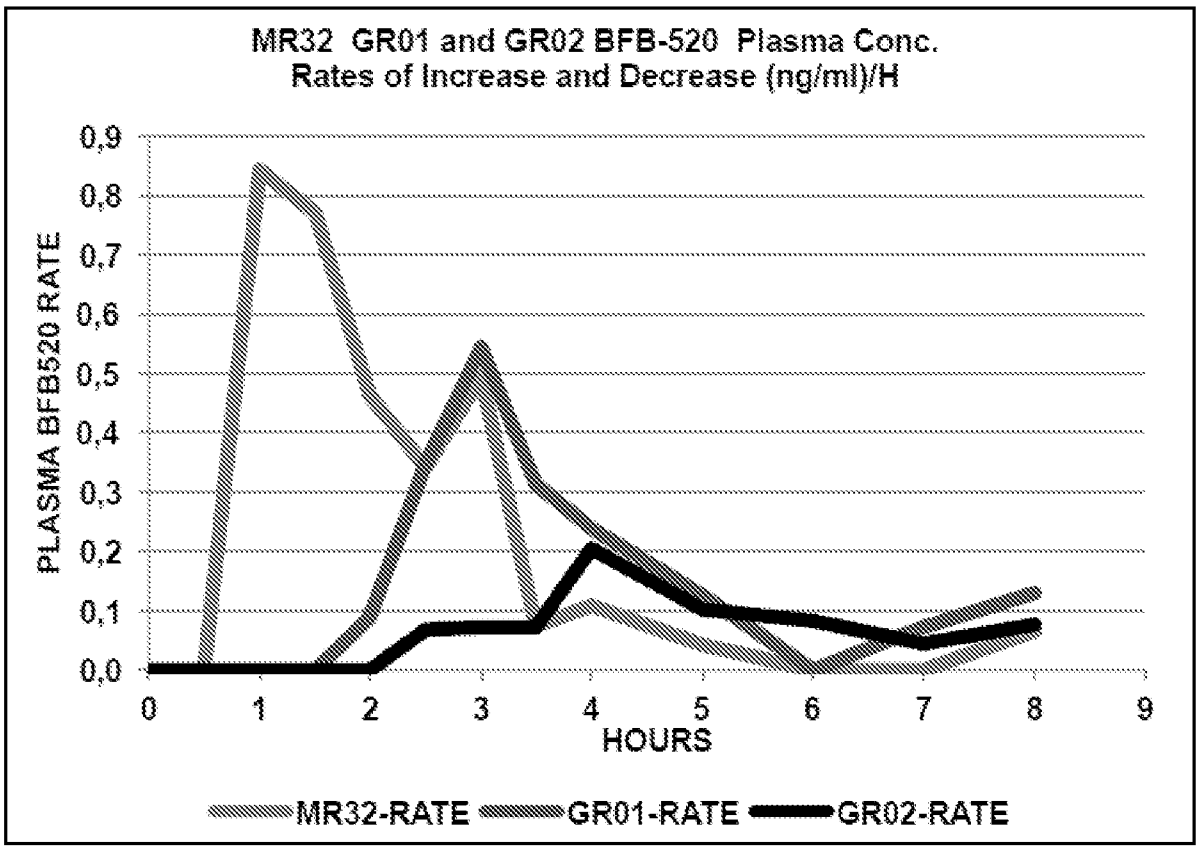
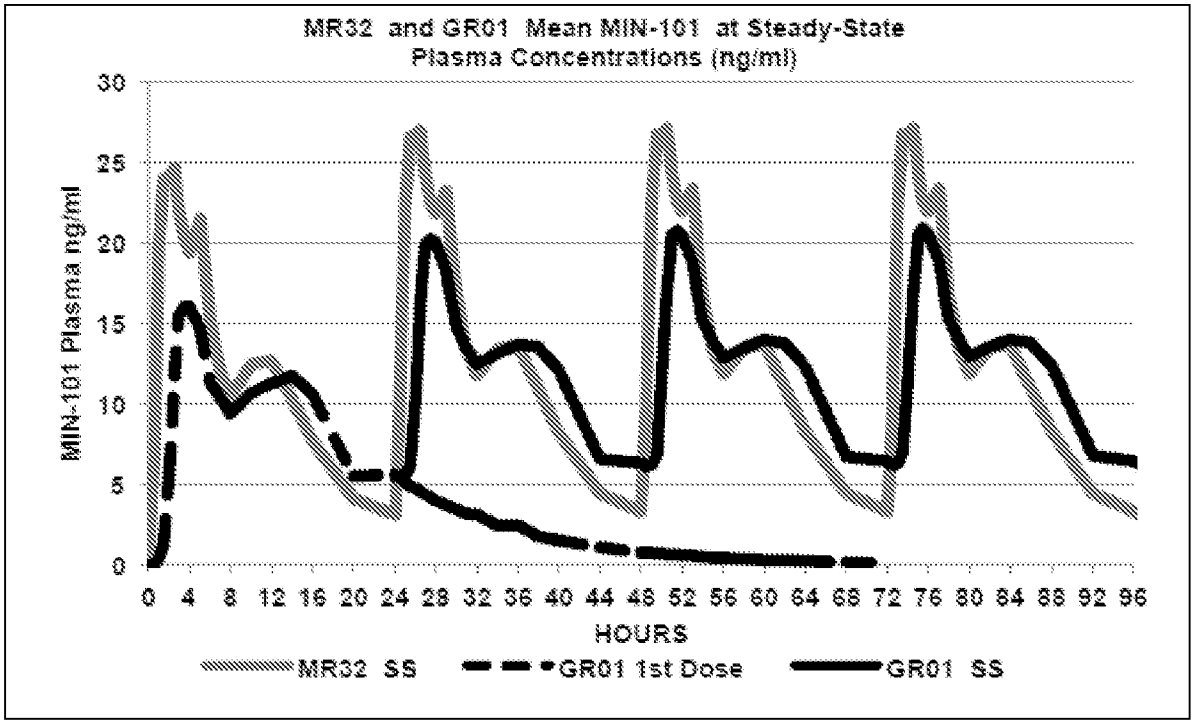

MR32 GR01 and GR02 BFB-520 Plasma Conc.
Rates of Increase and Decrease (ng/ml)/H
PLASMA BFB520 RATE
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0,0
0
1
2
3
4
5
6
7
8
9
HOURS
MR32-RATE
GR01-RATE
GR02-RATE

FIGURE 14


MR32 and GR01 Mean MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
30
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
HOURS
MR32 SS
GR01 1st Dose
GR01 SS

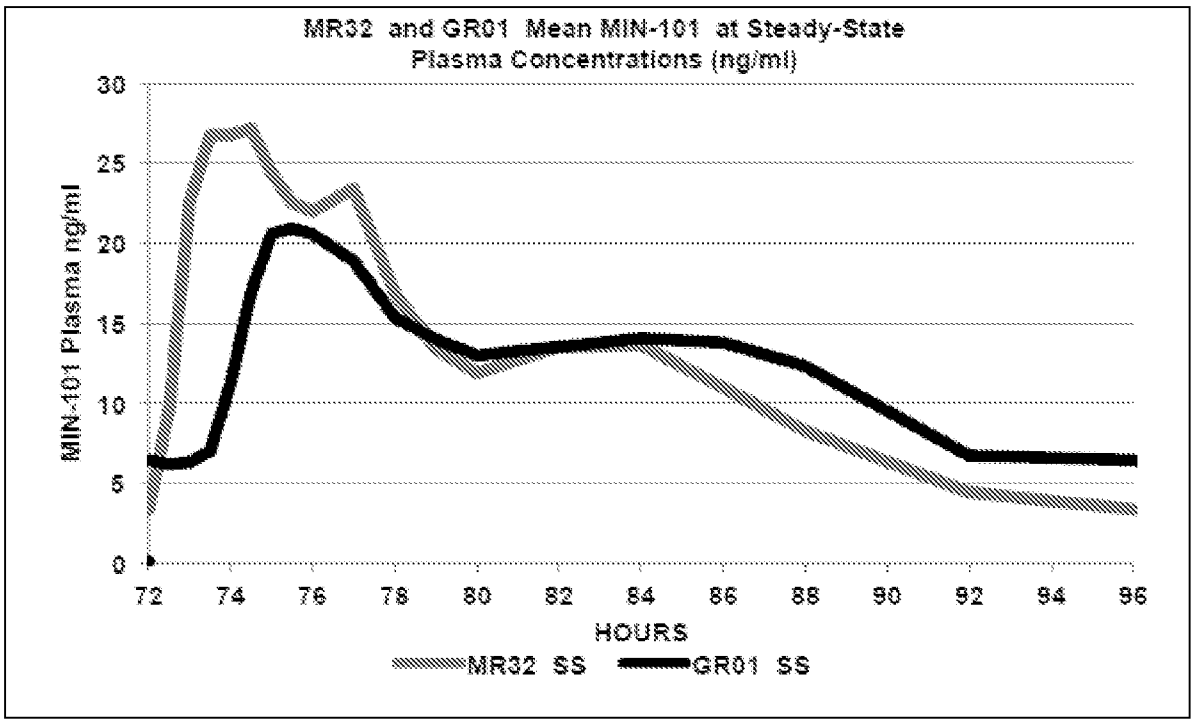
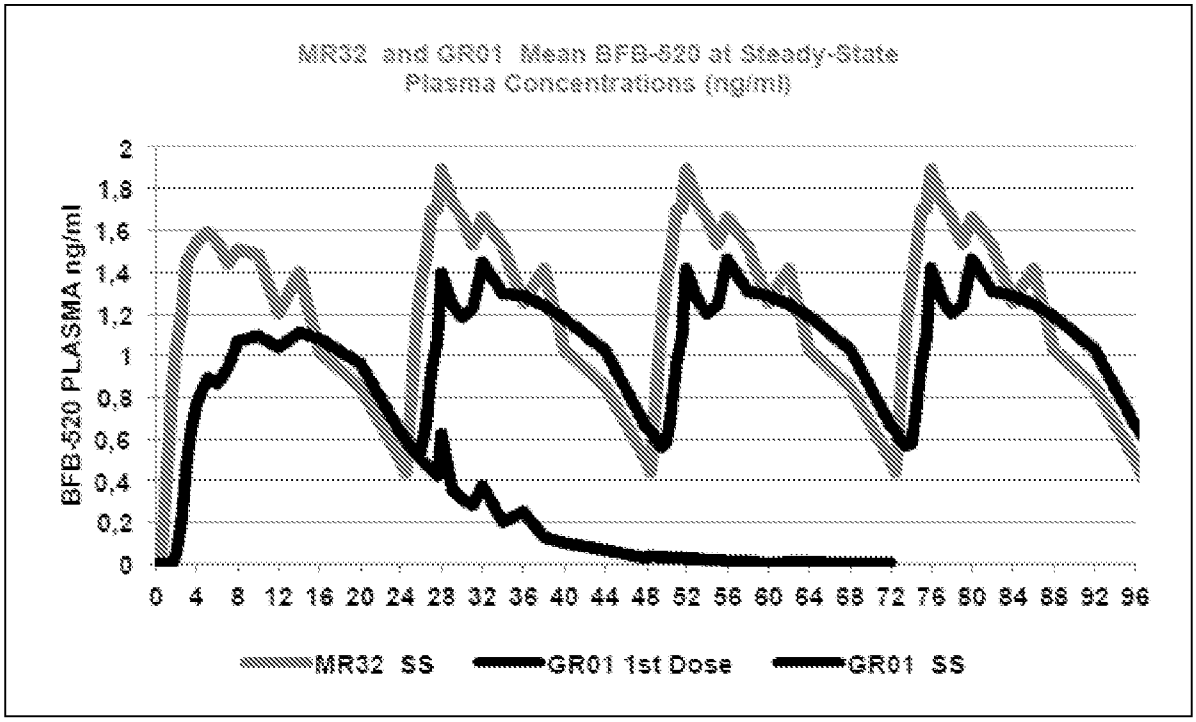

MR32 and GR01 Mean MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
30
25
20
15
10
5
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
MR32 SS
GR01 SS

FIGURE 15


MR32 and GR01 Mean BFB-520 at Steady-State
Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
MR32 SS
GR01 1st Dose
GR01 SS

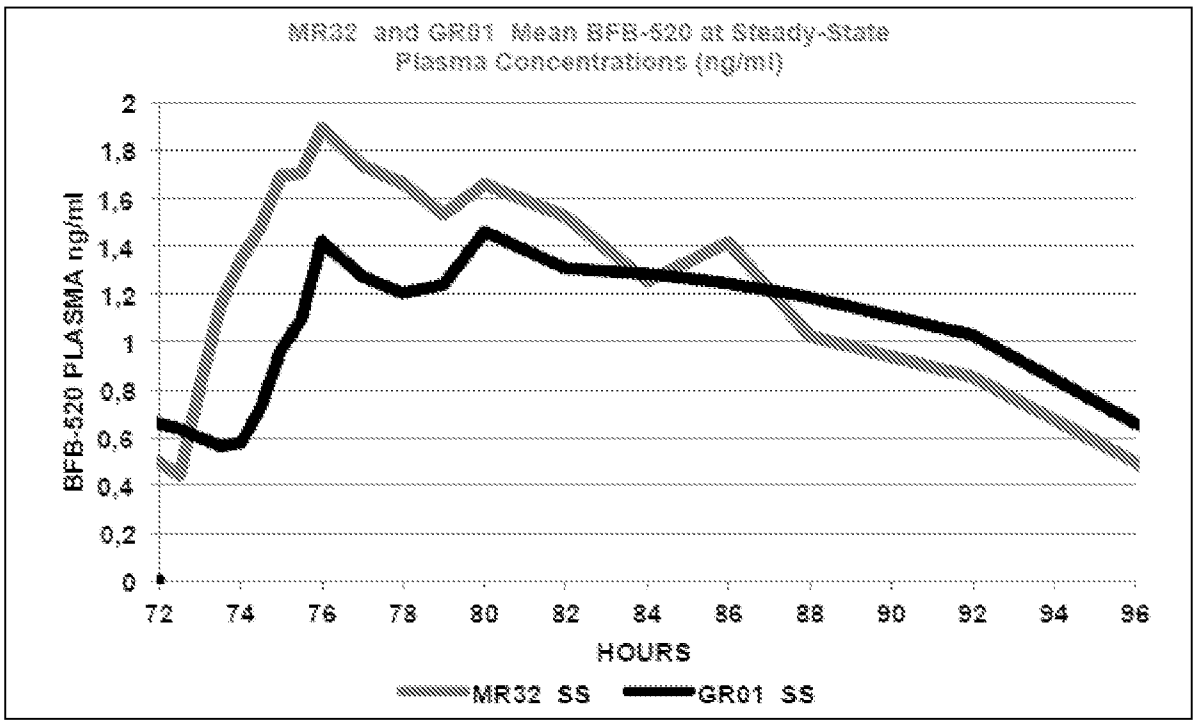
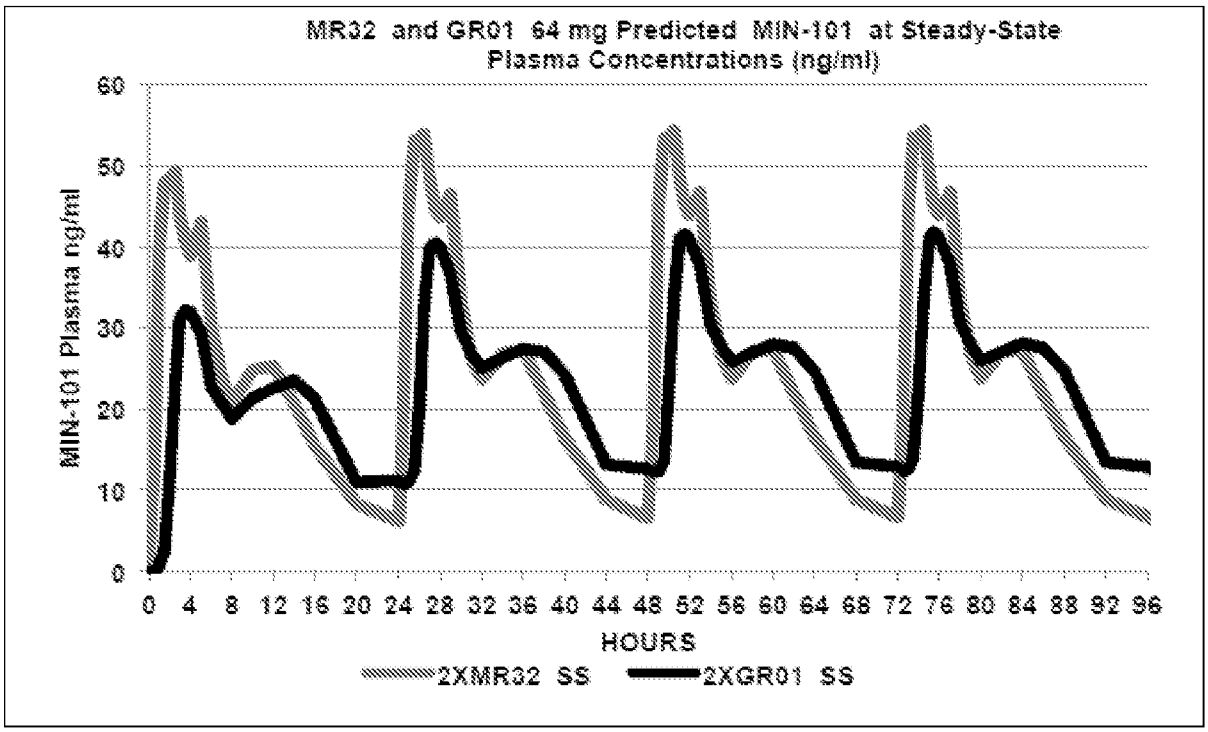

MR32 and GR01 Mean BFB-520 at Steady-State
Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
MR32 SS
GR01 SS

FIGURE 16


MR32 and GR01 64 mg Predicted MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
60
50
40
30
20
10
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
HOURS
2XMR32 SS
2XGR01 SS

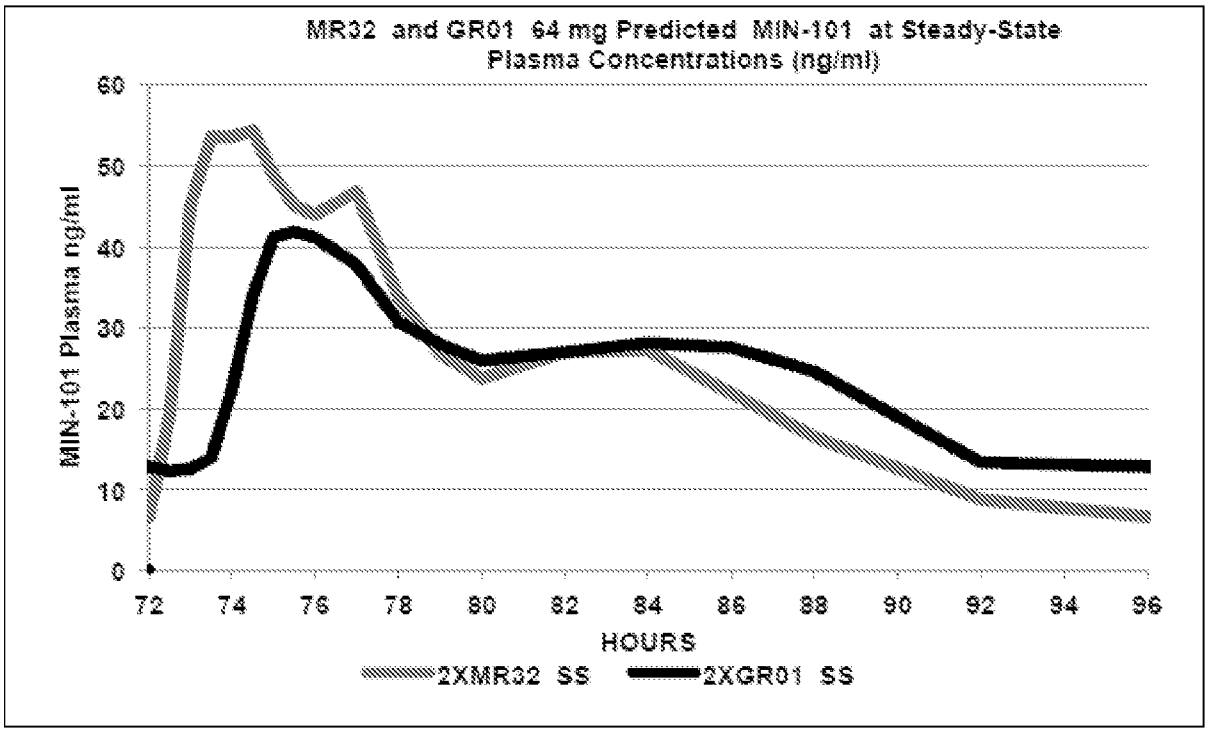

MR32 and GR01 64 mg Predicted MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
60
50
40
30
20
10
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
2XMR32 SS
2XGR01 SS

FIGURE 17

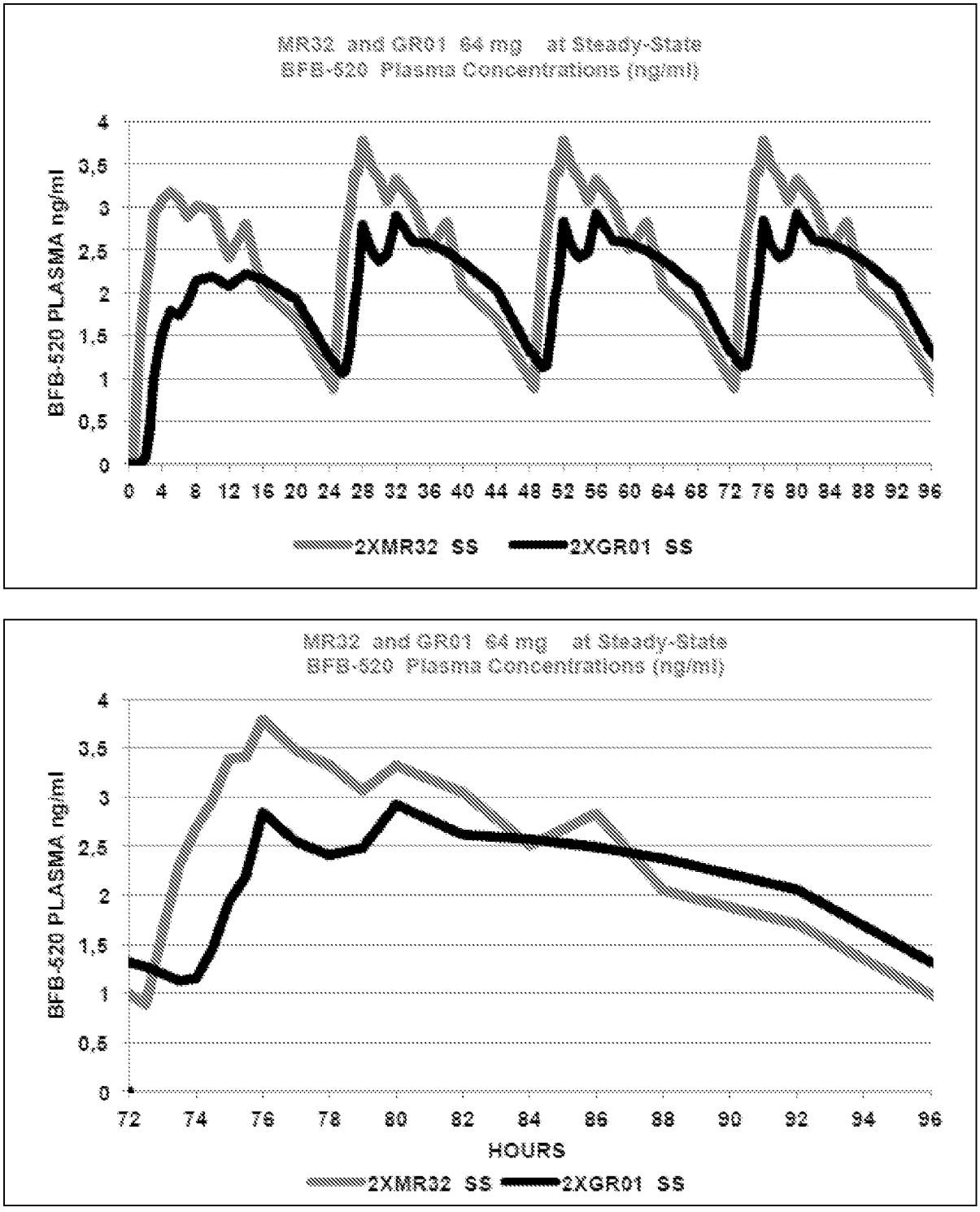

MR32 and GR01 64 mg at Steady-State
BFB-520 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
0
0,5
1
1,5
2
2,5
3
3,5
4
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
2XMR32 SS
2XGR01 SS
MR32 and GR01 64 mg at Steady-State
BFB-520 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
0
0,5
1
1,5
2
2,5
3
3,5
4
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
2XMR32 SS
2XGR01 SS

FIGURE 18

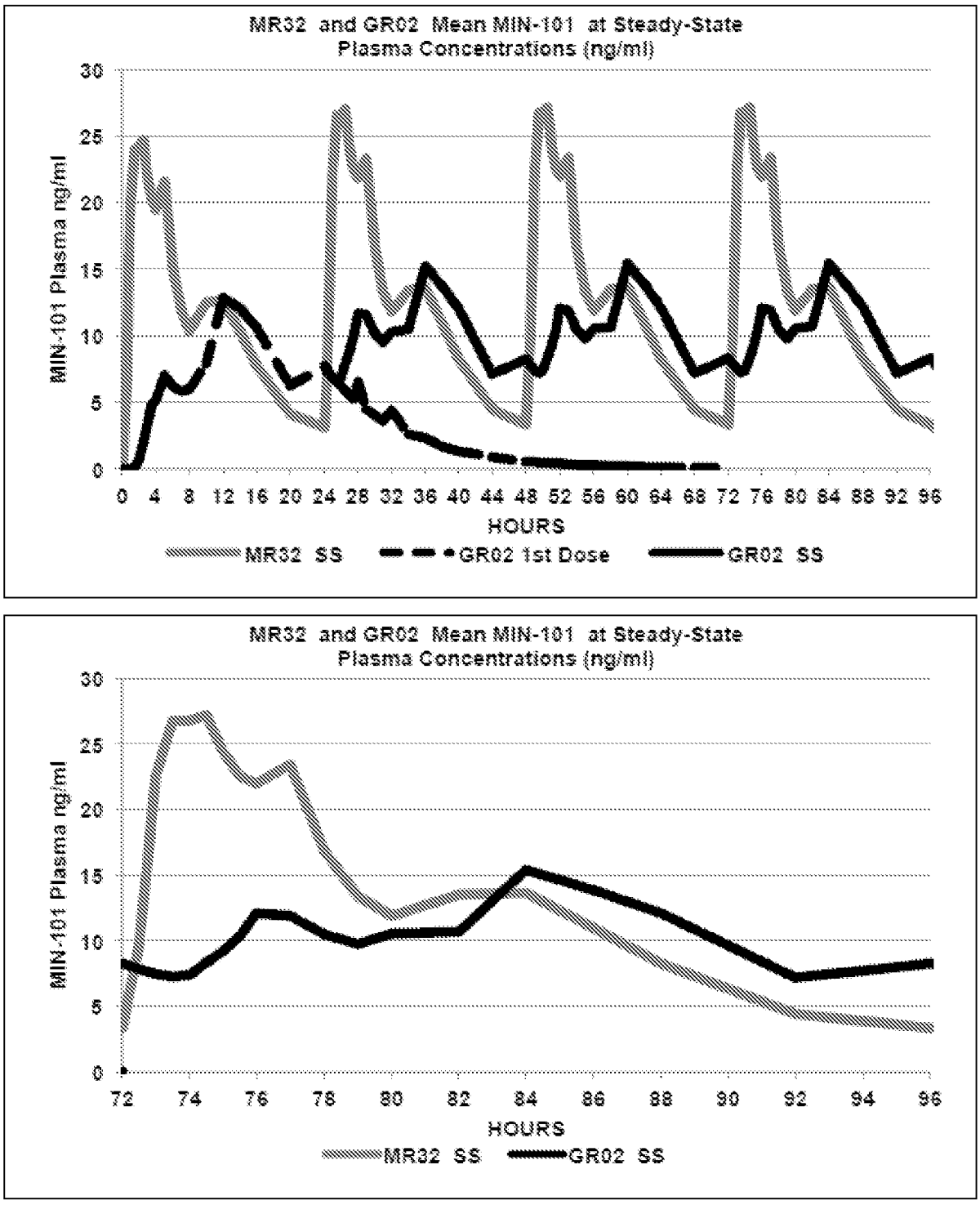
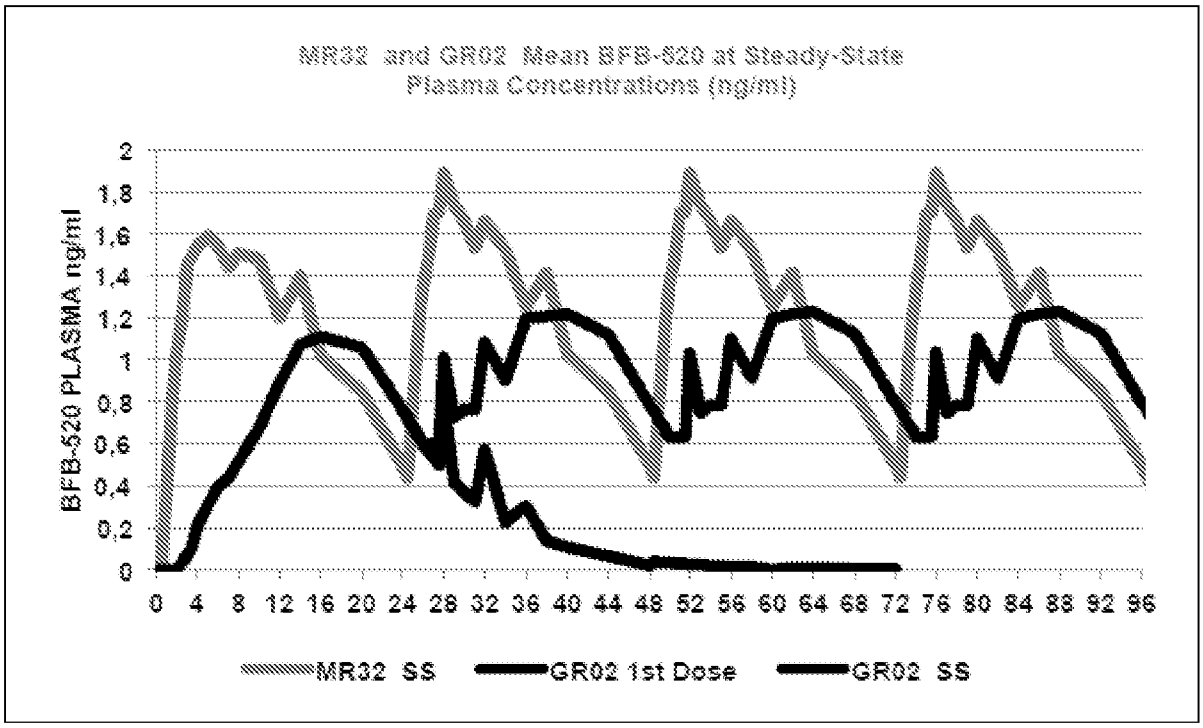

MR32 and GR02 Mean MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
30
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
HOURS
MR32 SS
GR02 1st Dose
GR02 SS
MR32 and GR02 Mean MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
30
25
20
15
10
5
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
MR32 SS
GR02 SS

FIGURE 19


MR32 and GR02 Mean BFB-520 at Steady-State
Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
MR32 SS
GR02 1st Dose
GR02 SS

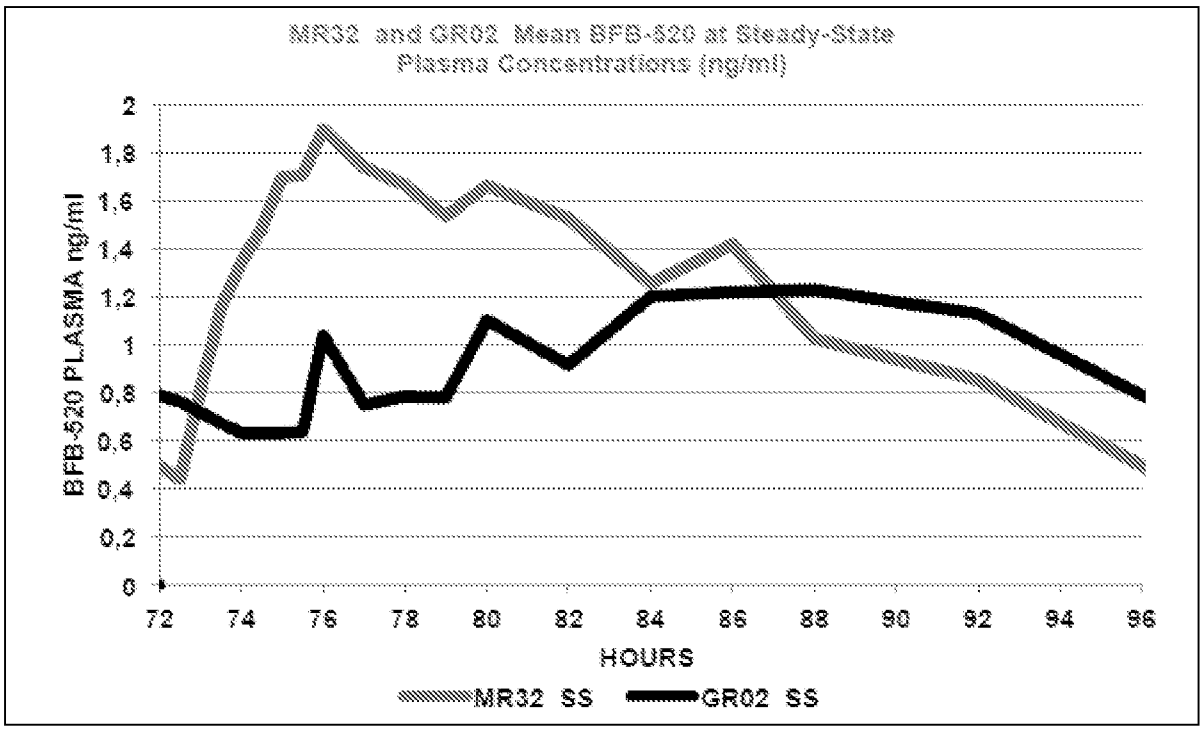
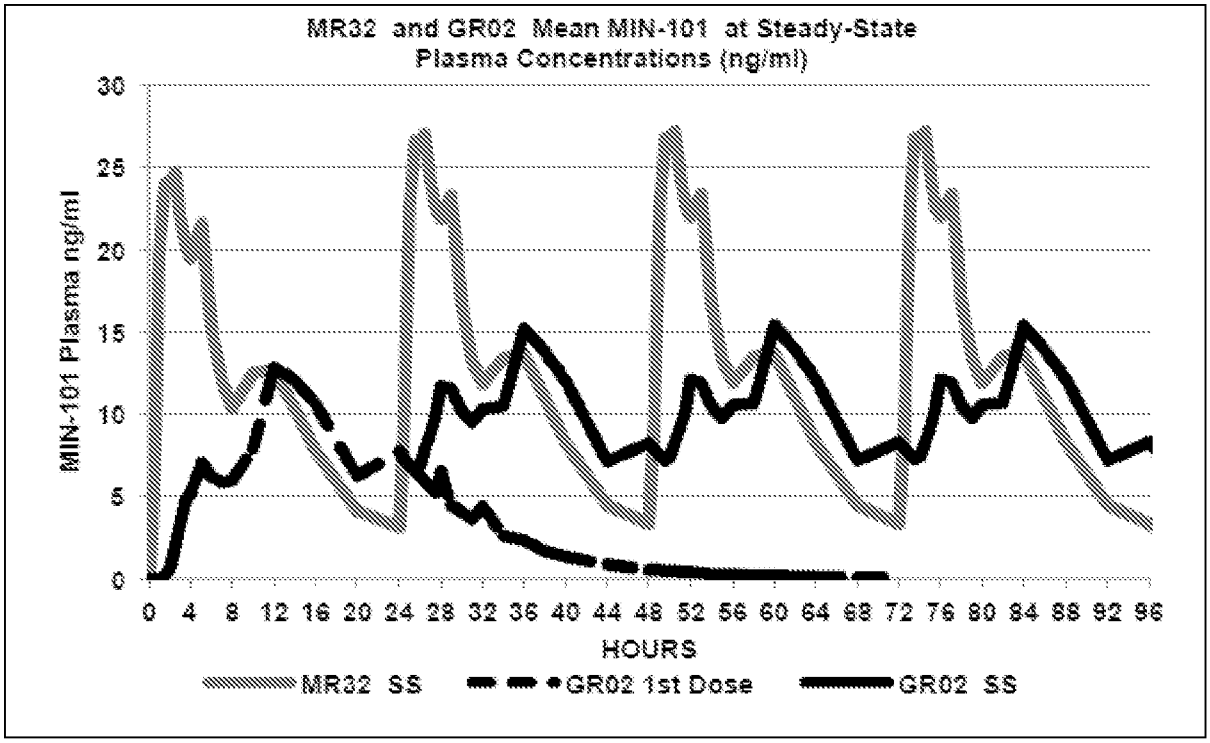

MR32 and GR02 Mean BFB-520 at Steady-State
Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
MR32 SS
GR02 SS

FIGURE 20


MR32 and GR02 Mean MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
30
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
HOURS
MR32 SS
GR02 1st Dose
GR02 SS

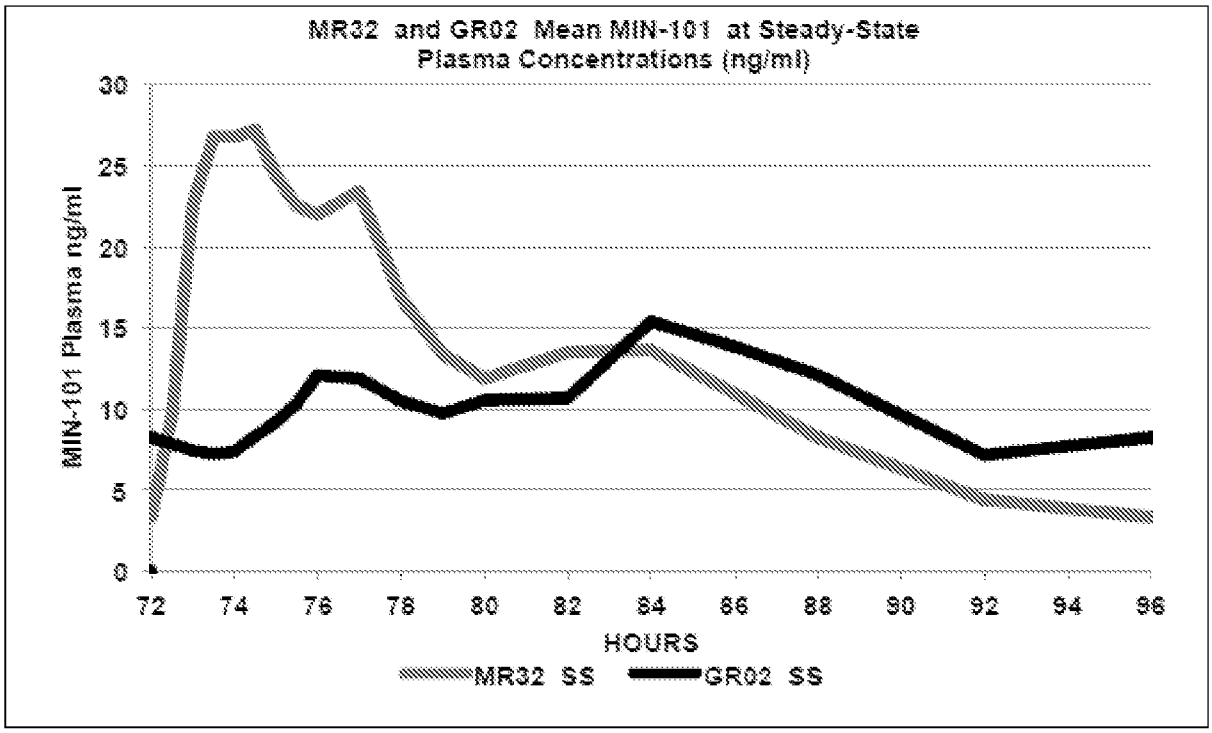
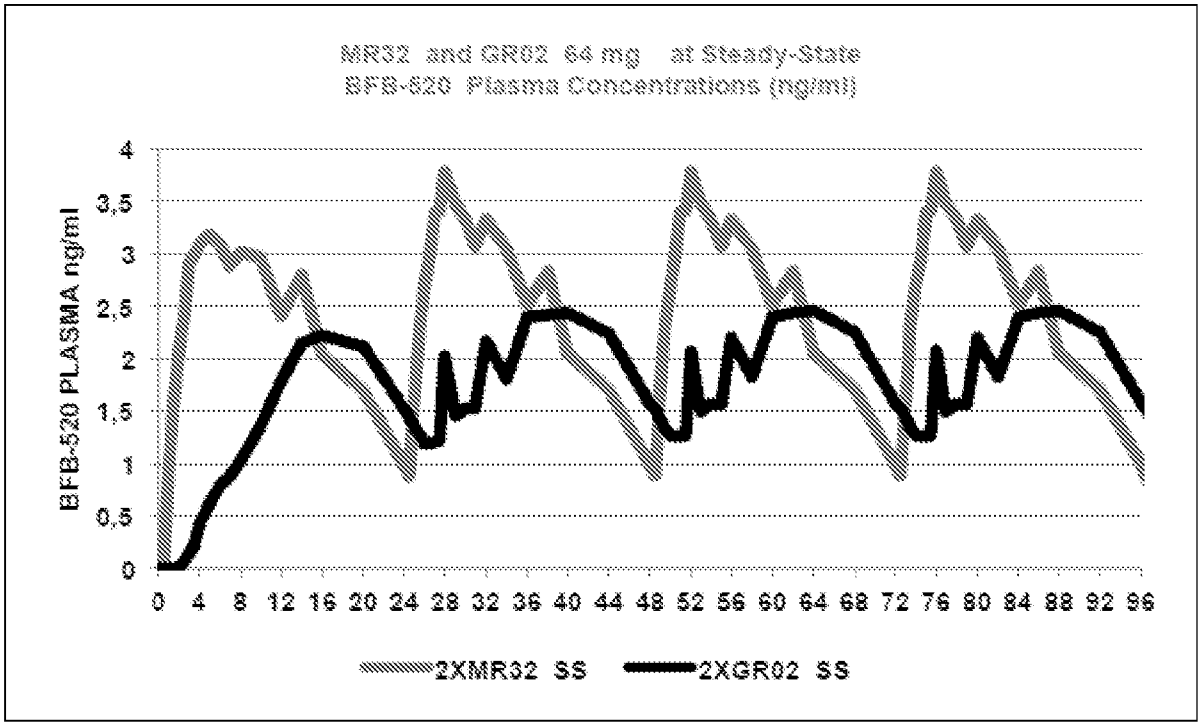

MR32 and GR02 Mean MIN-101 at Steady-State
Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
30
25
20
15
10
5
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
MR32 SS
GR02 SS

FIGURE 21


MR32 and GR02 64 mg at Steady-State
BFB-620 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
4
3,5
3
2,5
2
1,5
1
0,5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
2XMR32 SS
2XGR02 SS

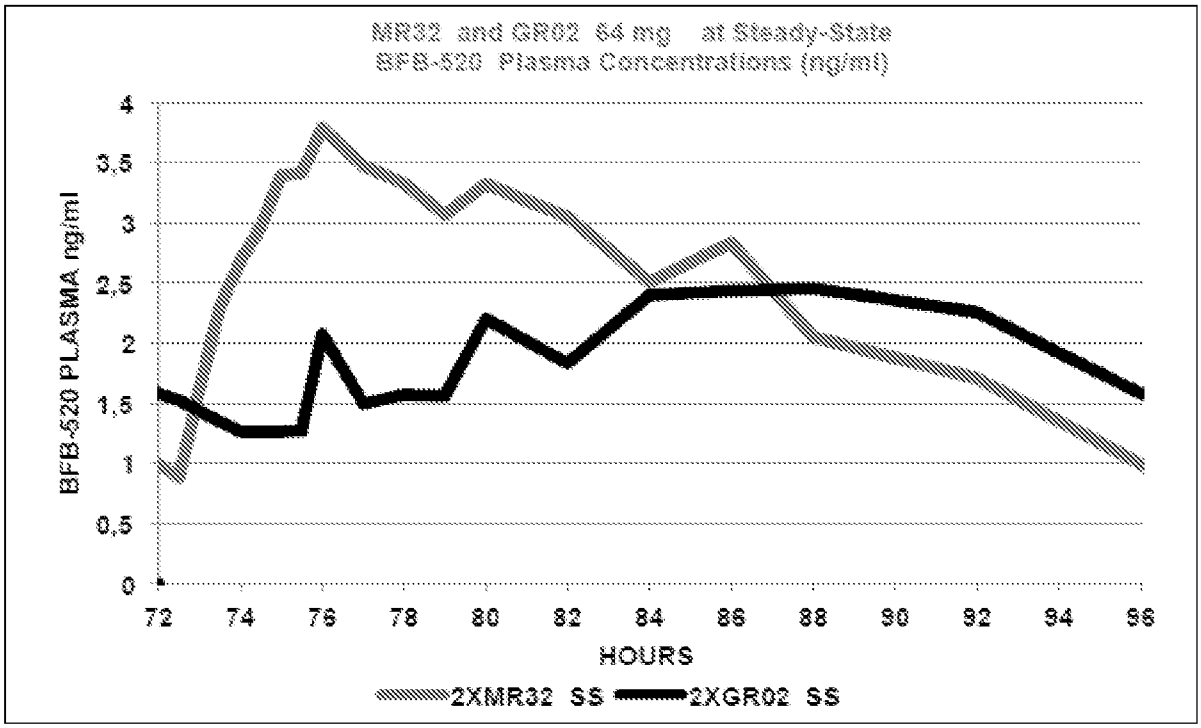

MR32 and GR02 64 mg at Steady-State
BFB-520 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
4
3,5
3
2,5
2
1,5
1
0,5
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
2XMR32 SS
2XGR02 SS

FIGURE 22

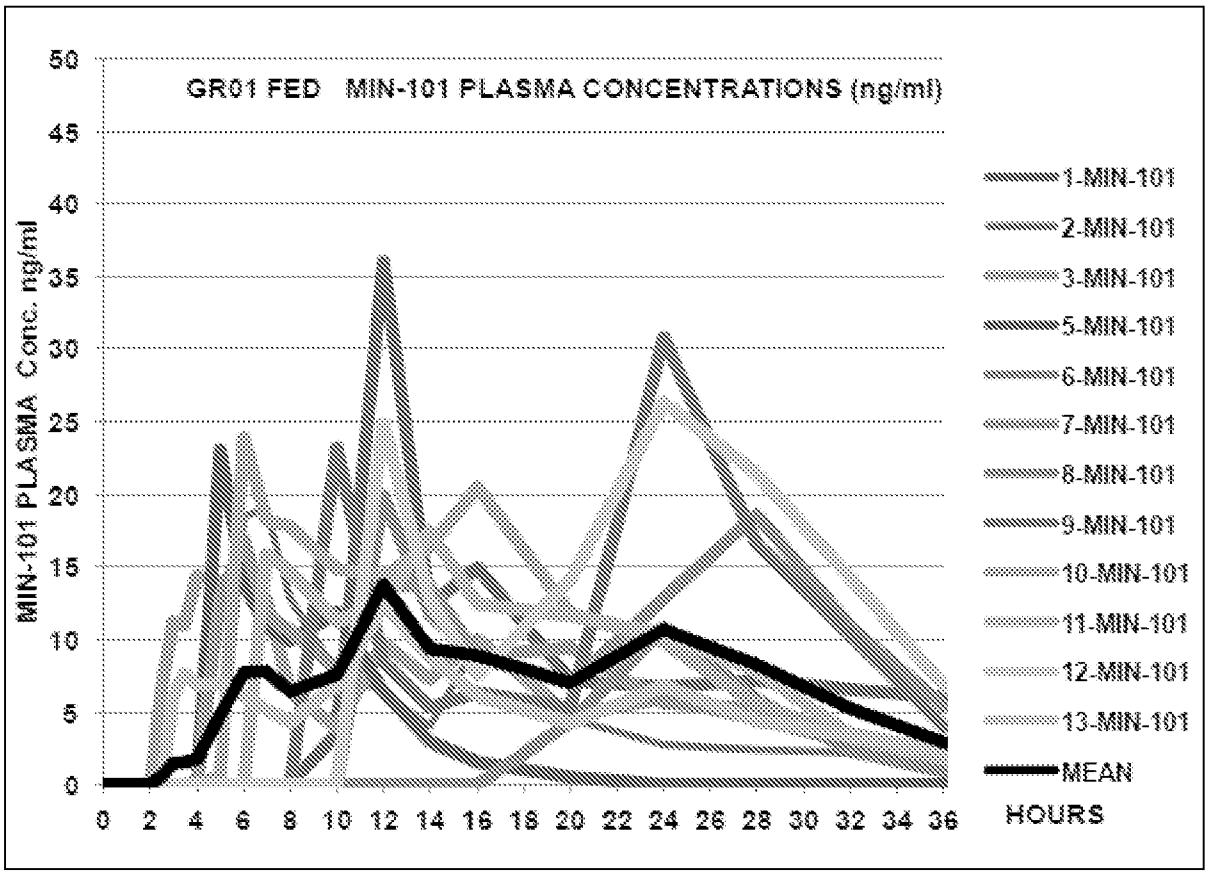

GR01 FED MIN-101 PLASMA CONCENTRATIONS (ng/ml)
MIN-101 PLASMA Conc. ng/ml
50
45
40
35
30
25
20
15
10
5
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
HOURS
1-MIN-101
2-MIN-101
3-MIN-101
5-MIN-101
6-MIN-101
7-MIN-101
8-MIN-101
9-MIN-101
10-MIN-101
11-MIN-101
12-MIN-101
13-MIN-101
MEAN

FIGURE 23

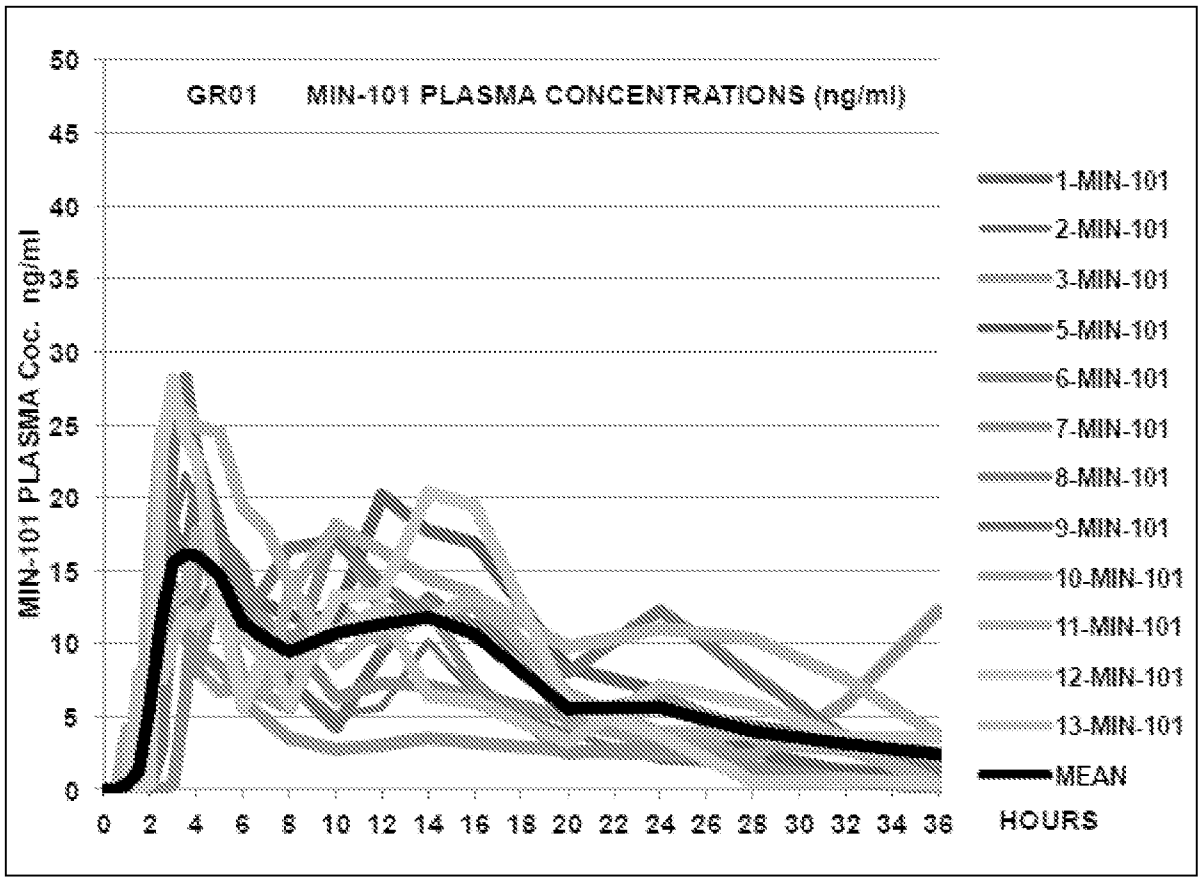

GR01 MIN-101 PLASMA CONCENTRATIONS (ng/ml)
MIN-101 PLASMA Conc. ng/ml
0
5
10
15
20
25
30
35
40
45
50
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
HOURS
1-MIN-101
2-MIN-101
3-MIN-101
5-MIN-101
6-MIN-101
7-MIN-101
8-MIN-101
9-MIN-101
10-MIN-101
11-MIN-101
12-MIN-101
13-MIN-101
MEAN

FIGURE 24

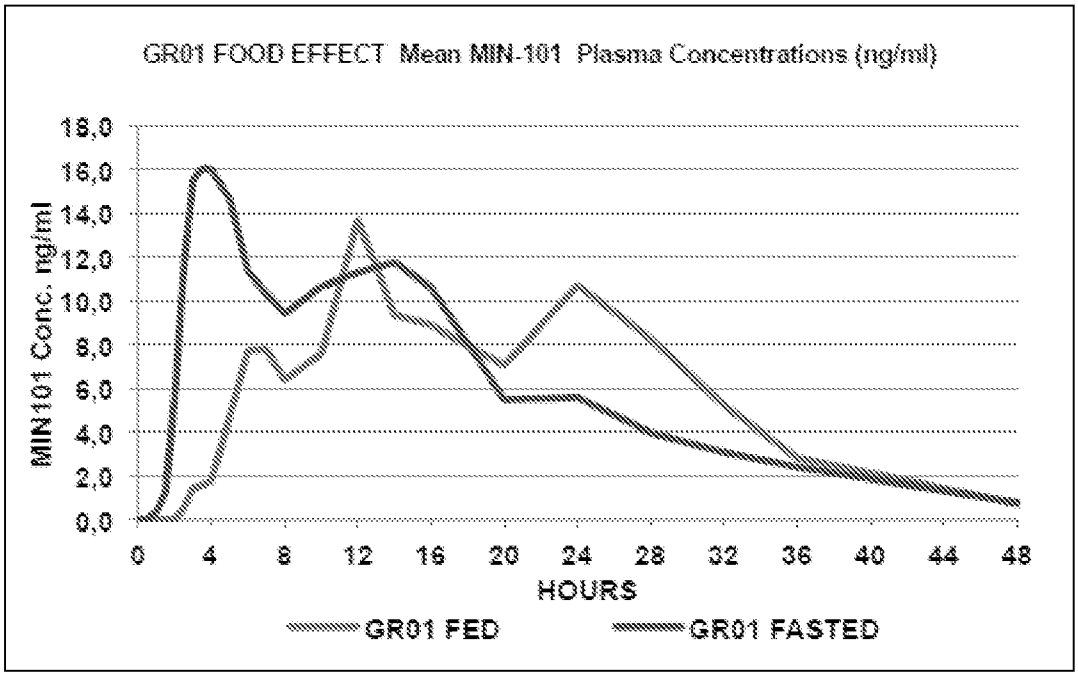

GR01 FOOD EFFECT Mean MIN-101 Plasma Concentrations (ng/ml)
MIN101 Conc. ng/ml
18,0
16,0
14,0
12,0
10,0
8,0
6,0
4,0
2,0
0,0
0
4
8
12
16
20
24
28
32
36
40
44
48
HOURS
GR01 FED
GR01 FASTED

FIGURE 25

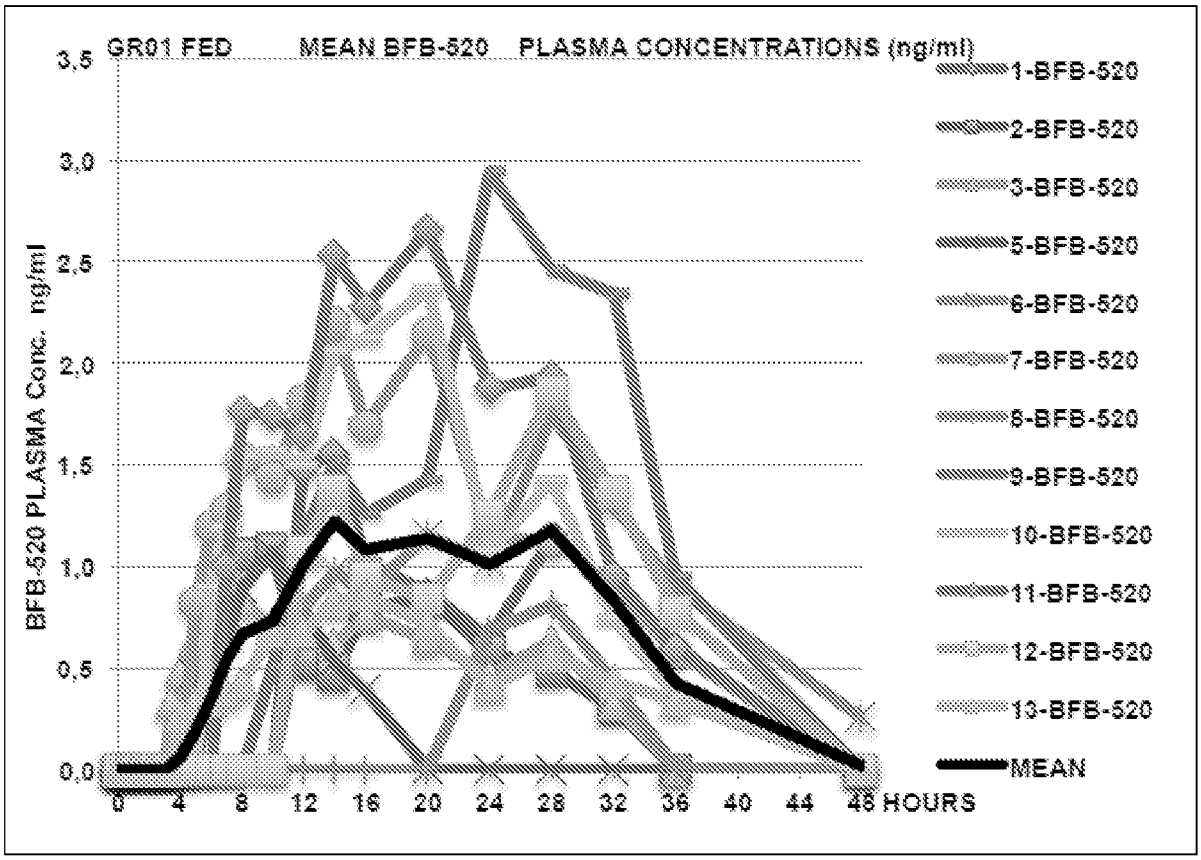

GR01 FED MEAN BFB-520 PLASMA CONCENTRATIONS (ng/ml)
BFB-520 PLASMA Conc. ng/ml
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
0 4 8 12 16 20 24 28 32 36 40 44 48 HOURS
1-BFB-520
2-BFB-520
3-BFB-520
5-BFB-520
6-BFB-520
7-BFB-520
8-BFB-520
9-BFB-520
10-BFB-520
11-BFB-520
12-BFB-520
13-BFB-520
MEAN

FIGURE 26

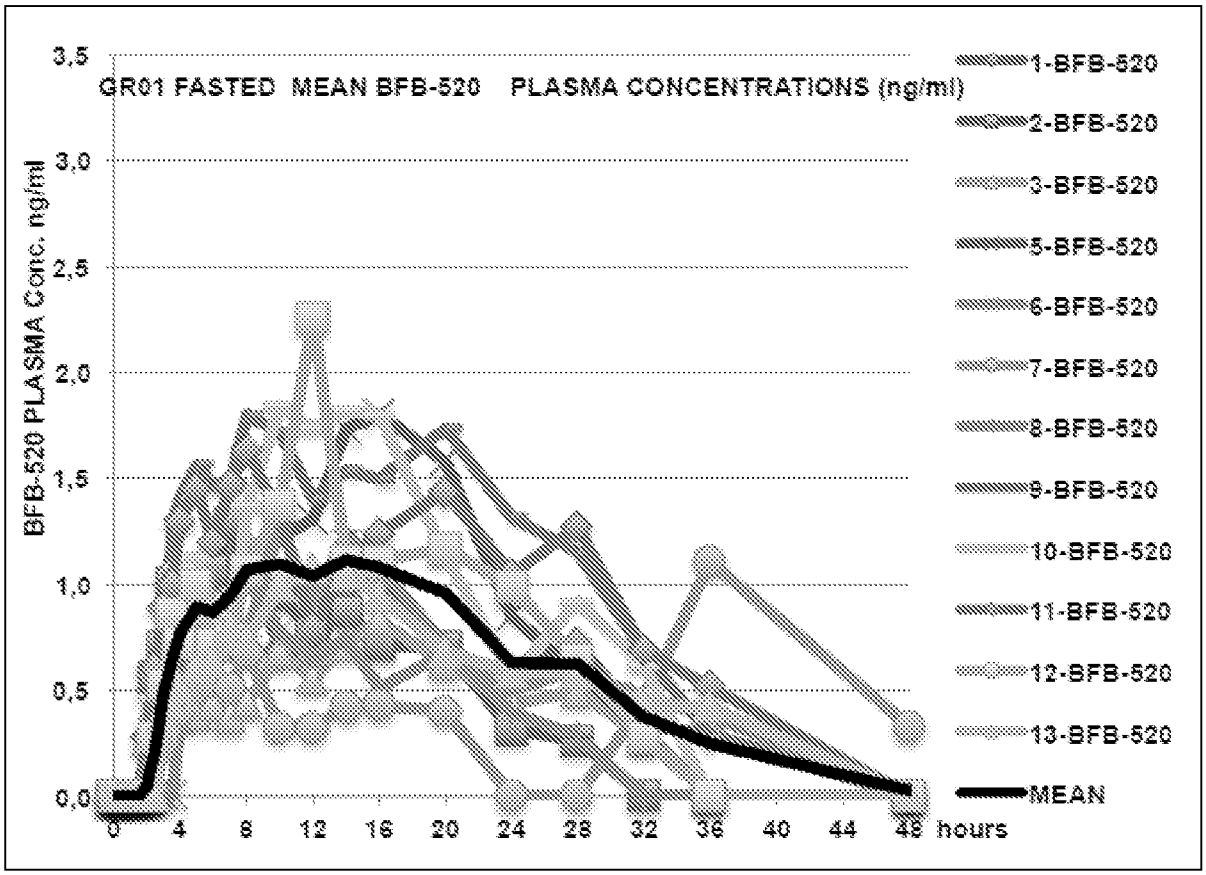

GR01 FASTED MEAN BFB-520 PLASMA CONCENTRATIONS (ng/ml)
BFB-520 PLASMA Conc, ng/ml
3,5
3,0
2,5
2,0
1,5
1,0
0,5
0,0
0
4
8
12
16
20
24
28
32
36
40
44
48
hours
1-BFB-520
2-BFB-520
3-BFB-520
5-BFB-520
6-BFB-520
7-BFB-520
8-BFB-520
9-BFB-520
10-BFB-520
11-BFB-520
12-BFB-520
13-BFB-520
MEAN

FIGURE 27

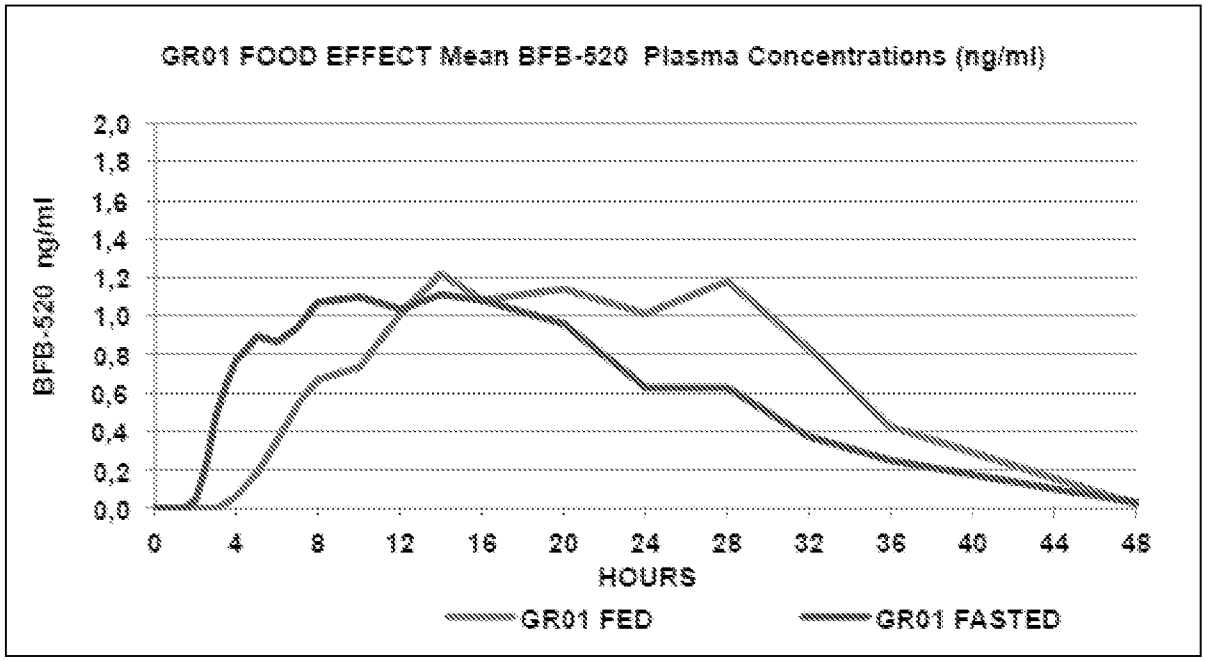
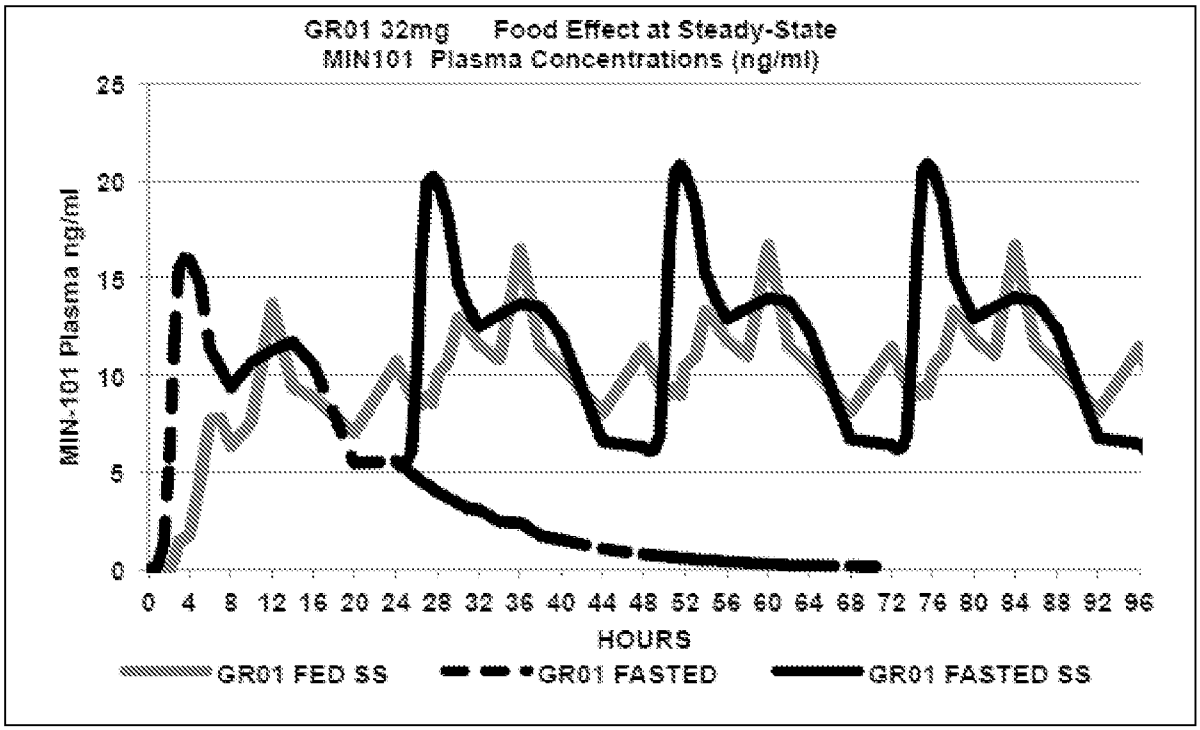

GR01 FOOD EFFECT Mean BFB-520 Plasma Concentrations (ng/ml)
BFB-520 ng/ml
2,0
1,8
1,6
1,4
1,2
1,0
0,8
0,6
0,4
0,2
0,0
0
4
8
12
16
20
24
28
32
36
40
44
48
HOURS
GR01 FED
GR01 FASTED

FIGURE 28


GR01 32mg Food Effect at Steady-State
MIN101 Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
HOURS
GR01 FED SS
GR01 FASTED
GR01 FASTED SS

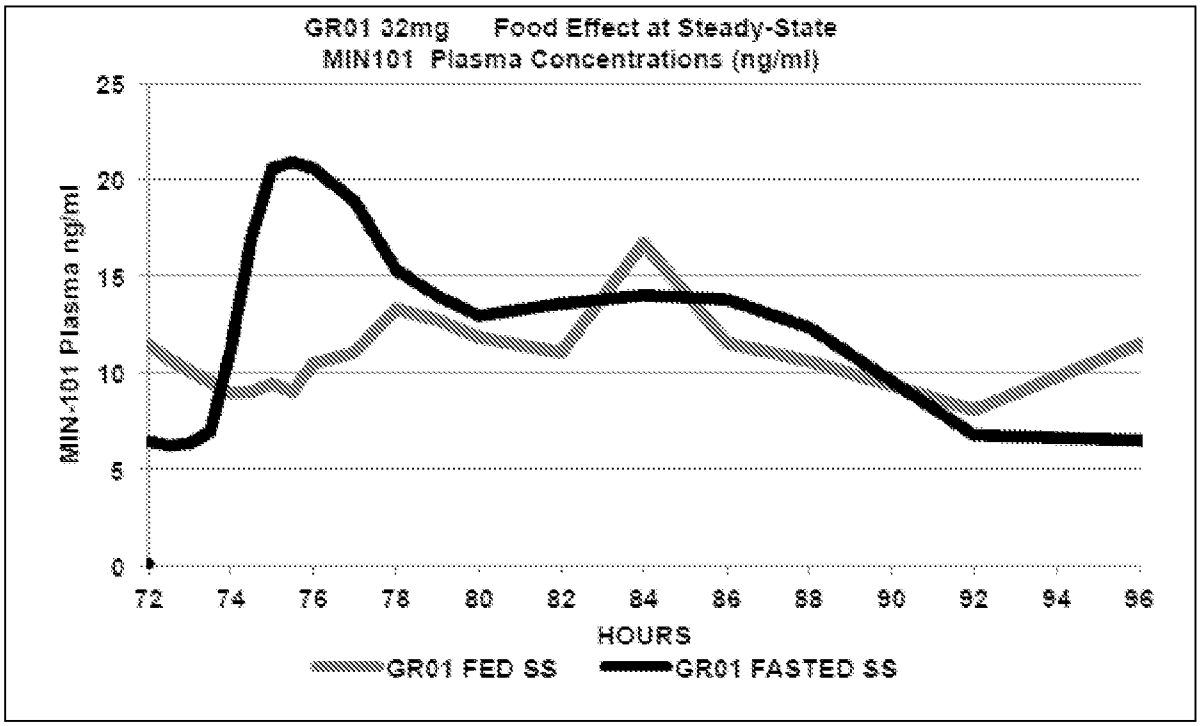
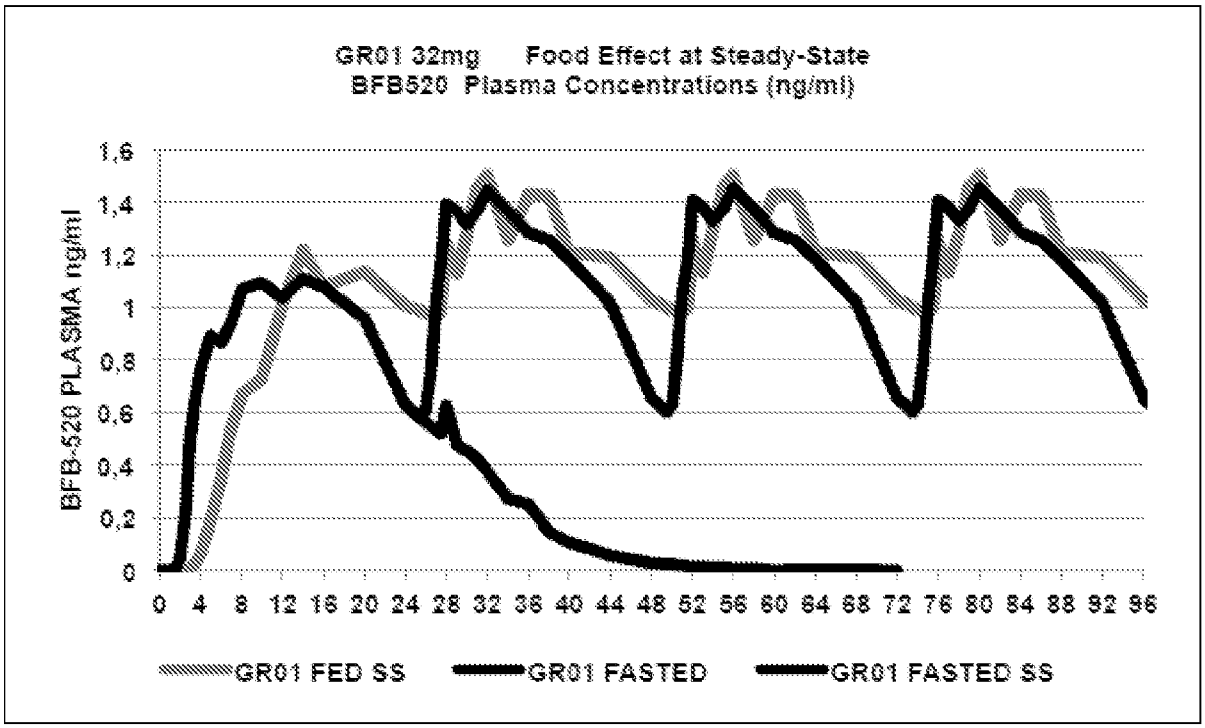

GR01 32mg Food Effect at Steady-State
MIN101 Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
25
20
15
10
5
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
GR01 FED SS
GR01 FASTED SS

FIGURE 29


GR01 32mg Food Effect at Steady-State
BFB520 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
GR01 FED SS
GR01 FASTED
GR01 FASTED SS

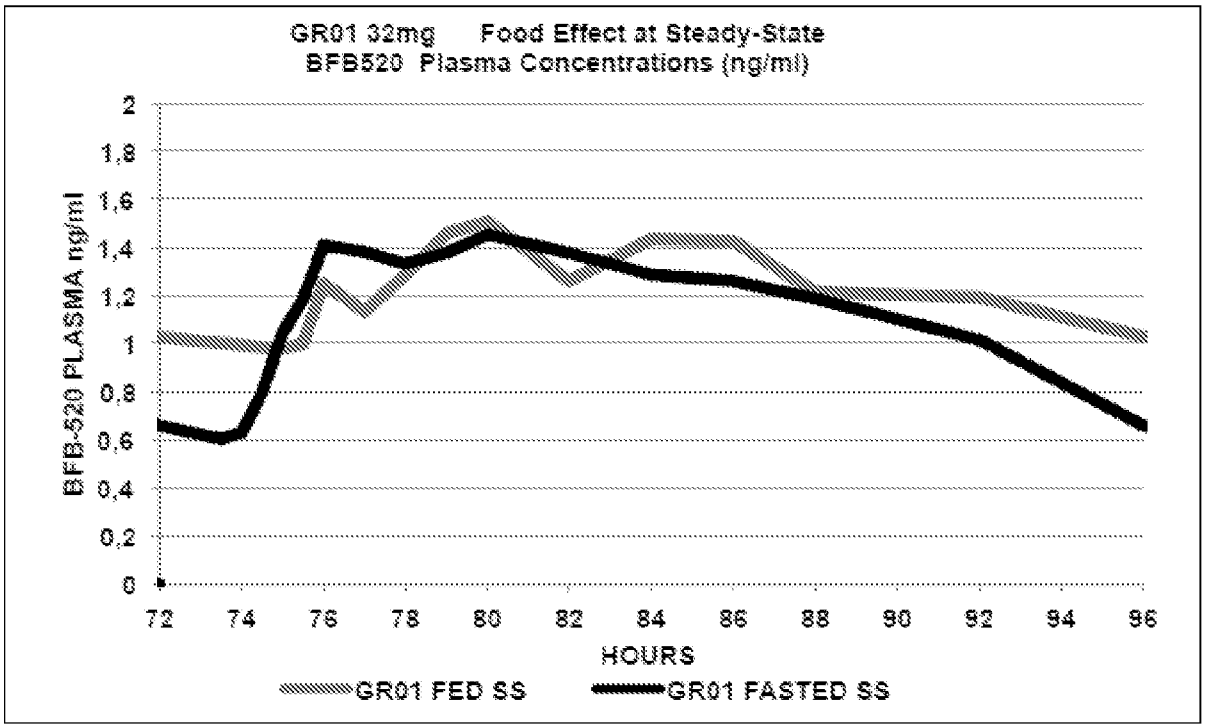
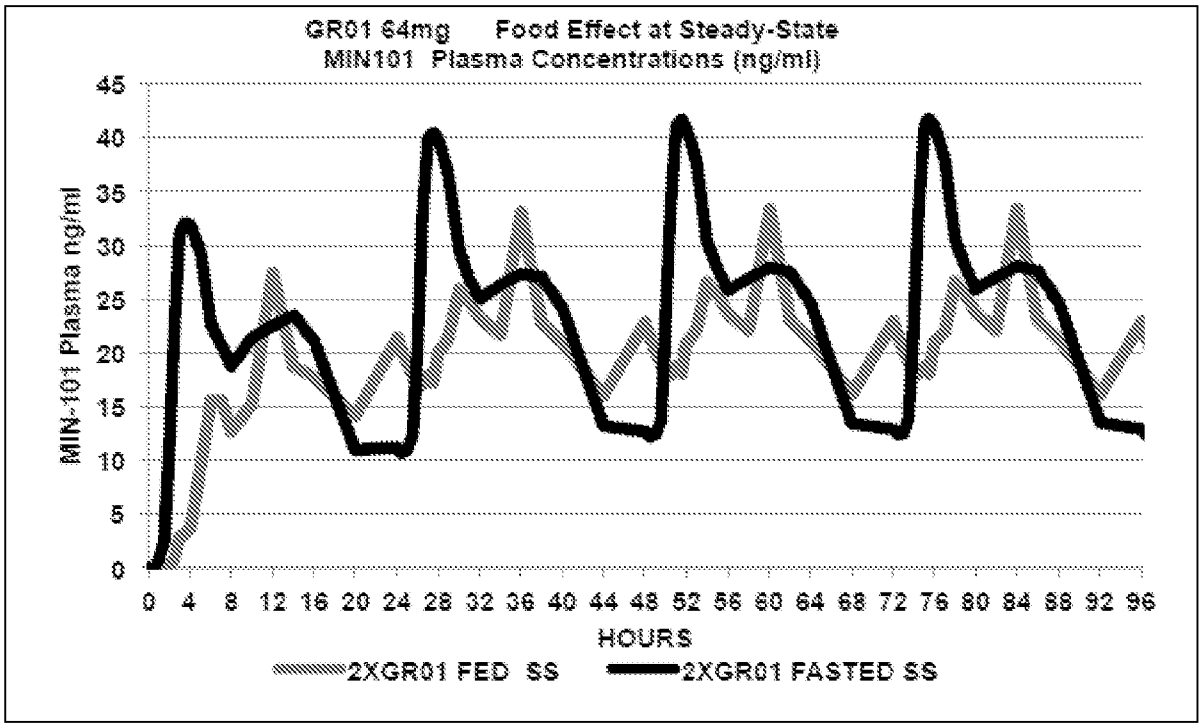

GR01 32mg Food Effect at Steady-State
BFB520 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
2
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
GR01 FED SS
GR01 FASTED SS

FIGURE 30


GR01 64mg Food Effect at Steady-State
MIN101 Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
45
40
35
30
25
20
15
10
5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
HOURS
2XGR01 FED SS
2XGR01 FASTED SS

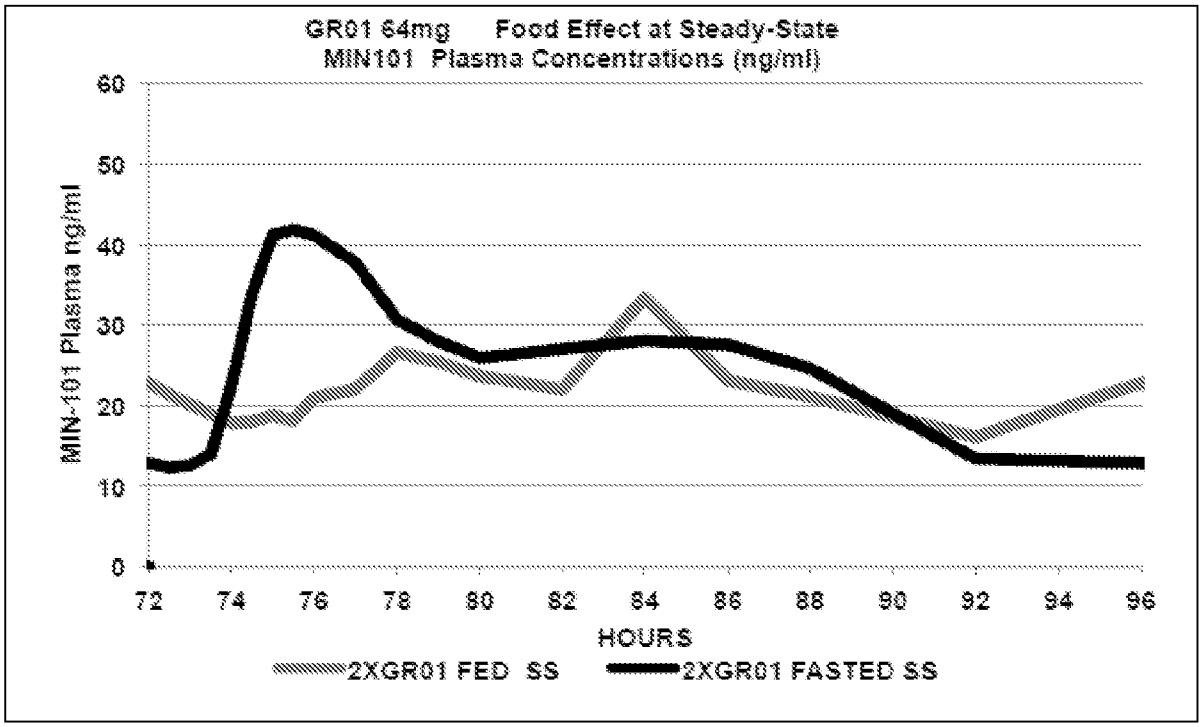
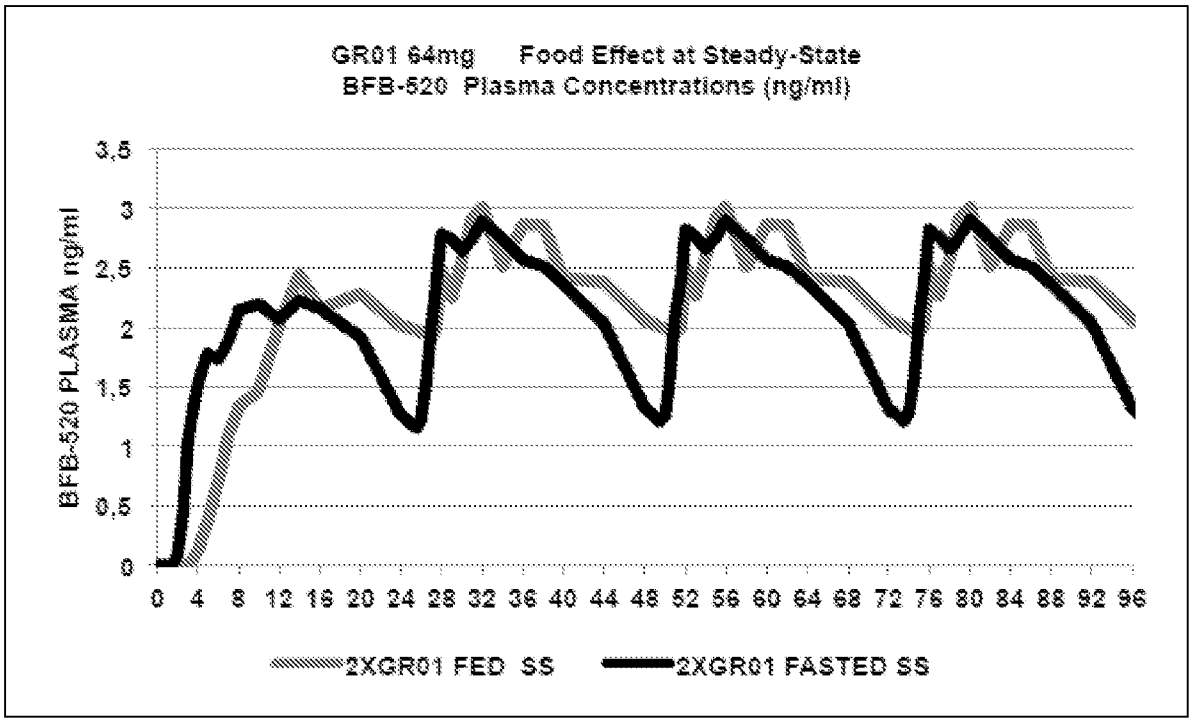
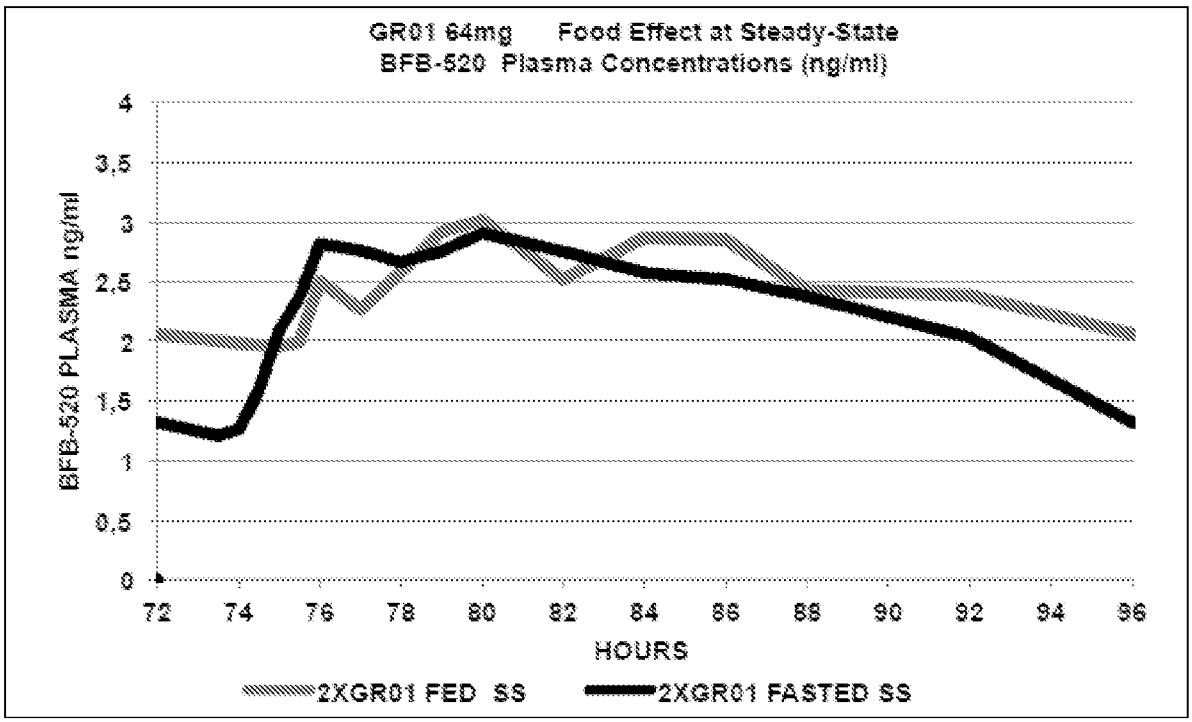

GR01 64mg Food Effect at Steady-State
MIN101 Plasma Concentrations (ng/ml)
MIN-101 Plasma ng/ml
60
50
40
30
20
10
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
2XGR01 FED SS
2XGR01 FASTED SS

FIGURE 31


GR01 64mg Food Effect at Steady-State
BFB-520 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
3,5
3
2,5
2
1,5
1
0,5
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 64 68 72 76 80 84 88 92 96
2XGR01 FED SS
2XGR01 FASTED SS


GR01 64mg Food Effect at Steady-State
BFB-520 Plasma Concentrations (ng/ml)
BFB-520 PLASMA ng/ml
4
3,5
3
2,5
2
1,5
1
0,5
0
72 74 76 78 80 82 84 86 88 90 92 94 96
HOURS
2XGR01 FED SS
2XGR01 FASTED SS

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/038853

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/28 A61K31/454
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2016/152597 A1 (LUTHRINGER REMY [US] ET AL) 2 June 2016 (2016-06-02) the whole document	1-53
Y	SINGH DEEP HUSSAN ET AL: "A review on recent advances of enteric coating", IOSR JOURNAL OF PHARMACY, INTERNATIONAL ORGANIZATION OF SCIENTIFIC RESEARCH, IN, vol. 2, no. 6, 1 November 2012 (2012-11-01), pages 5-11, XP002743136, ISSN: 2319-4219, DOI: 10.9790/3013-2610511 the whole document	1-53

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2018	13/09/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schüle, Stefanie

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/038853

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	S. KAMEL: "Pharmaceutical significance of cellulose: A review", EXPRESS POLYMER LETTERS, vol. 2, no. 11, 1 January 2008 (2008-01-01), pages 758-778, XP055224467, DOI: 10.3144/expresspolymlett.2008.90 abstract	1-53
A	WO 2012/012543 A1 (CYRENAIC PHARMACEUTICALS INC [US]; LUTHRINGER REMY HENRI [CH]; PELLEGR) 26 January 2012 (2012-01-26) the whole document	1-53

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2018/038853

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		KR 20170106310 A	20-09-2017
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		JP 2013531073 A	01-08-2013
		JP 2016199578 A	01-12-2016
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		KR 20130129906 A	29-11-2013
		RU 2013107378 A	27-08-2014
		TW 201211022 A	16-03-2012
		US 2013274290 A1	17-10-2013
		US 2016354357 A1	08-12-2016
		WO 2012012543 A1	26-01-2012