



(12) DEMANDE DE BREVET CANADIEN  
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2019/10/03  
(87) Date publication PCT/PCT Publication Date: 2020/04/09  
(85) Entrée phase nationale/National Entry: 2021/04/01  
(86) N° demande PCT/PCT Application No.: US 2019/054498  
(87) N° publication PCT/PCT Publication No.: 2020/072773  
(30) Priorités/Priorities: 2018/10/03 (US62/740,755);  
2018/12/14 (US62/780,049)

(51) Cl.Int./Int.Cl. A61K 9/14 (2006.01),  
A61K 9/16 (2006.01), A61K 9/48 (2006.01)

(71) Demandeur/Applicant:  
CAVION, INC., US

(72) Inventeurs/Inventors:  
LEE, MARGARET S., US;  
HIGGIN, MICHELLE S., US;  
DUVVURI, MURALIKRISHNA, US;  
REHLAENDER, BRUCE N., US;  
NEWBOLD, EVAN, US;  
PAPAPETROPOULOUS, SPYRIDON, US

(74) Agent: BERESKIN & PARR LLP/S.E.N.C.R.L., S.R.L.

(54) Titre : TRAITEMENT DES TREMBLEMENTS ESSENTIELS A L'AIDE DE (R)-2-(4-ISOPROPYLPHENYL)-N-(1-(5-(2,2,2-TRIFLUOROETHOXY)PYRIDIN-2-YL)ETHYL)ACETAMIDE  
(54) Title: TREATING ESSENTIAL TREMOR USING (R)-2-(4-ISOPROPYLPHENYL)-N-(1-(5-(2,2,2-TRIFLUOROETHOXY)PYRIDIN-2-YL)ETHYL)ACETAMIDE

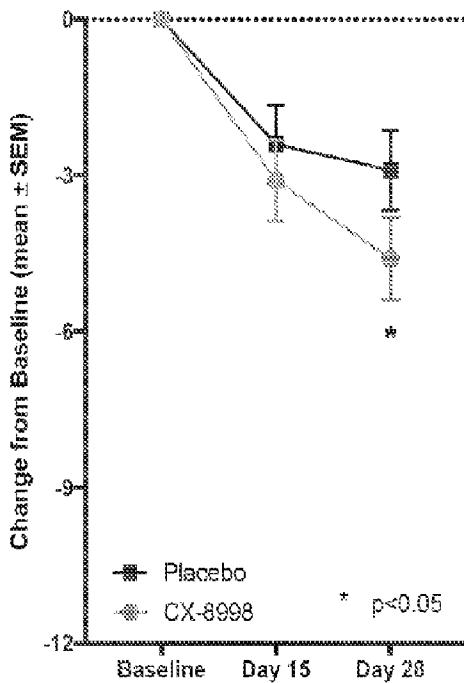


FIG. 1

(57) Abrégé/Abstract:

This invention relates to methods and materials for treating mammals having, or at risk of developing, one or more movement disorders (e.g., essential tremor, epilepsy, and/or Parkinson's disease). For example, compositions including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) are provided, as well as methods for administering such compositions to a mammal having, or at risk of developing, one or more movement disorders (e.g., essential tremor, epilepsy, and/or Parkinson's disease) to treat the mammal.

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

## CORRECTED VERSION

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
09 April 2020 (09.04.2020)

(10) International Publication Number  
**WO 2020/072773 A9**

## (51) International Patent Classification:

*A61K 9/14* (2006.01)      *A61K 9/48* (2006.01)  
*A61K 9/16* (2006.01)

**DER, Bruce**; 18051 Kelok Road, Lake Oswego, Oregon 97034 (US). **NEWBOLD, Evan**; 910 Rainier Road, Charlottesville, Virginia 22903 (US).

## (21) International Application Number:

PCT/US2019/054498

(74) Agent: **WILLIS, Margaret S.** et al.; Fish & Richardson P.C., P.O. Box 1022, Minneapolis, Minnesota 55440-1022 (US).

## (22) International Filing Date:

03 October 2019 (03.10.2019)

(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.

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

62/740,755      03 October 2018 (03.10.2018) US  
62/780,049      14 December 2018 (14.12.2018) US

(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,

(71) **Applicant: CAVION, INC.** [US/US]; 600 East Water Street, Suite E, Charlottesville, Virginia 22902 (US).

(72) **Inventors:** **LEE, Margaret S.**; 20 Pleasant Street, Middleton, Massachusetts 01949 (US). **PAPAPETROPOULOUS, Spyridon**; 22 Skyline Drive, Wellesley, Massachusetts 02482 (US). **HIGGIN, Michelle S.**; 5516 Solomon's Seal Court, Holly Springs, North Carolina 27540 (US). **DUVVURI, Muralikrishna**; 104 Bristol Drive, Chapel Hill, North Carolina 27516 (US). **REHLAEN-**

(54) **Title:** TREATING ESSENTIAL TREMOR TRIFLUOROETHOXY)PYRIDIN-2-YL)ETHYL)ACETAMIDE

USING (R)-2-(4-ISOPROPYLPHENYL)-N-(1-(5-(2,2-

(57) **Abstract:** This invention relates to methods and materials for treating mammals having, or at risk of developing, one or more movement disorders (e.g., essential tremor, epilepsy, and/or Parkinson's disease). For example, compositions including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) are provided, as well as methods for administering such compositions to a mammal having, or at risk of developing, one or more movement disorders (e.g., essential tremor, epilepsy, and/or Parkinson's disease) to treat the mammal.

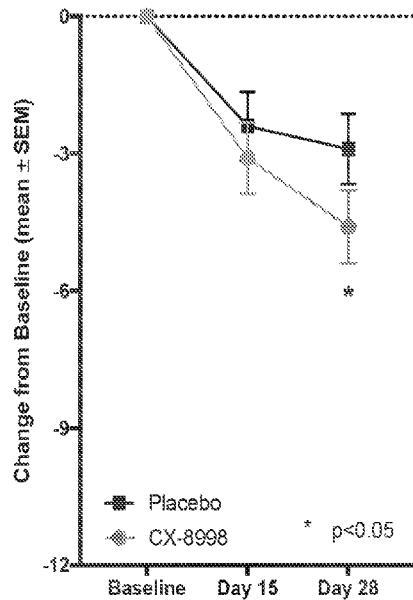


FIG. 1

# WO 2020/072773 A9



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))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

**Published:**

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

**(48) Date of publication of this corrected version:**

16 July 2020 (16.07.2020)

**(15) Information about Correction:**

see Notice of 16 July 2020 (16.07.2020)

# Treating Essential Tremor Using (R)-2-(4-Isopropylphenyl)-N-(1-(5-(2,2,2-Trifluoroethoxy)pyridin-2-yl)ethyl)acetamide

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Patent Application Serial No.

5 62/740,755, filed on October 3, 2018, and claims the benefit of U.S. Patent Application Serial No. 62/780,049, filed on December 14, 2018. The disclosure of the prior applications are considered part of (and is incorporated by reference in) the disclosure of this application.

## TECHNICAL FIELD

10 This invention relates to methods and materials for treating mammals having, or at risk of developing, one or more movement disorders (*e.g.*, essential tremor, epilepsy, and/or Parkinson's disease). In particular, this document relates to compositions including one or more T-type calcium channel antagonists (*e.g.*, one or more Cav3 antagonists such as CX-8998), and administering such compositions to a mammal having, or at risk of 15 developing, one or more movement disorders (*e.g.*, essential tremor, epilepsy, and/or Parkinson's disease) to treat the mammal.

## BACKGROUND

Essential Tremor is among the most prevalent of all movement disorders in adults. In a 2010 meta-analysis, Louis *et al.* (1998 *Movement Disorders*. 13(1):5-10) estimated 20 the pooled prevalence (all ages) to be 0.9%, with statistically significant heterogeneity across studies ( $I^2 = 99\%$ ,  $p < 0.001$ ). The prevalence in adults  $\geq 65$  years old was estimated to be 4.6% (Louis and Ferreira, 2010 *Mov Disord*. 25(5):534-541). While ET does not shorten life expectancy, its impact on the patient's ability to perform activities of daily living (ADLs, such as writing and eating) at home and in the work place negatively 25 affects quality of life, social interactions, and mental status (Lorenz *et al.*, 2006 *Mov Disord*. 21(8):1114-1118; Louis *et al.*, 2015 *Parkinsonism Relat Disord*. 21(7):729-735; George *et al.*, 1994 *Psychosomatics*. 35(6):520-523; and Zesiewicz *et al.*, 2011

5 *Neurology*. 77(19):1752-1755). It is increasingly recognized that ET is not a monosymptomatic disorder (Bermejo-Pareja, 2011 *Nature Reviews Neurology*. 7(5):273-282). Effects on cognitive functions are heterogeneous and include impairments in attention, executive function, verbal fluency, visuospatial functioning, memory, and  
10 working memory (Bermejo-Pareja *et al.*, 2012 “V. Cognitive Features of Essential Tremor: A Review of the Clinical Aspects and Possible Mechanistic Underpinnings,” pages 2:02-74-541-1 in *Tremor and Other Hyperkinetic Movements* (Louis, ed.) 2012). Sleep disturbances and fatigue are also more common in patients with ET than in their age-matched controls (Chandran *et al.*, 2012 *Acta Neurol Scand*. 125:332–7). Essential tremor typically worsens over time and can be severe in some people. It is a significant disability that affects many activities of daily living and can be a source of social embarrassment, phobia, depression & anxiety.

15 T-type calcium channels are members of a family of voltage-activated calcium channels (Cav), each of which is defined by a unique pore-forming alpha subunit with distinct physiological properties that can be further modulated by association with various accessory subunits (Zamponi *et al.*, 2015 *Pharmacol Rev*. 67:821-70). A unique and discriminating property of T-type calcium channels is their ability to activate upon small depolarizations of the membrane, at relatively low voltages, allowing a surge of calcium entry into excitable cells that leads to further membrane depolarization,  
20 activation of additional ion channel subtypes, and initiation of an action potential. Another important feature of this class of channels is their relatively rapid inactivation (the “T” in “T-type” is for transient) and relatively slow functional recovery from this inactivated state. Together these properties enable Cav3 channels to transiently respond to small changes in sensory input and then quickly reset, giving them a key role in setting of  
25 the resting membrane potential and, thus, in the overall excitability and oscillatory activity of the cell (Iftinca *et al.*, 2009 *Trends Pharmacol Sci*. 30:32-40).

30 The T-type calcium channel, Cav3, its isoforms (Cav3.1, Cav3.2, and Cav3.3), and their genes CACNA1G, CACNA1H, and CACNA1I were discovered and cloned in the early 1990s and their function as low-threshold, voltage-gated calcium channels was elucidated (Perez-Reyes, 1998 *Bioenerg Biomembr*. 30:313-8; Cribbs *et al.*, 1998 *Circ*

Res. 83:103-9; Lee *et al.*, 1999 *J Neurosci.* 19(6):1912-21). Isoforms of Cav3 are expressed throughout the central nervous system (CNS) and the peripheral nervous system, including the thalamocortical pathway, where Cav3.1 is the most common isoform (Ertel *et al.*, 2000 *Neuron.* 25:533-5). Deep cerebellar nuclei, substantia nigra, 5 globus pallidus externa, globus pallidus interna, subthalamic nucleus (STN), have been noted to have oscillations in healthy hosts and excessive rhythmicity in animals and humans with pathologic conditions of the nervous system. It has been discovered that Cav3 is a mediator of subthreshold oscillations and excessive rhythmicity in pathophysiologic states found in tremor, neuropathic pain, epilepsy, and Parkinson's 10 disease (Llinás, 2003 *An R Acad Nac Med (Madr).* 120:267-90; Handforth *et al.*, 2005 *Epilepsia.* 46:1860-70; Llinás *et al.*, 2007 *Proc Natl Acad Sci.* 104:17819-24; Park *et al.*, 2013 *Front Neural Circuits.* 7:172).

The inferior olive (IO) appears to function as a tremor generator, and animal 15 models suggest the IO functions as an intrinsic pacemaker (Long *et al.*, 2002 *J Neurosci.* 22:10898-905). Essential tremor (ET) may result from excessive rhythmic synchronous firing of populations of neurons in the IO, which affects the function of the cerebellum (Elbe *et al.*, 1996 *Mov Disord.* 11:70-78). Cav3 is highly expressed in the IO and the cerebellum. Cav3.1 is the predominate Cav3 isoform that is expressed in the IO. Within 20 the cerebellar system, it is also found on Purkinje cell bodies, deep cerebellar nuclei, stellate, basket, dendrites and Golgi cells (Molineux *et al.*, 2006 *Proc Natl Acad Sci U S A.* 103: 5555-60). In these locations, Cav3 functions as a tremor generator and ongoing rhythm pacemaker (Park *et al.*, 2010 *Proc Natl Acad Sci U S A.* 107:10731-6).

## SUMMARY

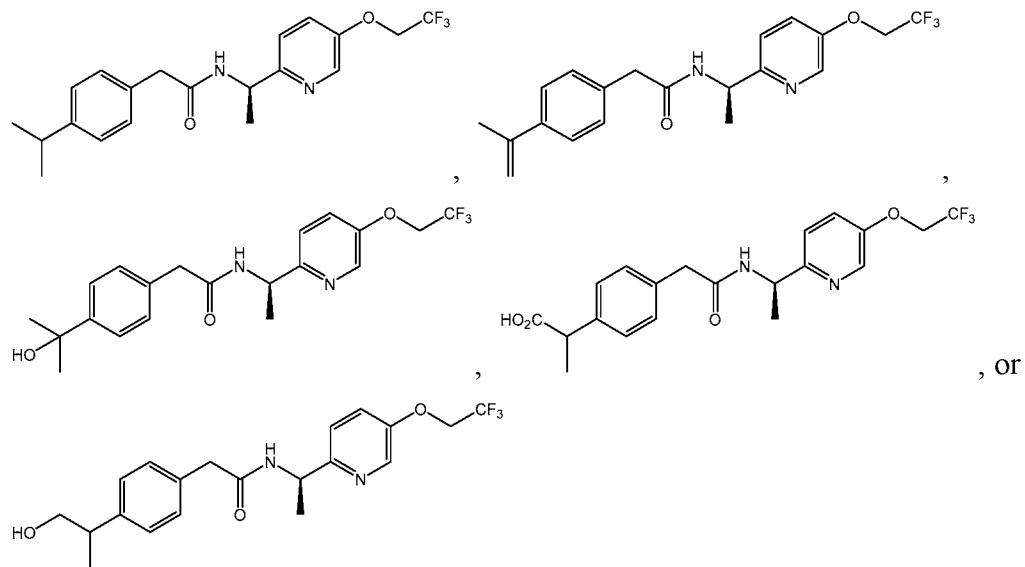
This document provides methods and materials for treating mammals having, or 25 at risk of developing, a movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease). For example, a composition including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be administered to a mammal in need thereof (e.g., a mammal having, or at risk of developing, a movement disorder) to treat the mammal. CX-8998 is a highly selective

voltage-activated Cav antagonist. As demonstrated herein, an oral dosage form of a composition including CX-8998 can be formulated to include a first component designed for delayed and/or sustained CX-8998 release and a second component designed for immediate CX-8998 release, such that the dosage form, when orally administered to a 5 mammal (e.g., a mammal having movement disorder) can provide the mammal with plasma levels of CX-8998 within a therapeutically beneficial range for about 12 hours (e.g., for twice daily dosing) or for about 24 hours (e.g., for once daily dosing).

Currently, propranolol is the only medication approved for the treatment of essential tremor in the United States. The lack of any new positive recommendations by 10 the 2011 Academy of Neurology evidence-based guideline update on the treatment of essential tremor (as compared to the 2005 guidelines) attests to the poor yield of present approaches to drug discovery (Zesiewicz *et al.*, 2011 *Neurology*. 77(19):1752-1755). Thus, the ability to deliver one or more T-type calcium channel antagonists (e.g., one or 15 more Cav3 antagonists such as CX-8998) in therapeutic amounts provides a unique and unrealized opportunity to treat humans having essential tremor. Further, delivering one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX- 20 8998) in a non-invasive manner while maintaining the therapeutic amounts for a sustained period of time can maximize daytime efficacy, limit  $C_{max}$  related adverse events, and limit nighttime sleep disturbances (and potentially hormonal effects), while reducing the frequency of dosing required for therapeutic benefit.

In general, one aspect of this document features an oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form includes a controlled release component including the Cav3 antagonist, and where the dosage form optionally contains an immediate release component including the Cav3 25 antagonist; where the oral dosage form, when administered to a human of about 35 years of age or older, can be effective to provide: a) a  $C_{max}$  of the Cav3 antagonist at steady state of no greater than twice the mean plasma concentration over 24 hours; and b) a plasma concentration of the Cav3 antagonist at steady state of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to the human, can be 30 effective to maintain the  $C_{max}$  of the Cav3 antagonist at steady state of from 1 to 2 times

the mean plasma concentration over 24 hours. The oral dosage form can be administered to the human once daily. The Cav3 antagonist can have a structure of:



5

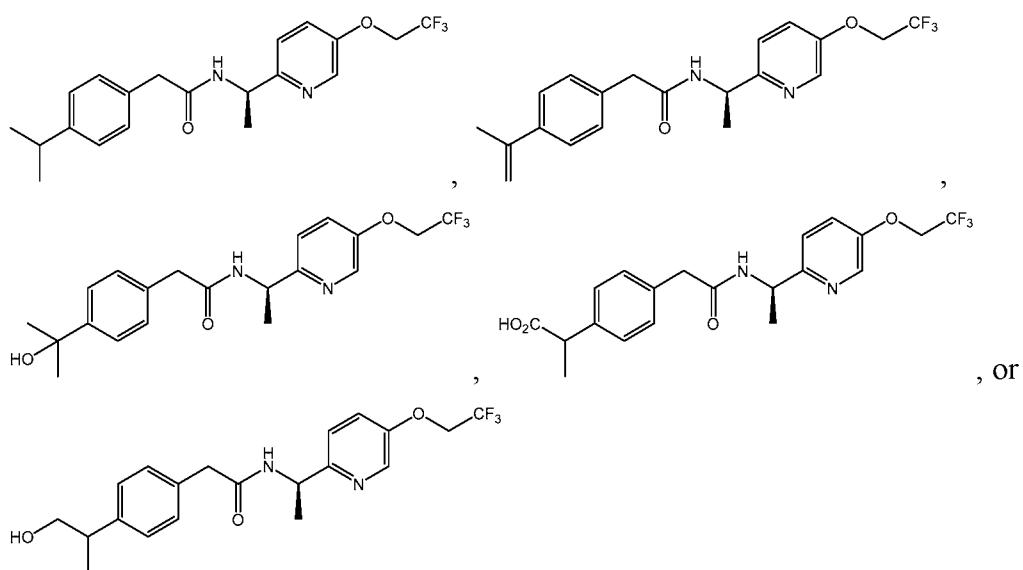
The Cav3 antagonist can include a hydrochloride salt. The oral dosage form can be a capsule, a pill, a tablet, or a suspension. The controlled release component can include particles, a tablet, a mini-tablet, a solution, a suspension, a capsule, or a mixture thereof.

10 The particles can be granules, pellets, beads, microparticles, or nanoparticles, or a mixture thereof. The oral dosage form can include a capsule. The capsule can be a gelatin capsule or a hydroxypropyl methylcellulose capsule. The at least one particle in a plurality of particles comprising the Cav3 antagonist in the controlled release component can include a coating comprising a pH-sensitive enteric polymer. In some cases, at least 15 a portion of the pH-sensitive enteric polymer coating can dissolve at a pH of about 6.

16 The pH-sensitive enteric polymer coating can dissolve at a pH of about 6, the pH-sensitive enteric polymer can include, by weight, about 6.25% methacrylic acid copolymer L, about 6.25% methacrylic acid copolymer S, about 1.25% triethyl citrate, and about 6.25% talc. In some cases, at least a portion of the pH-sensitive enteric 20 polymer coating can dissolve at a pH of about 7. The pH-sensitive enteric polymer coating can dissolve at a pH of about 7, the pH-sensitive enteric polymer can include, by weight, about 17.4% EUDRAGIT® FS 30 D, and about 2.6% PlasACRYL® T20. The

controlled release component can include, by weight, about 5.0% of the Cav3 antagonist, about 57.7% lactose monohydrate, about 25.0% crospovidone, about 8.0% citric acid anhydrous, about 2.0% sodium lauryl sulfate (SLS), about 2.0% hydroxypropyl cellulose (HPC), about 0.3% butylated hydroxyanisole (BHA), and about 0.1% butylated hydroxytoluene (BHT). The oral dosage form also can include the immediate release component, where the immediate release component includes a plurality of particles comprising the Cav3 antagonist. One or more of the particles in the immediate release component can include, by weight, about 5.0% of the Cav3 antagonist, about 57.7% lactose monohydrate, about 25.0% crospovidone, about 8.0% citric acid anhydrous, about 2.0% SLS, about 2.0% HPC, about 0.3% BHA, and about 0.1% BHT. One or more of the particles in the immediate release component, when the oral dosage form is administered to a human, can release at least 80% of the Cav3 antagonist present in the immediate release component within 45 minutes of administration. The oral dosage form can include about 30% of the Cav3 antagonist in the immediate release component and about 70% of the Cav3 antagonist in the controlled release component. The oral dosage form, when administered to a human, can be effective to reach at least 25% of the  $C_{max}$  of the Cav3 antagonist within 30 minutes. The Cav3 antagonist can reduce the activity of a T-type calcium channel.

In another aspect, this document features an oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form includes a controlled release component including the Cav3 antagonist, and where the dosage form optionally contains an immediate release component including the Cav3 antagonist; where the oral dosage form, when administered to a human less than about 35 years of age, can be effective to provide: a) a  $C_{max}$  of the Cav3 antagonist at steady state of no greater than 2.5 times the mean plasma concentration over 24 hours; and b) a plasma concentration of the Cav3 antagonist at steady state of from about 400 nM to about 1000 nM for at least 15 hours. The oral dosage form, when administered to the human, can be effective to maintain the  $C_{max}$  of the Cav3 antagonist at steady state of from 1 to 2.5 times the mean plasma concentration over 24 hours. The oral dosage form can be administered to the human once daily. The Cav3 antagonist can have a structure of:



5 The Cav3 antagonist can include a hydrochloride salt. The oral dosage form can be a capsule, a pill, a tablet, or a suspension. The controlled release component can include particles, a tablet, a mini-tablet, a solution, a suspension, a capsule, or a mixture thereof. The particles can be granules, pellets, beads, microparticles, or nanoparticles, or a mixture thereof. The oral dosage form can include a capsule. The capsule can be a

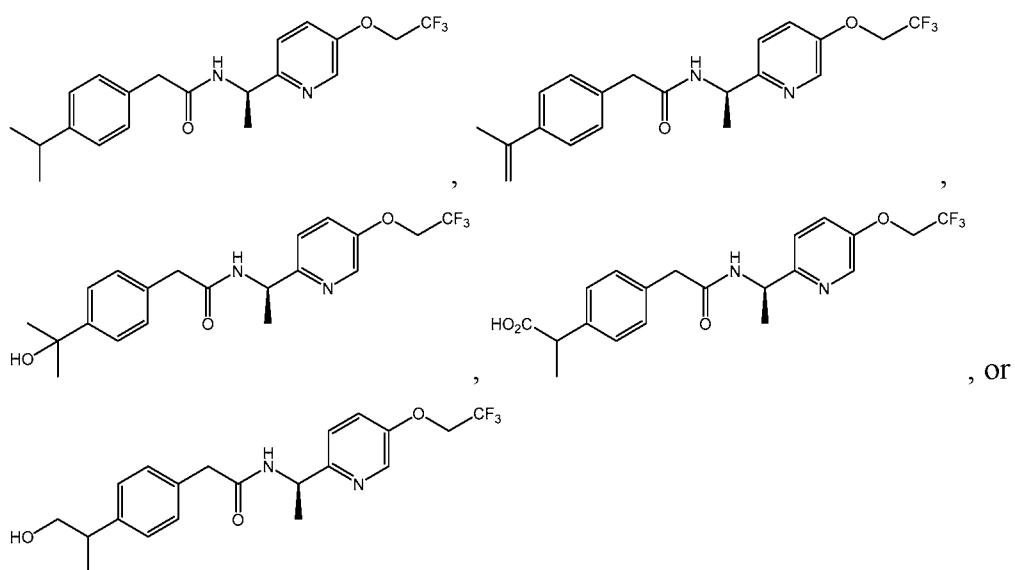
10 gelatin capsule or a hydroxypropyl methylcellulose capsule. The at least one particle in a plurality of particles comprising the Cav3 antagonist in the controlled release component can include a coating comprising a pH-sensitive enteric polymer. In some cases, at least a portion of the pH-sensitive enteric polymer coating can dissolve at a pH of about 6. The pH-sensitive enteric polymer coating can dissolve at a pH of about 6, the pH-

15 sensitive enteric polymer can include, by weight, about 6.25% methacrylic acid copolymer L, about 6.25% methacrylic acid copolymer S, about 1.25% triethyl citrate, and about 6.25% talc. In some cases, at least a portion of the pH-sensitive enteric polymer coating can dissolve at a pH of about 7. The pH-sensitive enteric polymer coating can dissolve at a pH of about 7, the pH-sensitive enteric polymer can include, by weight, about 17.4% EUDRAGIT® FS 30 D, and about 2.6% PlasACRYL® T20. The controlled release component can include, by weight, about 5.0% of the Cav3 antagonist, about 57.7% lactose monohydrate, about 25.0% crospovidone, about 8.0% citric acid

20

anhydrous, about 2.0% SLS, about 2.0% HPC, about 0.3% BHA, and about 0.1% BHT. The oral dosage form also can include the immediate release component, where the immediate release component includes a plurality of particles comprising the Cav3 antagonist. One or more of the particles in the immediate release component can include, 5 by weight, about 5.0% of the Cav3 antagonist, about 57.7% lactose monohydrate, about 25.0% crospovidone, about 8.0% citric acid anhydrous, about 2.0% SLS, about 2.0% HPC, about 0.3% BHA, and about 0.1% BHT. One or more of the particles in the immediate release component, when the oral dosage form is administered to a human, can release at least 80% of the Cav3 antagonist present in the immediate release 10 component within 45 minutes of administration. The oral dosage form can include about 30% of the Cav3 antagonist in the immediate release component and about 70% of the Cav3 antagonist in the controlled release component. The oral dosage form, when administered to a human, can be effective to reach at least 25% of the  $C_{max}$  of the Cav3 antagonist within 30 minutes. The Cav3 antagonist can reduce the activity of a T-type 15 calcium channel.

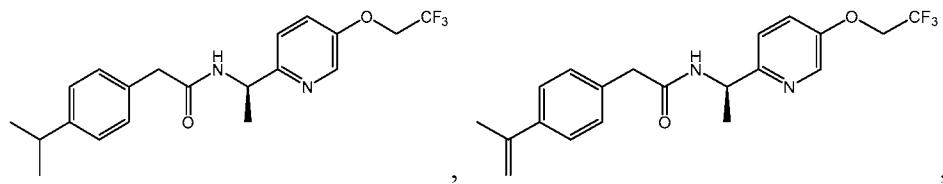
In another aspect, this document features an oral dosage form including a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form can include a capsule including: a) an immediate release component including one or more granules including the Cav3 antagonist, and b) a controlled release component including 20 one or more granules including the Cav3 antagonist; where the oral dosage form, when administered to a human, can be effective to maintain a mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean 25 plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours. The Cav3 antagonist can have a structure of:

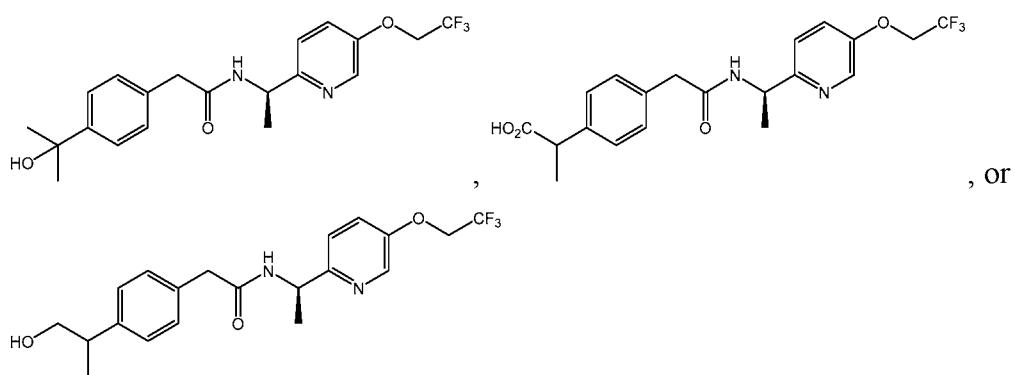


5 The Cav3 antagonist can include a hydrochloride salt. The Cav3 antagonist can reduce activity of a T-type calcium channel.

In another aspect, this document features an oral dosage form including a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form can include a tablet including: a) an immediate release component including one or more granules including the Cav3 antagonist, and b) a controlled release component including one or more granules including the Cav3 antagonist; where the oral dosage form, when administered to a human, can be effective to maintain a mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours. The Cav3 antagonist can have a structure of:

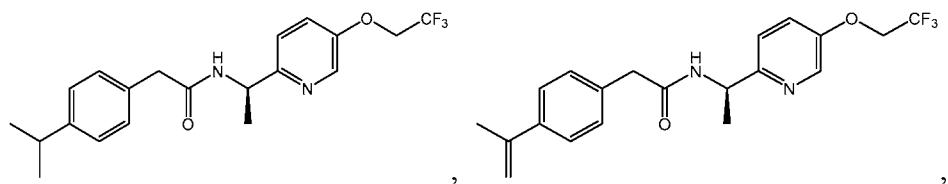
20

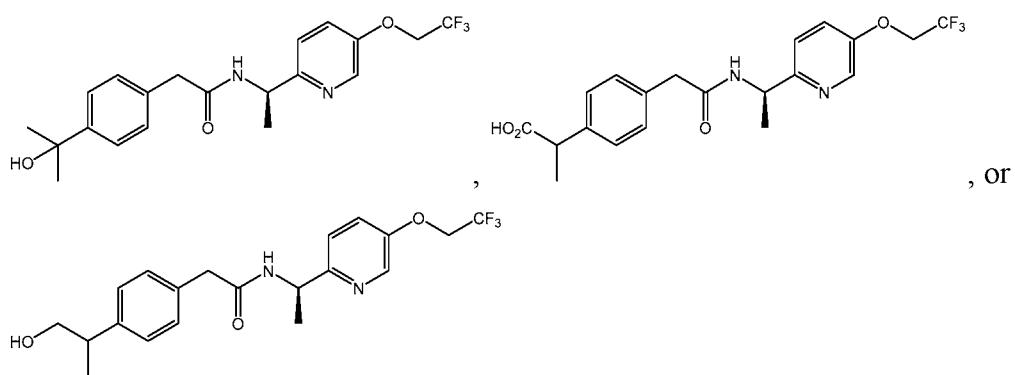




5 The Cav3 antagonist can include a hydrochloride salt. The Cav3 antagonist can reduce activity of a T-type calcium channel.

In another aspect, this document features an oral dosage form including a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form includes a capsule including: a) an immediate release component including the Cav3 antagonist, and b) a controlled release component including one or more tablets including the Cav3 10 antagonist; where the oral dosage form, when administered to a human, can be effective to maintain a mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours. The immediate release component can include a plurality of granules. The immediate release component can include a plurality of beads and/or pellets. The one or more tablets can include one or more mini-tablets. The oral 15 dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours. The Cav3 antagonist can 20 have a structure of:

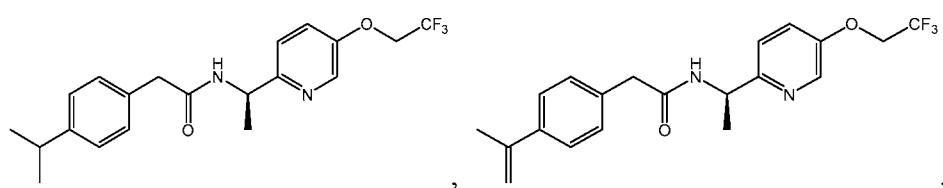


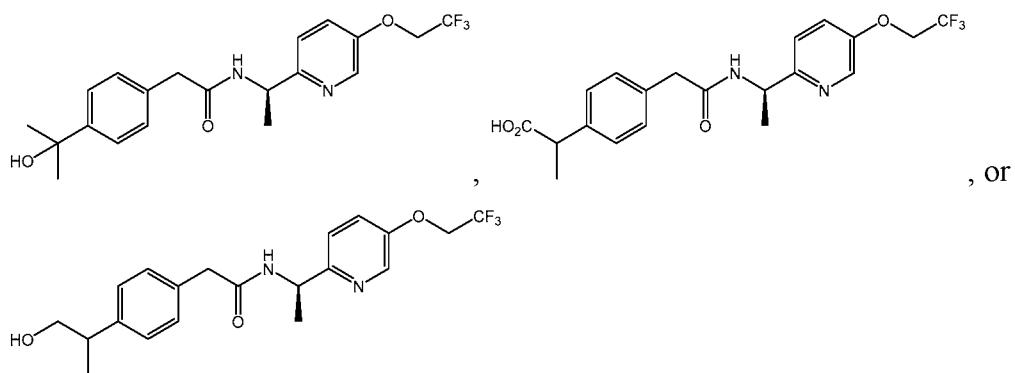


5 The Cav3 antagonist can include a hydrochloride salt. The Cav3 antagonist can reduce activity of a T-type calcium channel.

In another aspect, this document features an oral dosage form including a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form can include a capsule including: a) an immediate release component including the Cav3 antagonist, where the immediate release component can be a liquid, and b) a controlled release component including the Cav3 antagonist, where the controlled release component includes one or more solid components that can be granules, beads, pellets, and/or mini-tablets; where the oral dosage form, when administered to a human, can be effective to maintain a mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours. The Cav3 antagonist can have a structure of:

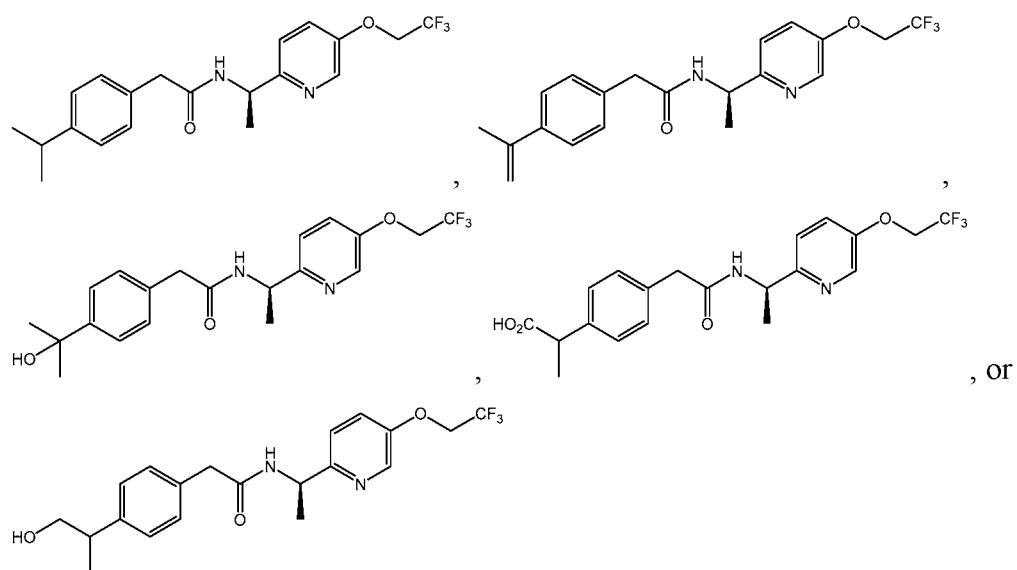
20





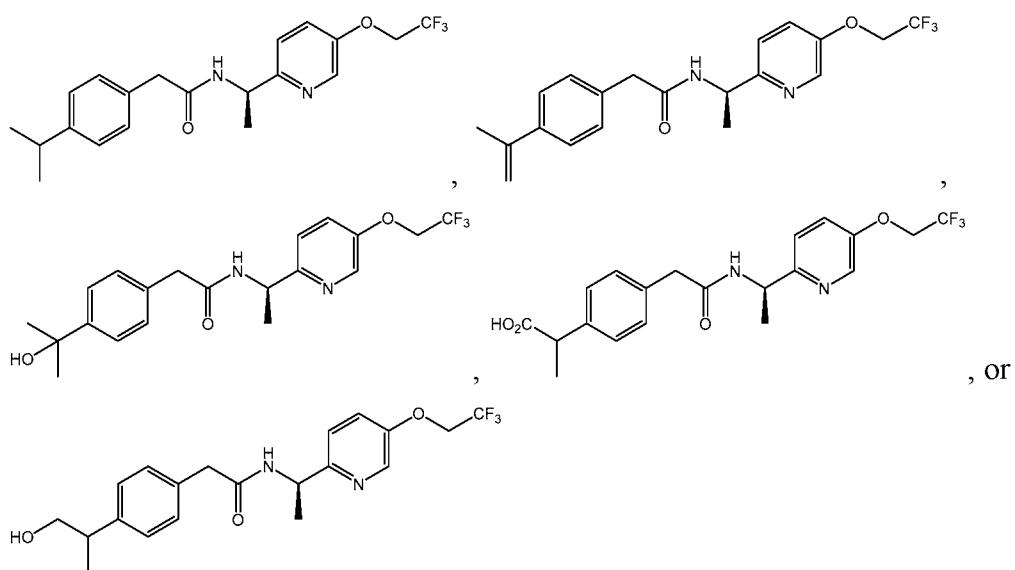
5 The Cav3 antagonist can include a hydrochloride salt. The Cav3 antagonist can reduce activity of a T-type calcium channel.

In another aspect, this document features an oral dosage form including a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form includes a capsule containing an interior capsule, where the interior capsule fits within the oral dosage capsule such that a space is present between an outer surface of the interior capsule and an inner surface of the oral dosage capsule; where the space present between the outer surface of the interior capsule and the inner surface of the oral dosage capsule can contain an immediate release component including the Cav3 antagonist, where the immediate release component can be a liquid; where the interior capsule contains a controlled release component including the Cav3 antagonist; and where the oral dosage form, when administered to a human, can be effective to maintain a mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours. The Cav3 antagonist can have a structure of:



5 The Cav3 antagonist can include a hydrochloride salt. The Cav3 antagonist can reduce activity of a T-type calcium channel.

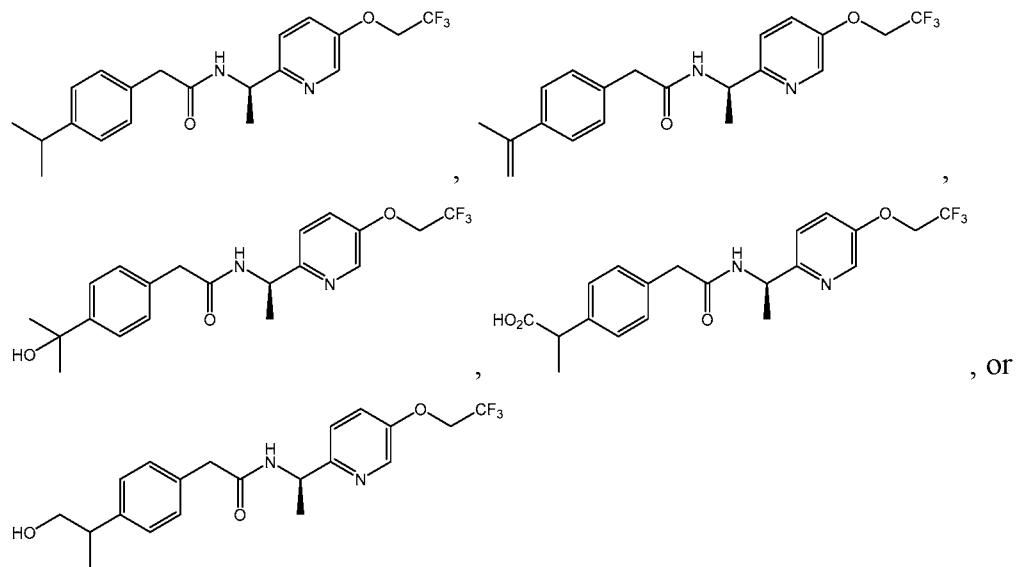
In another aspect, this document features an oral dosage form including a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form includes a suspension including: a) an immediate release component including the Cav3 antagonist, where the immediate release component is a liquid, and b) a controlled release component including the Cav3 antagonist, where the controlled release component includes one or more solid components that can be granules, beads, pellets, and/or mini-tablets; where the one or more solid components are suspended within the liquid; and where the oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours. The Cav3 antagonist can have a structure of:



5 The Cav3 antagonist can include a hydrochloride salt. The Cav3 antagonist can reduce activity of a T-type calcium channel.

In another aspect, this document features an oral dosage form including a Cav3 antagonist or a pharmaceutically acceptable salt thereof, where the dosage form includes a suspension including: a) a liquid phase, b) an immediate release component including the Cav3 antagonist, where the immediate release component includes one or more solid components that can be granules, beads, pellets, and/or mini-tablets; where the one or more solid components are suspended within the liquid, and c) a controlled release component including the Cav3 antagonist, where the controlled release component includes one or more solid components that can be granules, beads, pellets, and/or mini-tablets; where the one or more solid components are suspended within the liquid; and where the oral dosage form, when administered to a human, can be effective to maintain a mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of the Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours. The oral dosage form, when administered to a human, can be effective to maintain the mean plasma concentration of

the Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours. The Cav3 antagonist can have a structure of:



5

The Cav3 antagonist can include a hydrochloride salt. The Cav3 antagonist can reduce activity of a T-type calcium channel.

In another aspect, this document features methods for treating a patient having a movement disorder. The methods can include, or consist essentially of, administering to the patient in need thereof (e.g., a patient having a movement disorder) an oral dosage form provided herein. The patient can be a human adult 35 years of age or older. The patient can be human adult is less than about 35 years of age. The movement disorder can be essential tremor, idiopathic generalized epilepsy with absence seizures, or tremor associated with Parkinson's disease. The oral dosage form can be administered (e.g., can be administered once daily) to the patient between 6 am and noon. The oral dosage form can be administered (e.g., can be administered once daily) to the patient within 4 hours of waking. The controlled release component can include a plurality of particles including the Cav3 antagonist, where at least one particle in the plurality of particles including the Cav3 antagonist in the controlled release component includes a coating including a pH-sensitive enteric polymer, and where at least a portion of the pH-sensitive enteric polymer coating dissolves at an intestinal pH. The patient can have fasted for at least 4 hours prior

to being administered the oral dosage form. The Cav3 antagonist can be effective to reduce or eliminate tremors associated with the movement disorder. The patient can experience reduced adverse events as compared to a human that is administered only an immediate release component of the Cav3 antagonist. The adverse event can be 5 dizziness, headache, euphoria, disturbance in attention, paresthesia, hallucination, insomnia, dry mouth, dysguesia, hypoesthesia, somnolence, lethargy, sleep disturbance, nausea, vomiting, akathisia, decreased level of consciousness, syncope, memory impairment, anxiety, restlessness, fatigue, irritability, constipation, tinnitus, anorexia, 10 emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, morbilliform skin eruptions, granulocytopenia, agranulocytosis, red-cell hypoplasia, aplasia, or any combinations thereof.

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 invention pertains. For example, the terms “*e.g.*” and “such as,” and grammatical 15 equivalents thereof, the phrase “and without limitation” is understood to follow unless explicitly stated otherwise. For example, the singular forms “*a*,” “*an*,” and “*the*” include plural referents unless the context clearly dictates otherwise. For example, the term “about” means “approximately” (*e.g.*, plus or minus approximately 10% of the indicated value). Although methods and materials similar or equivalent to those described 20 herein can be used to practice the invention, suitable methods and materials are described below. It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in 25 any suitable subcombination. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more embodiments of the invention are set forth in the 30 accompanying drawings and the description below. Other features, objects, and

advantages of the invention will be apparent from the description and drawings, and from the claims.

## DESCRIPTION OF DRAWINGS

FIG. 1 is a graph showing the change from baseline to day 28 in the Tremor Research Group (TRG) Essential Tremor Rating Assessment Scale (TETRAS) – performance subscale (PS) as rated by investigator.

FIG. 2 is a graph showing the change from baseline to day 15 and day 28 in the TETRAS – activities of daily living (ADL).

FIG. 3 is a graph showing the change from baseline to day 15 and day 28 in the TETRAS total score.

FIG. 4 is a graph showing the change from baseline to day 28 in the TETRAS-PS spiral task.

FIG. 5 is a graph showing the change from baseline to day 15 and day 28 in functional tremor frequency measured by digital spirography.

FIG. 6 is a graph showing the difference from placebo in clinical global impression of improvement (CGI-I) at day 28.

FIG. 7 contains graphs showing the difference from placebo in patient global impression of change (PGIC) at day 15 and day 28.

FIG. 8 is a graph showing the difference from placebo in goal attainment scale (GAS).

FIG. 9 is a graph showing the increase vs placebo in a percentage of subjects satisfied with anti-tremor medication at day 15 and day 28 (QUEST sub-item).

FIG. 10 is a graph showing CX-8998 plasma concentrations resulting in clinical efficacy at day 15 and day 28.

FIGS. 11A – 11D contain graphs showing CX-8998 metabolite exposure following twice daily (BID) dosing of CX-8998. FIG. 11A shows CX-8998 metabolite M01. FIG. 11B shows CX-8998 metabolite M02. FIG. 11C shows CX-8998 metabolite M03. FIG. 11D shows CX-8998 metabolite M04.

FIG. 12 is a graph showing the relationship between CX-8998 plasma concentration and response. Baseline and placebo response is represented by the shaded region.

FIG. 13 contains graphs showing toleration to adverse events with dose titration.

5 FIG. 14 contains graphs showing a summary of electrocardiogram outliers in a safety analysis set.

FIG. 15 contains graphs showing no difference between CX-8998 and Placebo in a safety analysis set.

10 FIG. 16 is a dataset and forest plot for a subgroup analysis of TETRAS performance subscale total score in a physician rated full analysis set.

FIG. 17 is a dataset and forest plot for a subgroup analysis of TETRAS activities of daily living subscale in a full analysis set.

FIG. 18 contains chromatograms of CX-8998 showing partial separation and suboptimal peak widths for metabolites M01, M02, M03, and M04.

15 FIG. 19 contains chromatograms of CX-8998 showing unwanted secondary interactions resulting in poor peak shapes.

FIG. 20 contains chromatograms of CX-8998 showing near baseline separation of CX-8998 and its metabolites M01, M02, M03, and M04.

20 FIG. 21 contains chromatograms showing that acetylation with acetic anhydride under basic conditions appeared to be selective for M04 and showed high reaction yield.

FIG. 22 is a graph showing a reaction time course at 50 °C for M04-Ac formed in individuals analyte reaction vs mixed analyte reaction.

25 FIG. 23 is a graph showing the percent of M04 remaining following an increase of either acetic anhydride or pyridine during the derivatization reaction at 50 °C for 30 minutes in human plasma extracts.

FIG. 24 is a graph showing a reaction time course at 50 °C in samples containing individual analytes based on peak areas.

FIG. 25 is a representative chromatogram of CX-8998, M01, M02, M03, and M04 in human plasma sample.

FIG. 26 is a graph showing a release CX-8998 from an immediate release (IR) bead.

FIG. 27 contains graphs showing a profile of immediate release of CX-8998 of a single daily dose and the steady state of the daily dose.

5 FIG. 28 contains graphs showing a release profile of CX-8998 of a single dose in elderly males and of 7 daily doses young males.

FIG. 29 is a graph showing an age effect on the release of CX-8998.

FIG. 30 is a graph showing an age effect on pharmacokinetics (PK).

10 FIG. 31 contains graphs of plasma concentrations of CX-8998 in elderly patients following a single morning dose.

FIG. 32 contains graphs showing output correlations.

FIG. 33 contains graphs of plasma concentrations of CX-8998 in young patients following a single morning dose.

FIG. 34 contains graphs showing output correlations.

15 FIG. 35 contains graphs of plasma concentrations of CX-8998 in young patients following multiple doses.

FIG. 36 contains graphs showing a release profile for young adult males having about a 6 mg burst followed by ~12 mg at an almost constant rate over 12 hours.

20 FIG. 37 contains graphs showing a release profile for elderly adult males having about a 7 mg burst followed by ~12 mg at a slightly diminishing rate over 12 hours.

FIG. 38 contains graphs showing zero order release from an osmotic pump tablet.

FIG. 39 contains graphs showing first order release from a matrix tablet having coated beads in a capsule.

25 FIG. 40 contains graphs showing a burst and zero order release from an osmotic pump tablet with an IR release coating.

FIG. 41 contains graphs showing a burst and first order release from a mixture of IR beads and slow release beads in a matrix tablet with an IR coating.

30 FIG. 42 contains graphs showing a double burst with a 3 hour delay from a mixture of IR beads and pH 6 enteric-coated beads from an IR tablet with enteric coating and an IR coating.

FIG. 43 contains graphs showing a double burst with a 6 hour delay from a mixture of IR beads and pH 7 enteric-coated beads from an IR tablet with enteric coating and an IR coating.

FIG. 44 contains graphs showing target range exposure of CX-8998 in TETRAS and Global responders.

FIG. 45 contains a graph showing upper dose limits.

FIG. 46 is a graph showing target exposure levels and PK profiles of total and unbound CX-8998 in plasma and TAM following administration of CX-8998 10 mg BID.

FIGS. 47A – 47B show exemplary T-CALM designs. FIG. 47A contains a schematic of an exemplary T-CALM Design. FIG. 47B contains a flow chart of an exemplary T-CALM Design.

FIGS. 48A – 48D contain graphs showing changes from baseline in investigator rated TETRAS-PS.

FIGS. 49A – 49D contain graphs showing change from baseline for TETRAS-ADL and total TETRAS

FIGS. 50A – 50B contain graphs showing clinical global impression of improvement at day 28.

FIG. 51 contains graphs showing differences in TETRAS performance subscores. The upper panel shows the difference scores by item, where negative scores indicate lower scoring by the independent video rater (CR) than the investigator (PR). The upper panel shows difference scores across all visits.

FIG. 52 contains a graph showing intrinsic dissolution of CX-8998 free base (FB) and CX-8998 HCl formulations.

FIG. 53 contains a graph showing release from IR beads.

FIGS. 54A – 54B contain graphs showing dissolution rates from IR beads having a first formulation (FIG. 54A) and second formulation (FIG. 54B).

FIGS. 55A – 55B contain graphs showing dissolution rates of CX-8998 formulations in acidic conditions (FIG. 55A) and pH neutral conditions (FIG. 55B).

FIG. 56 contains a graph showing CX-8998 release profile of IR beads, MR1 beads, and MR2 beads.

FIGS. 57A – 57C contain graphs showing CX-8998 release profile of IR beads (FIG. 57A), MR1 beads (FIG. 57B), and MR2 beads (FIG. 57C) after storage.

FIG. 58 contains graphs showing simulated dissolution rates of various ratios of IR and MR1 beads in the elderly.

5 FIG. 59 contains graphs showing simulated dissolution rates of various ratios of IR and MR2 beads in the elderly.

FIG. 60 contains graphs showing simulated dissolution rates of various ratios of IR and MR1 beads in the non-elderly.

10 FIG. 61 contains graphs showing simulated dissolution rates of various ratios of IR and MR2 beads in the non-elderly.

FIGS. 62A – 62C contain graphs showing simulated dissolution rates of formulations having 40% IR, 25% MR1 (pH 6), and 35% MR2 (pH 7) at various dosage forms of 25 mg (FIG. 62A), 15 mg (FIG. 62B), and 8 mg (FIG. 62C).

15 FIGS. 63A – 63B contain graphs showing an exemplary distribution of  $C_{max}$  (FIG. 63A) and  $AUC_{0-72h}$  values (FIG. 63B) for CX-8998 following single-dose administration of CX-8998 (1 x 8 mg).

FIGS. 64A – 64D contain graphs showing onset time (FIG. 64A), resolution time (FIG. 64B), duration time (FIG. 64C), and onset concentration (FIG. 64D) of adverse events following single-dose administration of CX-8998 (1 x 8 mg).

20 FIG. 65 contains a graph showing a PK profile of single-dose administration of IR CX-8998 (1 x 8 mg) in contrast with CNS and psychiatric adverse events concentrations. The shaded area represents the 5<sup>th</sup> – 95<sup>th</sup> percentiles.

25 FIG. 66 contains a graph showing a PK profile of single-dose administration of MR1 CX-8998 (1 x 8 mg) in contrast with CNS and psychiatric adverse events concentrations. The shaded area represents the 5<sup>th</sup> – 95<sup>th</sup> percentiles.

FIG. 67 contains a graph showing a PK profile of single-dose administration of MR2 CX-8998 (1 x 8 mg) in contrast with CNS and psychiatric adverse events concentrations. The shaded area represents the 5<sup>th</sup> – 95<sup>th</sup> percentiles.

FIG. 68 contains graphs showing adverse events by treatment period.

FIG. 69 contains a graphs showing an exemplary dissolution profile of IR CX-8998 beads from lot L364-01036.

FIG. 70 contains a graphs showing an exemplary dissolution profile of CR (pH 6) CX-8998 beads from lot L364-01037.

5 FIG. 71 contains a graphs showing an exemplary dissolution profile of CR (pH 7) CX-8998 beads from lot L364-01038.

FIGS. 72A – 72C contain graphs showing plasma concentrations of CX-8998, metabolite M01, and metabolite M02 following single-dose administration of IR CX-8998 (FIG. 72A), MR1 CX-8998 (FIG. 72B), or MR2 CX-8998 (FIG. 72C).

10 FIGS. 73A – 73B contains a graph showing plasma concentrations of CX-8998 over time (in hours) in fasted versus fed patients on average (FIG. 73A) and for individual patients (FIG. 73B) where diamonds represent fasted state samples and triangles represent fed state samples.

15 FIG. 74 contains a graph showing an exemplary once daily dosing of MR2 CX-8998 and twice daily dosing of an IR CX-8998.

Like reference symbols in the various drawings indicate like elements.

## DETAILED DESCRIPTION

This document provides methods and materials for treating mammals (e.g., a human patient) having, or at risk of developing, a movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease). In some cases, this document provides 20 compositions including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) as well as the use of such compositions in the manufacture of a medicament for treating a movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease).

25 In some cases, a composition including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be a controlled release composition that includes one or more components of compositions, where each component can be formulated to modify the release rate of the one or more T-type calcium channel antagonists from the composition (e.g., to achieve specific target

pharmacokinetic outcomes) when administered to a human patient. For example, a composition including CX-8998 can be an oral dosage form having a first component designed for delayed and/or sustained CX-8998 release and, optionally, a second component designed for immediate CX-8998 release, such that the dosage form, when orally administered to a mammal (e.g., a human patient having movement disorder) can provide the mammal with therapeutically effective plasma levels of CX-8998 for about 12 hours or about 24 hours.

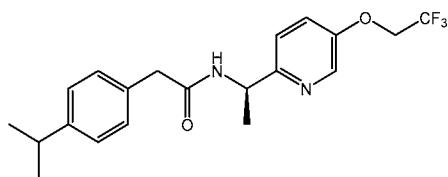
In some cases, a composition including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be designed to provide specific target pharmacokinetic outcomes when administered to a human patient. For example, because T-type calcium channel antagonists can cause undesirable symptoms (e.g., adverse effects or side effects) when plasma concentrations in a human patient are too high, and because T-type calcium channel antagonists can have little or no effect (e.g., little or no therapeutic effect) when plasma concentrations are too low, it is desirable that a dosage form, after administration to a human patient, can provide a plasma concentration of a T-type calcium channel antagonist that is above an effective minimum concentration while minimally exceeding a maximum concentration above which certain undesirable symptoms become more common, and can do so for an extended period of time. For example, a composition including one or more T-type calcium channel antagonists, when administered as a single oral dose, may yield a maximal plasma concentration in a human patient of, on average, not more than 1200 nM while maintaining plasma concentrations, on average, of above 400 nM, and can maintain such a plasma concentration for at least 12 hours, at least 15 hours, or at least 18 hours.

In some cases, this document provides methods of using compositions including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998). For example, a composition including one or more T-type calcium channel antagonists (e.g., an oral dosage form having a first component designed for delayed and/or sustained CX-8998 release and, optionally, a second component designed for immediate CX-8998 release, such that the dosage form, when orally administered to a patient having movement disorder can provide the patient with therapeutically effective

plasma levels of CX-8998 for about 12 hours) can be administered to a patient having, or at risk of developing, a movement disorder to treat the patient. The methods and materials provided herein can be used to provide a patient in need thereof with sustained CX-8998 action over a long period of time (e.g., about 24 hours). For example, when an oral 5 dosage form of a composition including CX-8998 includes a first component designed for delayed and/or sustained CX-8998 release and a second component designed for immediate CX-8998 release, the immediate release component can be effective to quickly achieve therapeutically effective plasma levels of CX-8998 within a patient, and the delayed and/or sustained release component can be effective to sustain the therapeutically 10 effective plasma levels of CX-8998 within the patient.

### *Compositions*

This document provides compositions (e.g., pharmaceutically acceptable compositions) including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998). In some cases, a T-type calcium channel 15 antagonist can inhibit (e.g., can reduce or eliminate) activity of a T-type calcium channel. In some cases, this document provides compositions including CX-8998. CX-8998 (also referred to as MK-8998) is a highly selective voltage-activated calcium channel (Cav) antagonist that can inhibit Cav3 (e.g., can inhibit Cav3 with nanomolar (nM) potency), and is highly selective for Cav3 (e.g., having >100-fold selectivity against other ion 20 channel targets). CX-8998 can be used for dose-dependent tremor reduction, reduction and/or elimination of seizures, and/or reduction and/or elimination of pain. As used herein, the term “CX-8998” can also refer to CX-8998 structural analogs provided that the CX-8998 structural analog maintains the pharmaceutical function of CX-8998 as 25 described herein (e.g., dose-dependent tremor reduction, reduction and/or elimination of seizures, and/or reduction and/or elimination of pain). Chemical names for CX-8998 include, without limitation, (R)-2-(4-Isopropylphenyl)-N-(1-(5-(2,2,2-Trifluoroethoxy)pyridin-2-yl)ethyl)acetamide and 2-(4-Isopropylphenyl)-N-{1R)-1-(5-(2,2,2-trifluoroethoxy)pyridine-2-yl)ethyl}acetamide hydrochloride. The chemical structure of CX-8998 is as shown below.

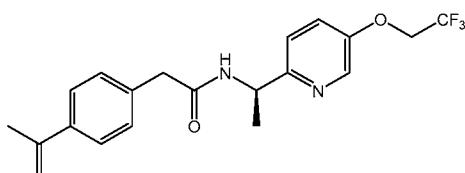


CX-8998 can be in any appropriate form of CX-8998. In some cases, CX-8998 can be in the form of a base (e.g., a free base form of the compound). In some cases, CX-8998 can be in the form of a salt (e.g., a salt form of the compound). In cases where CX-8998 is a salt, the CX-8998 salt can be any appropriate salt. A CX-8998 salt can include a salt formed with any appropriate acid (e.g., hydrochloric acids, citric acids, hydrobromic acids, maleic acids, phosphoric acids, sulfuric acids, fumaric acids, and tartaric acids). For example, CX-8998 can be a CX-8998 hydrochloride salt (e.g., CX-8998-HCl). In some cases, CX-8998 can be deuterated. In some cases, CX-8998 can be in the form of a CX-8998 polymorph. In some cases, CX-8998 can be the form of a structural isomer of CX-8998 (e.g., a CX-8998 tautomer).

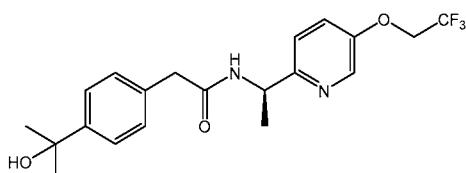
In some cases, one or more components of compositions (e.g., pharmaceutically acceptable compositions) provided herein (e.g., compositions including one or more T-type calcium channel antagonists such as CX-8998) can cross the blood brain barrier. For example, when a composition includes CX-8998, the CX-8998 can cross the blood brain barrier. For example, when a composition including CX-8998 also includes one or more additional components, the CX-8998 can be released from the composition and can cross the blood brain barrier. For example, when a composition including CX-8998 also includes one or more additional components, the CX-8998 can be released from the composition and can cross the blood brain barrier while the one or more additional components do not cross the blood brain barrier.

In some cases, one or more components of compositions (e.g., pharmaceutically acceptable compositions) provided herein (e.g., compositions including one or more T-type calcium channel antagonists such as CX-8998) do not cross the blood brain barrier. For example, when a composition including CX-8998 also includes one or more additional components, the CX-8998 can be released from the composition and can cross the blood brain barrier while the one or more additional components do not cross the blood brain barrier.

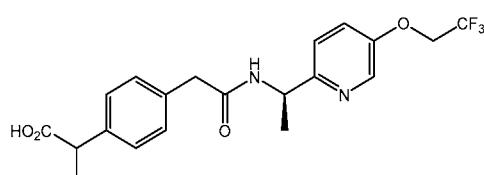
A composition (e.g., a pharmaceutically acceptable composition) including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can include, in addition to or in place of a T-type calcium channel antagonist, a metabolite of a T-type calcium channel antagonist. In some implementations, a T-type calcium channel antagonist present in a compositions described herein can be metabolized into (e.g., metabolized by a mammal following administration of the composition to the mammal) one or more metabolites of a T-type calcium channel antagonist. In some cases, a metabolite of a T-type calcium channel antagonist such as a metabolite of CX-8998 can be a T-type calcium channel antagonist (e.g., a Cav3 antagonist). For example, when a composition includes CX-8998, the composition can include one or more CX-8998 metabolites and/or the CX-8998 can be metabolized into one or more CX-8998 metabolites. A CX-8998 metabolite can be any appropriate metabolite. In some cases, a metabolite can be bound to a protein (e.g., a plasma protein). In some cases, a metabolite can be free (e.g., not bound to any protein). In some cases, a metabolite can cross the blood brain barrier (e.g., can be present in the cerebrospinal fluid (CSF) and/or the CNS). Examples of CX-8998 metabolites include, without limitation metabolite 01 (M01), M02, M03, and M04. In some cases, a composition described herein can include and/or be metabolized into M01 and M02. The chemical structures of exemplary CX-8998 metabolites are as shown below.



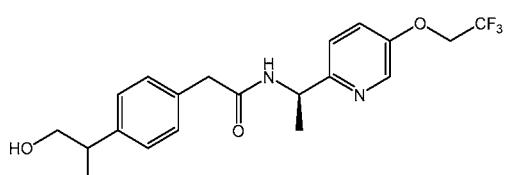
M01



M02



M03



M04

20 In some cases, a T-type calcium channel antagonist in a composition (e.g., pharmaceutically acceptable composition) including one or more T-type calcium channel

antagonists (*e.g.*, one or more Cav3 antagonists such as CX-8998) can be selective for (*e.g.*, can selectively bind to) all 3 Cav3 isoforms. “Selective” in this context means that the Cav3 antagonist is more potent at antagonizing Cav3 channels compared with other voltage activated calcium channels (*e.g.*, high voltage activated channels such as an L-type cardiac channel (Cav1)) and/or compared with other types of ion channels (*e.g.*, chloride channels, potassium channels, and sodium channels). Selectivity can be determined using any appropriate method. For example, selectivity can be determined by comparing the IC<sub>50</sub> of a Cav3 antagonist in inhibiting a first type of ion channel (*e.g.*, a Cav3 channel) with its IC<sub>50</sub> in inhibiting a second type of ion channel (*e.g.*, a sodium channel). If the IC<sub>50</sub> for inhibiting the first type of channel is lower than the IC<sub>50</sub> for inhibiting the second type of channel, then the Cav3 antagonist can be considered selective for the first type of channel. An IC<sub>50</sub> ratio of 0.1 (or lower) denotes 10-fold (or greater) selectivity. An IC<sub>50</sub> ratio of 0.01 (or lower) denotes 100-fold (or greater) selectivity. An IC<sub>50</sub> ratio of 0.001 (or lower) denotes 1000-fold (or greater) selectivity. In some cases, a T-type calcium channel antagonist in a composition described herein can have selectivity for Cav3 that is 10-fold or greater, 100-fold or greater, or 1000-fold or greater compared with other types of ion channels. For example, when a T-type calcium channel antagonist in a composition described herein is CX-8998, the composition can have greater than 100-fold selectivity against other ion channels. In some cases, a T-type calcium channel antagonist in a composition described herein can selectively target one or more Cav3 isoforms (*e.g.*, Cav3.1, Cav3.2, and/or Cav3.3). In some cases, a composition described herein can selectively target all three Cav3 isoforms (*e.g.*, Cav3.1, Cav3.2, and Cav3.3).

In some cases, a T-type calcium channel antagonist in a composition described herein (*e.g.*, a composition containing one or more T-type calcium channel antagonists such as CX-8998) can have selectivity for Cav3 in a state-dependent manner. In some cases, a T-type calcium channel antagonist in a composition described herein can have from about 29-fold to about 45-fold greater selectivity for Cav3 under hyperpolarizing conditions as compared to depolarizing conditions. For example, when a T-type calcium channel antagonist in a composition described herein is CX-8998, the CX-8998 can have

selectivity for Cav3 (*e.g.*, Cav3.3) can have an IC<sub>50</sub> of about 3.6 nM under depolarizing conditions, and can have an IC<sub>50</sub> of about 161 nM under hyperpolarizing conditions. For example, when a T-type calcium channel antagonist in a composition described herein is CX-8998, the CX-8998 can have an IC<sub>50</sub> for antagonizing Cav3.3 of about 84 nM under 5 depolarizing conditions, and can have an IC<sub>50</sub> for antagonizing Cav3.3 of about 2.4  $\mu$ M under hyperpolarizing conditions. For example, when a T-type calcium channel antagonist in a composition described herein is CX-8998, the CX-8998 can have selectivity for Cav3.1 can have an IC<sub>50</sub> of about 69 nM under depolarizing conditions, and can have an IC<sub>50</sub> of about 2.4  $\mu$ M under hyperpolarizing conditions.

10 In some cases, a T-type calcium channel antagonist in a composition (*e.g.*, pharmaceutically acceptable composition) including one or more T-type calcium channel antagonists (*e.g.*, one or more Cav3 antagonists such as CX-8998) can be a potent Cav3 antagonist. For example, when a T-type calcium channel antagonist in a composition described herein is CX-8998, the CX-8998 can be more potent at antagonizing Cav3 than 15 other ion channels. For example, CX-8998 can have nM potency (*e.g.*, nM levels of CX-8998 are sufficient to antagonize Cav3). In some cases, a T-type calcium channel antagonist in a composition described herein can potently inhibit one or more Cav3 isoforms (*e.g.*, Cav3.1, Cav3.2, and/or Cav3.3). In some cases, a T-type calcium channel antagonist in a composition described herein can potently inhibit all three Cav3 isoforms 20 (*e.g.*, Cav3.1, Cav3.2, and Cav3.3).

A composition (*e.g.*, a pharmaceutically acceptable composition) including one or more T-type calcium channel antagonists (*e.g.*, one or more Cav3 antagonists such as CX-8998) can include the one or more Cav3 antagonists as the sole active ingredient(s).

25 A composition (*e.g.*, a pharmaceutically acceptable composition) including one or more T-type calcium channel antagonists (*e.g.*, one or more Cav3 antagonists such as CX-8998) can include the one or more T-type calcium channel antagonists together with one or more additional active ingredients. For example, a composition can include one or more T-type calcium channel antagonists together with one or more additional agents used to treat one or more movement disorders (*e.g.*, essential tremor, epilepsy, and/or 30 Parkinson's disease). Examples of agents used to treat one or more movement disorders

include, without limitation, beta blockers (*e.g.*, propranolol), anti-seizure medications (*e.g.*, primidone, gabapentin, topiramate, zonisamide, ethosuximide, pregabalin, valproate, phenytoin, and mibepradil), tranquilizers (*e.g.*, alprazolam and clonazepam), administering one or more dopamine agonists (*e.g.*, carbidopa-levodopa, pramipexole, 5 ropinirole, rotigotine, and apomorphine), monoamine oxidase B (MAO B) inhibitors (*e.g.*, selegiline, rasagiline, and safinamide), catechol O-methyltransferase (COMT) inhibitors (*e.g.*, entacapon, and tolcapone), and anticholinergics (*e.g.*, benztropine and trihexyphenidyl).

10 A composition (*e.g.*, a pharmaceutically acceptable composition) described herein (*e.g.*, a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include one or more additional components (*e.g.*, one or more inactive ingredients). For example, a therapeutically effective amount of CX-8998 can be formulated into a composition including one or more additional components and administered to a mammal having, or at risk of developing, one or more movement 15 disorders (*e.g.*, essential tremor, epilepsy, and/or Parkinson's disease) to treat the mammal. Any additional components (*e.g.*, pharmaceutically acceptable carriers) used to formulate a composition (*e.g.*, a pharmaceutically acceptable composition) described herein (*e.g.*, containing one or more T-type calcium channel antagonists) can be of high purity and can be substantially free of potentially harmful contaminants (*e.g.*, at least 20 National Formulary (NF) grade and/or United States Pharmacopeia (USP) grade). For example, when intended for administration to a human, a composition described herein can be manufactured or formulated under Good Manufacturing Practice standards as defined in the applicable regulations of the U.S. Food and Drug Administration and/or by similar regulatory bodies in other countries. For example, compositions described herein 25 can be sterile and/or substantially isotonic and/or in full compliance with all (*e.g.*, current) Good Manufacturing Practice regulations of the U.S. Food and Drug Administration.

30 A composition described herein (*e.g.*, a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be formulated into a pharmaceutically acceptable composition. For example, a therapeutically effective

amount of CX-8998 can be formulated into a pharmaceutically acceptable composition and administered to a mammal having, or at risk of developing, one or more movement disorders (*e.g.*, essential tremor, epilepsy, and/or Parkinson's disease) to treat the mammal. As used herein, the term "pharmaceutically acceptable" refers to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. For example, a therapeutically effective amount of CX-8998 can be formulated together with one or 5 more pharmaceutically acceptable carriers (*e.g.*, additives, diluents, and/or excipients). In some cases, pharmaceutically acceptable carrier can be an active component of a composition described herein. When a pharmaceutically acceptable carrier is an active component of a composition described herein, the pharmaceutically acceptable carrier can have any one or more functions in the composition. For example, a pharmaceutically acceptable carrier can be a filler, a diluent, a bulking agent, a binder, a disintegrant, a 10 wicking agent, a matrix-forming polymer, a coating agent, a pH-sensitive polymer, a pore-former, a glidant, a lubricant, an osmotic agent, a humectant, an antioxidant, an antimicrobial, a solubility enhancer, a penetration enhancer, a crystallization inhibitor, and/or a solvent in a composition described herein. In some cases, a pharmaceutically acceptable carrier can be an inactive component of a composition described herein. A pharmaceutically acceptable carrier can be a solid, semi-solid, or liquid material. A pharmaceutically acceptable carrier can be any pharmaceutically acceptable compound 15 which acts as a vehicle, carrier, or medium for one or more T-type calcium channel antagonists. Examples of pharmaceutically acceptable carriers that may be used in a pharmaceutically acceptable composition described herein include, without limitation, lactose monohydrate, crospovidone, citric acid, sodium lauryl sulfate, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial 20 glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium 25

30

chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose, cellulose-based substances, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol (PEG; PEG-containing molecules such as vitamin E PEG succinate and PEG-200), Tween such as 5 Tween-80, cyclodextrin, dimethylsulfoxide (DMSO), wool fat, lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, syrup, and methyl cellulose. A composition described herein also can include, for example, fillers 10 (e.g., lactose, sucrose, mannitol, modified or unmodified starches, cellulose derivatives such as microcrystalline cellulose, hydroxypropyl cellulose, and croscarmellose sodium, and mineral salts such as calcium phosphate), disintegrants (e.g., croscarmellose, sodium starch glycolate, and crospovidone), binders (e.g., hydrophilic polymers such as cellulose derivatives (e.g., hydroxypropyl methylcellulose), carbopol, povidone, and modified starches), surfactants (e.g., acyl sulfates, polysorbates such as polysorbate-80, fatty acids 15 and their derivatives, poloxamers, tergitol, and other amphiphilic molecules), lubricating agents (e.g., talc, magnesium stearate, and mineral oil) wetting agents, emulsifying and suspending agents, preserving agents (e.g., methyl- and propylhydroxy-benzoates), sweetening agents, and/or flavoring agents. In some cases, a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein 20 can include lactose monohydrate, crospovidone, citric acid, and sodium lauryl sulfate. For example, when a composition described herein includes CX-8998, the composition can include, by weight, about 5% CX-8998, about 60% lactose monohydrate, about 25% crospovidone, about 8% citric acid, and about 2% sodium lauryl sulfate. It will be understood that use of certain additional components (e.g., pharmaceutically acceptable 25 carriers) can result in the formation of pharmaceutical salts from one or more T-type calcium channel antagonists (e.g., a pharmaceutically acceptable salt of CX-8998 such as a CX-8998-HCl salt).

A composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as 30 CX-8998) can be formulated in a unit dosage form. The term “unit dosage forms” refers

to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. In some cases, a unit dosage can be administered once a day (e.g., a once daily dose). In some cases, a unit dosage can be administered more than once a day (e.g., BID or three times a day (TID)). For example, a unit dosage can contain from about 0.5 mg to about 1,000 mg (1 g) of one or more T-type calcium channel antagonists per day (e.g., from about 0.5 mg to about 900 mg, from about 0.5 mg to about 800 mg, from about 0.5 mg to about 700 mg, from about 0.5 mg to about 600 mg, from about 0.5 mg to about 500 mg, from about 0.5 mg to about 400 mg, from about 0.5 mg to about 300 mg, from about 0.5 mg to about 200 mg, from about 0.5 mg to about 100 mg, from about 0.5 mg to about 50 mg, from about 0.5 mg to about 30 mg, from about 0.5 mg to about 20 mg, from about 5 mg to about 1,000 mg, from about 10 mg to about 1,000 mg, from about 25 mg to about 1,000 mg, from about 100 mg to about 1,000 mg, from about 200 mg to about 1,000 mg, from about 300 mg to about 1,000 mg, from about 400 mg to about 1,000 mg, from about 500 mg to about 1,000 mg, from about 600 mg to about 1,000 mg, from about 750 mg to about 1,000 mg, from about 5 mg to about 750 mg, from about 10 mg to about 500 mg, from about 15 mg to about 400 mg, from about 20 mg to about 300 mg, from about 25 mg to about 250 mg, from about 30 mg to about 200 mg, from about 3 mg to about 30 mg, from about 5 mg to about 25 mg, from about 8 mg to about 16 mg, from about 40 mg to about 150 mg, or from about 50 mg to about 100 mg of CX-8998 per day). In some cases, each dosage contains about 8 mg of CX-8998. In some cases, each dosage contains about 10 mg of CX-8998. In some cases, each dosage contains about 16 mg of CX-8998. In some cases, each dosage contains about 20 mg of CX-8998. In some cases, each dosage contains about 24 mg of CX-8998.

A composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include any appropriate amount of one or more T-type calcium channel antagonists (e.g., CX-8998). The amount (e.g., proportion or concentration) of one or more T-type calcium channel antagonists in a composition described herein can vary

depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, when a composition includes CX-8998, the composition can include, by weight, from about 0.5% to about 60% CX-8998 (e.g., from about 1% to about 60%, from about 3% to about 60%, from 5 about 5% to about 60%, from about 8% to about 60%, from about 10% to about 60%, from about 12% to about 60%, from about 15% to about 60%, from about 20% to about 60%, from about 25% to about 60%, from about 30% to about 60%, from about 40% to about 60%, from about 50% to about 60%, from about 0.5% to about 50%, from about 0.5% to about 40%, from about 0.5% to about 30%, from about 0.5% to about 20%, from 10 about 0.5% to about 15%, from about 0.5% to about 10%, from about 0.5% to about 7%, from about 0.5% to about 5%, from about 0.5% to about 2%, from about 1% to about 50%, from about 5% to about 30%, from about 10% to about 20%, from about 1% to about 5%, from about 5% to about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 30%, from about 30% to about 40%, or from 15 about 40% to about 50% CX-8998). In some cases, a composition can include, by weight, about 5% CX-8998.

A composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be formulated for administration in any appropriate form. A composition described herein can be in a solid form (e.g., a tablet or a capsule), a liquid form (e.g., a solution or a suspension), or a semi-solid form (e.g., a gel, a lotion, a cream, an ointment, a soft gel, or a gummy). Examples of forms in which a composition described herein can be formulated include, without limitation, solutions, suspensions, tablets, pellets, beads, pills, powders (e.g., lyophilized powders), granules, lozenges, sachets, cachets, elixirs, emulsions, syrups, aerosols (e.g., solid aerosols or liquid aerosols), lotions, creams, and ointments. In some cases, a dosage form of a composition described herein also can include one or more additional components (e.g., cosmetic and/or flavor components). When a composition is in a solid form, the solid composition can include one or more particles (e.g., one or more granules, one or more pellets, one or more beads, one or more microparticles, and/or one or more nanoparticles, or mixtures of granules, pellets, beads, 25 30

microparticles, and nanoparticles, and subcombinations thereof). When a composition includes one or more particles, a particle can be any appropriate size. For example, a particle can have a longest dimension (e.g., a diameter) that is from about 0.2 mm to about 2.0 mm (e.g., from about 0.2 mm to about 1.8 mm, from about 0.2 mm to about 1.5 mm, from about 0.2 mm to about 1.2 mm, from about 0.2 mm to about 1.0 mm, from about 0.2 mm to about 0.8 mm, from about 0.2 mm to about 0.6 mm, from about 0.5 mm to about 2.0 mm, from about 0.7 mm to about 2.0 mm, from about 1.0 mm to about 2.0 mm, from about 1.2 mm to about 2.0 mm, from about 1.5 mm to about 2.0 mm, from about 1.8 mm to about 2.0 mm, from about 0.3 mm to about 1.8 mm, from about 0.5 mm to about 1.5 mm, from about 0.5 mm to about 1.0 mm, or from about 1.0 mm to about 1.5 mm). In some cases, a particle can have a longest dimension that is from about 0.5 mm to about 1 mm. When a composition includes one or more particles, a particle can be any appropriate shape. For example, a particle can be round (e.g., spherical). For example, a dosage form can include one or more non-functional coatings (e.g., one or more coatings that do not include one or more T-type calcium channel antagonists and do not alter the release of the one or more T-type calcium channel antagonists in a composition described herein). In some cases, one or more forms of a composition described herein (e.g., oral dosage forms) can be contained within a capsule (e.g., a soft gelatin capsule, a hard gelatin capsule, or a hard hydroxypropyl methylcellulose capsule). For example, a composition described herein can be contained within a hard gelatin capsule or a hard hydroxypropyl methylcellulose capsule. A capsule can be any shape (e.g., oval-shaped). When a composition described herein is contained within a capsule, the capsule can be any appropriate size (e.g., a size 4, size 3, size 2, size 1, size 0, size 00, size 000, size 0EL, or size 00 EL capsule). In some cases, a pharmaceutically acceptable composition containing one or more T-type calcium channel antagonists can be a sterile composition. For example, a pharmaceutically acceptable composition containing one or more T-type calcium channel antagonists can include aqueous and non-aqueous sterile injection solutions that can contain anti-oxidants (e.g., butylated hydroxyanisole (BHA) and/or butylated hydroxytoluene (BHT)), stabilizers, buffers, bacteriostats, and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and

non-aqueous sterile suspensions which may include suspending agents and thickening agents. In some cases, a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein can include a capsule containing a plurality of Cav3 antagonist-containing pellets and/or Cav3 antagonist-containing beads.

5 For example, when a composition described herein includes CX-8998, the composition can include a capsule containing a plurality of CX-8998-containing pellets and/or CX-8998-containing beads.

A composition (*e.g.*, a pharmaceutically acceptable composition) described herein (*e.g.*, a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be formulated for administration in any appropriate timing. In some cases, a pharmaceutically acceptable composition containing CX-8998 can be an immediate release composition. The term “immediate release” as used herein refers to a composition that is formulated to release all (*e.g.*, 100%) or substantially all (*e.g.*, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 97%, at least 98%, or at least 99%) of the active ingredient (*e.g.*, one or more T-type calcium channel antagonists such as CX-8998) within about 30 minutes (*e.g.*, about 35 minutes, about 40 minutes, about 45 minutes, about 50 minutes, or about 60 minutes) following administration of the composition. For example, an immediate release composition including CX-8998 can be formulated to release at least 75% of the CX-8998 within about 45 minutes. In some cases, in an immediate release composition no deliberate effort is made to modify the release rate of the active ingredient. In some cases, a pharmaceutically acceptable composition containing CX-8998 can be a controlled release composition (*e.g.*, a modified release composition) such as a delayed release composition, a sustained release composition, or an extended release composition. The term “controlled release” as used herein refers to a compositions that is formulated to release the active ingredient (*e.g.*, one or more T-type calcium channel antagonists such as CX-8998) in a manner that can optimize a plasma concentration profile of the active ingredient and/or is more convenient for the patient (*e.g.*, allows for less frequent administration). In some cases a controlled release composition can contain a single component. In some cases, a controlled release composition can include a plurality (*e.g.*,

two, three, or more) of components each of which is formulated to release the active ingredient in a specific manner. For example, a controlled release composition can include one or more components formulated for immediate release and one or more components formulated for delayed and/or sustained release. The term “delayed release” 5 as used herein refers to a composition that is formulated to delay release of the active ingredient (e.g., one or more T-type calcium channel antagonists such as CX-8998). For example, when the composition is an oral dosage form, a delayed release composition can be formulated to delay release of the active ingredient until the composition has passed through the stomach (e.g., to prevent the drug from being destroyed or inactivated 10 by, for example, gastric juices or where it may irritate the gastric mucosa). In some cases, a delayed release composition can be formulated to delay release until the dosage form or one or more components of the dosage form has passed further down the intestinal tract. For example, a composition including CX-8998 can be coated with a delayed release 15 coating to obtain a delayed release composition. In some cases, delayed release coatings can be formed from one or more slowly eroding polymers. In some cases, delayed release coatings can be formed from one or more pH independent polymers. In some cases, delayed release coatings can be formed from one or more pH-sensitive polymers. For example, pH-sensitive enteric polymers are insoluble at low pH but soluble at higher pH, such that an enteric polymer can form an impermeable layer in the low pH of the stomach 20 (e.g., at a pH of about 1 to about 3) but can swell and then erode once exposed to the more neutral pH of the intestines (e.g., at a pH of about 5 to about 8), such as a pH of greater than about 6 as in the small intestine or a pH of greater than about 7 as in the colon. For example, pH-sensitive carbomers are substantially insoluble at low pH (e.g., at 25 a pH of about 1 to about 5) but swell to form thick gels at neutral and alkaline pH values (e.g., at a pH of greater than about 6). In some cases, a pharmaceutically acceptable composition containing CX-8998 can be a sustained release composition. When a composition (e.g., a solid composition including one or more particles such as one or more granules, one or more pellets, one or more beads, one or more microparticles, and/or one or more nanoparticles) contains a coating, the coating can be any appropriate 30 thickness. For example, a coating can have a thickness that is from about 50  $\mu\text{m}$  to about

100  $\mu\text{m}$  (e.g., from about 50  $\mu\text{m}$  to about 90  $\mu\text{m}$ , from about 50  $\mu\text{m}$  to about 80  $\mu\text{m}$ , from about 50  $\mu\text{m}$  to about 70  $\mu\text{m}$ , from about 50  $\mu\text{m}$  to about 60  $\mu\text{m}$ , from about 60  $\mu\text{m}$  to about 100  $\mu\text{m}$ , from about 70  $\mu\text{m}$  to about 100  $\mu\text{m}$ , from about 80  $\mu\text{m}$  to about 100  $\mu\text{m}$ , from about 90  $\mu\text{m}$  to about 100  $\mu\text{m}$ , from about 60  $\mu\text{m}$  to about 90  $\mu\text{m}$ , from about 70  $\mu\text{m}$  to about 80  $\mu\text{m}$ , from about 60  $\mu\text{m}$  to about 70  $\mu\text{m}$ , from about 70  $\mu\text{m}$  to about 80  $\mu\text{m}$ , or from about 80  $\mu\text{m}$  to about 90  $\mu\text{m}$ ). For example, a coating can have a thickness that is effective to increase the weight the coated particle (e.g., as compared to a particle that is not coated) by about 20%. The term “sustained release” (SR) as used herein refers to a composition that is formulated to release the active ingredient (e.g., one or more T-type calcium channel antagonists such as CX-8998) at a rate that can maintain a substantially constant drug concentration (e.g., a minimum effective concentration) for a prolonged period of time. In some cases, sustained release compositions can maintain a substantially constant drug concentration (e.g., a minimum effective concentration) for a specific period of time. For example, sustained release compositions can include one or more hydrophilic polymers that can swell upon contact with water and can impede the release of the active agent. For example, sustained release compositions can include one or more coatings comprising an insoluble polymer such as ethyl cellulose and a soluble pore-forming agent. For example, when a sustained release composition is formulated as a bead or a pellet, the sustained release composition can include one or more polymers (e.g., pH-insensitive polymers and/or pH-sensitive polymers) in the formulation. In some cases, a pharmaceutically acceptable composition containing CX-8998 can be a controlled release composition.

25 In some cases, a controlled released composition release at least a portion of the active ingredient (e.g., one or more T-type calcium channel antagonists such as CX-8998) rapidly in what is termed “burst release.” In some cases, a burst release from a controlled release composition or from a component of a controlled release composition can be used as in addition to an immediate release component of a composition. In some cases, a burst release from a controlled release composition or from a component of a controlled release composition can be used as a substitute for an immediate release component of a composition.

In some cases, a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein can include at least one component (e.g., a first component) that includes a delayed release and/or sustained release composition, and, optionally, a component (e.g., a second component) that includes an immediate release composition. For example, when a composition described herein includes CX-8998, the composition can, in some embodiments include at least a first component that is formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component that is formulated for immediate release of CX-8998. In some cases where a pharmaceutically acceptable composition includes one or more T-type calcium channel antagonists described herein includes at least a first component formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component that is formulated for immediate release of CX-8998, the composition can include any appropriate ratio of the components. When a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein includes a first component formulated for delayed and/or sustained release of CX-8998 and a second component that is formulated for immediate release of CX-8998, the composition can include any appropriate amount (e.g., about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%) of the first component and any appropriate amount (e.g., about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%) of the second component. For example, the composition can include about 40% of a first component that is formulated for delayed and/or sustained release of CX-8998 and about 60% of a second component that is formulated for immediate release of CX-8998. For example, the composition can include about 25% of a first component that is formulated for delayed and/or sustained release of CX-8998 and about 35% of a second component that is formulated for delayed and/or sustained release of CX-8998 (e.g., a second component that is formulated for a delayed and/or sustained release of CX-8998 that is different (e.g., in its composition and/or in its release profile) of the first

component), and about 40% of a third component that is formulated for immediate release of CX-8998. In some cases where a composition is designed to release the active ingredient (e.g., one or more T-type calcium channel antagonists such as CX-8998) at two or more different times, a first release (e.g., a delayed and/or sustained release) and a 5 subsequent release (e.g., an immediate release) can overlap. In some cases where a composition is designed to release the active ingredient (e.g., one or more T-type calcium channel antagonists such as CX-8998) at two or more different times, a first release (e.g., a delayed and/or sustained release) and a subsequent release (e.g., an immediate release) can be serial (e.g., do not overlap).

10 The release rate of a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be determined using any appropriate method. For example, dissolution testing (e.g., single-stage or two-stage dissolution 15 testing) with high-performance liquid chromatography (HPLC) and/or spectrophotometry can be used to determine the rate at which one or more T-type calcium channel antagonists (e.g., CX-8998) is/are released from a composition containing one or more T-type calcium channel antagonists. In some cases, the release rate of a composition can be determined as described elsewhere (see, e.g., United States Pharmacopeia (USP) chapter 117).

20 A T-type calcium channel antagonist in a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can have any appropriate dissolution rate. In some cases, a T-type calcium channel antagonist in a composition described herein can have essentially the same rate of dissolution (e.g., a rate of dissolution that is 25 about 90% to about 110% the same) as a substantially pure T-type calcium channel antagonist (e.g., a T-type calcium channel antagonist that is not present in a composition). For example, when a T-type calcium channel antagonist in a composition described herein is CX-8998, the CX-8998 in the composition can have essentially the same rate of dissolution as substantially pure CX-8998 (e.g., when surface area, stirring speed, pH, 30 and/or ionic-strength of the dissolution medium are kept constant).

A composition (*e.g.*, a pharmaceutically acceptable composition) described herein (*e.g.*, a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be designed for any appropriate type of administration (*e.g.*, oral, topical, parenteral, or inhaled administration). In some cases, a composition can be designed for 5 oral administration (*e.g.*, as an oral dosage form). For example, when a composition includes CX-8998, the composition can be designed as an oral CX-8998 dosage form.

When being administered by oral administration, a pharmaceutical composition containing one or more T-type calcium channel antagonists (*e.g.*, one or more Cav3 antagonists such as CX-8998) can be in the form of, for example, a pill, tablet, capsule, 10 solution, or suspension. In some cases, a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein can include a capsule including a plurality of Cav3 antagonist-containing pellets and/or Cav3 antagonist-containing beads. In some cases, a capsule can include a component (*e.g.*, a first component) that includes a delayed release and/or sustained release composition, 15 and, optionally, a component (*e.g.*, a second component) that includes an immediate release composition. For example, when a composition includes CX-8998, the composition can include a capsule containing a plurality of CX-8998-containing pellets and/or CX-8998-containing beads, a portion of which are formulated for immediate release and a portion of which are formulated for delayed and/or sustained release. In 20 some cases, a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein can include a capsule including a plurality of Cav3 antagonist-containing granules. For example, when a composition includes CX-8998, the composition can include a capsule containing a plurality of CX-8998-containing granules, a portion of which are formulated for immediate release and a 25 portion of which are formulated for delayed and/or sustained release. In some cases, a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein can include a tablet including two or more (*e.g.*, two, three, four, or more) layers. In some cases, a tablet can include a component (*e.g.*, a first layer) that includes a delayed release and/or sustained release composition, and, optionally, a 30 component (*e.g.*, a second layer) that includes an immediate release composition. For

example, when a composition includes CX-8998, the composition can include a tablet containing a layer of CX-8998 formulated for immediate release and a layer of CX-8998 formulated for delayed and/or sustained release. In some cases, a pharmaceutically acceptable composition including one or more T-type calcium channel antagonists described herein can include a tablet including a core and one or more (e.g., one, two, three, or more) coatings. For example, in some cases where a tablet includes a core and a coating, a tablet core can contain CX-8998 formulated for delayed and/or sustained release, and the tablet core can be coated with a coating containing CX-8998 formulated for immediate release. For example, in some cases where a tablet includes a core and a coating, a tablet core containing CX-8998 can be coated with a coating that delays and/or sustains the release of CX-8998 from the core, and the tablet core can be further coated with CX-8998 formulated for immediate release. In some cases, where a tablet includes a core and a coating, the tablet can be an osmotic pump tablet (e.g., a tablet have an osmotic pressure-driven delivery system). For example, an osmotic pump tablet can include a core and a coating where the tablet core can include CX-8998 and an osmotic agent, and the tablet core can be coated with a coating containing a semipermeable membrane having one or more holes (e.g., at least one precisely drilled hole) such that water diffusing across the semipermeable membrane can generate an osmotic pressure that can force the CX-8998, as a solution and/or suspension, out of the tablet core through the hole(s). In some cases, an osmotic pump table can be coated one or more coatings containing CX-8998 (e.g., CX-8998 formulated for immediate release). In some cases, a capsule can include a component (e.g., one or more particles such as a tablet, beads, pellets, granules, and/or a powder, or mixtures thereof) that includes an immediate release composition, and a component (e.g., a tablet or a coating) that includes CX-8998 formulated for delayed release and/or sustained release. For example, when a composition includes CX-8998, the composition can include a first tablet containing CX-8998 formulated for delayed and/or sustained release and, optionally, a second tablet containing CX-8998 formulated for immediate release. For example, when a composition includes CX-8998, the composition can include a plurality of beads, pellets, granules, and/or a powder containing CX-8998 formulated for immediate release and a

tablet containing CX-8998 formulated for delayed and/or sustained release. In some cases, the composition comprises one or more components for immediate release and one or more components for delayed and/or sustained release.

When being administered by topical administration, a pharmaceutical composition containing one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be administered transdermally, epidermally, ophthalmically, and/or to mucous membranes (e.g., intranasally, vaginally, and rectally). When being administered by topical administration, a pharmaceutical composition containing one or more Cav3 antagonists can be in the form of, for example, transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders (e.g., lyophilized powders).

When being administered by parenteral administration, a pharmaceutical composition containing one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be administered by intravenous, intraarterial, subcutaneous, intraperitoneal, intramuscular intracranial (e.g., intrathecal or intraventricular) injection or infusion. When being administered by parenteral administration, a pharmaceutical composition containing one or more T-type calcium channel antagonists can be in the form of, for example, liquids, gels, drops, suppositories, sprays, powders (e.g., lyophilized powders), emulsions, suspensions, microparticles, in-situ gels, and drug-containing implants. When being administered by parenteral administration, a pharmaceutical composition containing one or more T-type calcium channel antagonists can be administered in the form of a one or more bolus doses or may be administered by a continuous perfusion (e.g., by an infusion pump or by an implantable device that provides gradual release).

When being administered by inhaled administration (e.g., inhalation), a pharmaceutical composition containing one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be pulmonary (e.g., can be administered to the nasal cavity, upper airways, or lower airways). For example, administration of a pharmaceutical composition containing one or more T-type calcium channel antagonists can include inhalation or insufflation of a liquid (e.g., an aerosol)

and/or a solid (e.g., powder). When being administered by inhaled administration, a pharmaceutical composition containing one or more T-type calcium channel antagonists can be in the form of, for example, liquids (e.g., solutions and suspensions), gels, and powders (e.g., lyophilized powders). When being administered by inhaled  
5 administration, a pharmaceutical composition containing one or more T-type calcium channel antagonists can be administered by, for example, a nasal spray pump, a nebulizer, a metered dose inhaler, or a dry powder inhaler.

A composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be administered locally or systemically. In some cases, a composition containing one or more T-type calcium channel antagonists can be administered systemically by an oral administration to a mammal (e.g., a human). For example, when a composition includes CX-8998, the composition can be formulated as an oral dosage form such as a capsule (e.g., a capsule containing a plurality of CX-8998-containing pellets and/or CX-8998-containing beads, a portion of which are formulated for immediate release and a portion of which are formulated for delayed and/or sustained release).

Any appropriate method can be used to formulate a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998). Examples of methods that can be used to formulate solid compositions described herein include, without limitation, dry blending, wet granulation, spray-drying, hot-melt extrusion, roller compaction, compression, extrusion, spheroidization, fluid bed drying, tray drying, fluid bed coating, pan coating, and encapsulation. Examples of methods that can be used to formulate liquid and semisolid compositions described herein include, without limitation, blade mixing, high-shear mixing, homogenization, microfluidizing, media milling, filtration, lyophilization, and autoclaving. In cases where a composition described herein includes pellets and/or beads, the pellets and/or beads can be generated by extrusion and spheroidization of a wet mass containing the active ingredient (e.g., one or more T-type calcium channel antagonists such as CX-8998) and, optionally, additional components  
25  
30

such as selected excipients (e.g., lactose monohydrate, crospovidone (e.g., polyplasdone XL-10), citric acid, sodium lauryl sulfate (SLS), hydroxypropylcellulose (HPC) such as HPC-SL, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, povidone, and talc). For example, extrusion and 5 spheronization of a wet mass of CX-8998, lactose monohydrate, crospovidone, citric acid, and sodium lauryl sulfate can be used to generate pellets and/or beads (e.g., immediate release pellets and/or beads) containing, by weight, about 5% CX-8998, about 60% lactose monohydrate, about 25% crospovidone, about 8% citric acid, and about 2% SLS. For example, extrusion and spheronization of a wet mass of CX-8998, lactose 10 monohydrate, crospovidone, citric acid, and sodium lauryl sulfate can be used to generate pellets and/or beads (e.g., immediate release pellets and/or beads) containing, by weight, about 5% CX-8998, about 60% lactose monohydrate, about 25% crospovidone, about 8% citric acid, and about 2% SLS. In some cases, the pellets and/or beads can be prepared by blending the dry ingredients, slowly adding water while stirring in a planetary mixer, 15 extruding the resulting wet mass, spheronizing the extrudate, and then drying the resulting pellets and/or beads in a fluid bed dryer. These processes will be understood by those skilled in the art. In cases where a composition described herein includes granules, the granules can be generated by wet granulation of a wet mass containing the active ingredient (e.g., one or more T-type calcium channel antagonists such as CX-8998) and, 20 optionally, additional components such as selected excipients (e.g., lactose monohydrate, crospovidone (e.g., polyplasdone XL-10), citric acid, SLS, HPC such as HPC-SL, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and TPGS). For example, wet granulation of a wet mass of CX-8998, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, HPC, magnesium stearate, and TPGS 25 can be used to generate granules (e.g., immediate release granules) containing, by weight, about 2% CX-8998, about 20% lactose monohydrate, about 63% microcrystalline cellulose, about 3% croscarmellose sodium, about 3% HPC, about 0.5% magnesium stearate, and about 10% TPGS. In some cases, the granules can be prepared by blending dry powders in a V-blender or in the bowl of a planetary mixer or high-shear granulator, 30 granulating with addition of water or binder solution in a planetary mixer or high-shear

mixer, milling or screening, drying in a fluid bed dryer or tray dryer, optionally milling the dried granules, and then blending them with lubricant and/or glidant. These processes will be understood by those skilled in the art.

In cases where a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) includes delayed release pellets and/or beads and/or sustained release pellets and/or beads, the delayed release pellets and/or beads and/or sustained release pellets and/or beads can be generated by coating pellets and/or beads with a sustained release coating and/or a delayed release coating. For example, pellets and/or beads (e.g., immediate release pellets and/or beads) can be coated with a sustained release coating and/or a delayed release coating using a fluid bed coater with Wurster inserts. For example, inert, edible spheres such as sugar spheres (nonpareils) or microcrystalline cellulose spheres (suglets) (e.g., edible spheres containing (e.g., coated with) one or more T-type calcium channel antagonists) can be coated with a sustained release coating and/or a delayed release coating using a fluid bed coater with Wurster inserts. In some cases, a coating can be applied (e.g., to a sphere, pellet, and/or bead) using a film coating method such as using a fluidized bed spray coating process. Other processes for coating spheres, pellets, and/or beads are understood by those skilled in the art. In some cases, a sustained release bead/pellet and/or a delayed release pellet/bead can be generated by coating an immediate release pellet/bead. For example, a delayed release pellet/bead and/or a sustained release bead/pellet can be generated by coating an immediate release pellet/bead with a sustained release coating and/or a delayed release coating. In some cases, a delayed release pellet/bead and/or a sustained release bead/pellet can be generated independently of any immediate release pellet/bead. For example, a delayed release pellet/bead and/or a sustained release bead/pellet can be generated by formulating a pellet/bead (e.g., an uncoated pellet/bead) to provide gradual release of the active ingredient (e.g., CX-8998).

A composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be sterilized using any appropriate method. In some cases, a composition

described herein can be sterilized by conventional sterilization techniques. In some cases, a composition described herein can be filtration sterilized.

A composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can have any appropriate pH. For example, the pH of a pharmaceutically acceptable composition containing one or more T-type calcium channel antagonists can be from about 3 to about 11. In some cases, the pH of a pharmaceutically acceptable composition containing one or more T-type calcium channel antagonists can be from 5 to about 9. In some cases, the pH of a pharmaceutically acceptable composition containing one or more T-type calcium channel antagonists can be from about 7 to about 8. It will be understood that use of certain additional components (e.g., pharmaceutically acceptable carriers) can alter (e.g., can be used to alter) the pH of a composition described herein.

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include one or more detectable labels. In some cases, a detectable label can be suitable for *in vivo* use within a mammal (e.g., a human).

Examples of detectable labels include, without limitation, radioisotopes (e.g., <sup>14</sup>C), non radioactive isotopes (e.g., deuterium, and <sup>13</sup>C), spin labels, fluorescent tags, and enzymes. For example, when a composition includes CX-8998, the CX-8998 can be <sup>14</sup>C-labeled CX-8998. For example, a detectable label can be detected to allow imaging of the compositions following administration to a mammal. Imaging can enable a physician or another professional in the field to determine the spatial and/or temporal presence of an administered composition within a mammal.

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include one or more T-type calcium channel antagonists, methylcellulose, polyethylene glycol (PEG) 400, PEG-200, Tween-80, and/or cyclodextrin. For example, when a composition includes CX-8998, the composition can include CX-8998 and about 0.5 to about 1% methylcellulose. For example, when a composition includes CX-8998, the composition can include CX-8998

and about 90% PEG 400. For example, when a composition includes CX-8998, the composition can include CX-8998 and about 80% PEG-200. For example, when a composition includes CX-8998, the composition can include CX-8998 and about 10% Tween-80. For example, when a composition includes CX-8998, the composition can 5 include CX-8998 and about 30% cyclodextrin.

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include one or more T-type calcium channel antagonists, methylcellulose, and/or polysorbate-80. For example, when a composition 10 includes CX-8998, the composition can include CX-8998, about 0.5% methylcellulose, and about 10% polysorbate-80. For example, when a composition includes CX-8998, the composition can include CX-8998, about 0.5% methylcellulose, and about 0.1% polysorbate-80.

In some cases, a composition (e.g., a pharmaceutically acceptable composition) 15 described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include about 2 milligrams of one or more T-type calcium channel antagonists as a blend of components that are wet granulated together and magnesium stearate. For example, when a composition includes CX-8998, the composition can include about 2 milligrams of CX-8998 (e.g., a free base equivalent of 20 CX-8998) as a blend with microcrystalline cellulose, lactose, croscarmellose sodium, vitamin E PEG succinate, and hydroxypropyl cellulose that are wet granulated together, and magnesium stearate.

In some cases, a composition (e.g., a pharmaceutically acceptable composition) 25 described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include about 10 mg of one or more T-type calcium channel antagonists in an immediate release component and about 10 mg of one or more T-type calcium channel antagonists in a delayed release component. For example, when a composition includes CX-8998, the composition can include about 10 mg of CX-8998 (e.g., a free base equivalent of CX-8998) in an immediate release component and about 30 10 mg of CX-8998 (e.g., a free base equivalent of CX-8998) in a delayed release

component. In some cases, the immediate release component can include immediate release beads formed by extrusion and spheronization, and the delayed release component can include beads formed by extrusion and spheronization and coated with one or more pH-sensitive enteric polymers having a dissolution pH or about pH 5.5 to about pH 7 (e.g., pH 6, pH 6.5, or pH 7).

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include about 7 milligrams of one or more T-type calcium channel antagonists in an immediate release component and about 13 milligrams of one or more T-type calcium channel antagonists in a delayed release component. For example, when a composition includes CX-8998, the composition can include about 7 milligrams of CX-8998 (e.g., a free base equivalent of CX-8998) in an immediate release component and about 13 milligrams of CX-8998 (e.g., a free base equivalent of CX-8998) in a delayed release component. In some cases, the immediate release component can include immediate release beads formed by extrusion and spheronization, and the delayed release component can include beads formed by extrusion and spheronization and coated with one or more pH-sensitive enteric polymers having a dissolution pH of about pH 5.5 to about pH 7 (e.g., pH 6, pH 6.5, or pH 7).

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be a controlled release composition in a solid dosage form (e.g., a pill, a capsule, and a tablet) including a first component having granules containing CX-8998 which are formulated for delayed and/or sustained release of CX-8998 and a second component having granules containing CX-8998 which are formulated for immediate release of CX-8998. For example, a controlled release capsule can include a first component having granules containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, also can include a second component having granules containing CX-8998 and formulated for immediate release of CX-8998. For example, a controlled release tablet can include a first component having granules containing CX-8998 and formulated for delayed and/or sustained release of CX-8998.

and, optionally, also can include a second component having granules containing CX-8998 and formulated for immediate release of CX-8998. In some cases, a first component having granules containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component having granules containing CX-8998 and formulated for immediate release of CX-8998 can be compressed into tablets (e.g., monolithic tablets and tablets having two or more layers).

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be a controlled release composition including two or more (e.g., two, three, four, or more) solid dosage forms (e.g., pills, capsules, and tablets) where at least one solid dosage form contains CX-8998 which is formulated for immediate release of CX-8998 and at least one solid dosage form contains CX-8998 which is formulated for delayed and/or sustained release of CX-8998. For example, a controlled release composition includes two or more solid dosage forms where at least one solid dosage form contains CX-8998 which is formulated for immediate release of CX-8998 and at least one solid dosage form contains CX-8998 which is formulated for delayed and/or sustained release of CX-8998, the two or more solid dosage forms can be make up single dose.

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be a controlled release composition having a capsule containing a first component having one or more (e.g., one, two, three, four, or more) tablets containing CX-8998 which are formulated for delayed and/or sustained release of CX-8998 and/or one or more (e.g., one, two, three, four, or more) mini-tablets containing CX-8998 which are formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component containing CX-8998 which is formulated for immediate release of CX-8998. For example, a controlled release capsule can include a first component having one or more tablets and/or one or more mini-tablets containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, also can include a second component containing CX-8998 and formulated for immediate

release of CX-8998. In some cases, a first component having one or more tablets and/or one or more mini-tablets containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component having one or more tablets and/or one or more mini-tablets containing CX-8998 and formulated for  
5 immediate release of CX-8998 can be within a capsule. In some cases, a first component having one or more tablets and/or one or more mini-tablets containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component having a powder containing CX-8998 formulated for immediate release of CX-8998 can be within a capsule. In some cases, a first component having one or more tablets and/or one or more mini-tablets containing CX-8998 and formulated for delayed  
10 and/or sustained release of CX-8998 and, optionally, a second component having granules containing CX-8998 formulated for immediate release of CX-8998 can be within a capsule. In some cases, a first component having one or more tablets and/or one or more mini-tablets containing CX-8998 and formulated for delayed and/or sustained  
15 release of CX-8998 and, optionally, a second component having beads and/or pellets containing CX-8998 formulated for immediate release of CX-8998 can be within a capsule.

In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel  
20 antagonists such as CX-8998) can be a controlled release composition having a capsule containing a first solid component (e.g., granules, beads, pellets, and tablets) containing CX-8998 which is formulated for delayed and/or sustained release of CX-8998 and, optionally, a second liquid component (e.g., a solution or a suspension) containing CX-8998 which is formulated for immediate release of CX-8998. For example, a controlled  
25 release capsule can include a first solid component having granules containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and can include a second liquid component containing CX-8998 formulated for immediate release of CX-8998. In some cases, a first component having granules containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, a second liquid component  
30 containing CX-8998 formulated for immediate release of CX-8998 can be within a

capsule. In some cases, a first component having beads and/or pellets containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, a second liquid component containing CX-8998 formulated for immediate release of CX-8998 can be within a capsule. In some cases, a first component having one or more (e.g., 5 one, two, three, four, or more) tablets containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, a second liquid component containing CX-8998 formulated for immediate release of CX-8998 can be within a capsule and/or one or more (e.g., one, two, three, four, or more) mini-tablets containing CX-8998 which are formulated for delayed and/or sustained release of CX-8998.

10 In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be a controlled release composition having a first (e.g., exterior) capsule and a second (e.g., interior) capsule (e.g., a second capsule sized to fit within the first capsule such that a space is present between the outer surface of the 15 second capsule and the inner surface of the first capsule) and containing a first component containing CX-8998 which is formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component containing CX-8998 which is formulated for immediate release. For example, a controlled release capsule that includes an interior capsule that fits within the controlled release capsule, can include a first 20 component containing CX-8998 and formulated for delayed and/or sustained release of CX-8998, and, optionally, can include a second component having granules containing CX-8998 and formulated for immediate release of CX-8998 contained within the interior capsule and/or in the space present between the interior capsule and the exterior capsule. In some cases, an exterior capsule can contain an interior capsule containing a first 25 component that is a solid component (e.g., granules, beads, pellets, and tablets such as mini-tablets) containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component that is a liquid component (e.g., a solution or a suspension) containing CX-8998 formulated for immediate release of CX-8998, where the liquid component containing CX-8998 and formulated for immediate release of 30 CX-8998, when present, is present in a space between the outer surface of the interior

capsule and the inner surface of the exterior capsule. In some cases, an exterior capsule can contain an interior capsule having a first component containing CX-8998 formulated for immediate release of CX-8998, and the interior capsule can include a coating that can delay the release of the first component containing CX-8998 formulated for immediate release of CX-8998.

5 In some cases, a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be a controlled release composition that is a suspension including a liquid phase (e.g., a solution) and a plurality of solid components (e.g., granules, beads, pellets, and tablets such as mini-tablets) suspended in the liquid phase. For example, a controlled release suspension including a liquid phase and a plurality of solid components can include one or more T-type calcium channel antagonists such as CX-8998 in a liquid phase, can include one or more T-type calcium channel antagonists in solid components suspended in the liquid phase, or can include one or 10 more T-type calcium channel antagonists in both a liquid phase and in solid components suspended in the liquid phase. In some cases, a plurality of solid components containing CX-8998 and formulated for immediate release of CX-8998 and a second plurality of solid components containing CX-8998 and formulated for delayed and/or sustained 15 release of CX-8998 can be suspended in a liquid phase of a controlled release suspension. In some cases, a controlled release suspension can include a liquid phase containing CX- 20 8998 and formulated for immediate release of CX-8998 and can include a plurality of solid components containing CX-8998 and formulated for delayed and/or sustained release of CX-8998 suspended in the liquid phase.

#### *Treatment Methods*

25 This document also provides methods for treating a mammal (e.g., a human) having, or risk or developing, one or more movement disorders. For example, a mammal having, or at risk of developing, one or more movement disorders can be administered a composition described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) to treat the mammal. The term “treating” or

“treatment” refers to one or more of (1) preventing a movement disorder; *e.g.*, preventing a movement disorder in an individual who may be predisposed to the movement disorder but does not yet experience or display the pathology or symptomatology of the movement disorder; (2) inhibiting a movement disorder; *e.g.*, inhibiting a movement disorder in an individual who is experiencing or displaying the pathology or symptomatology of the movement disorder (*i.e.*, arresting further development of the pathology and/or symptomatology); and (3) ameliorating a movement disorder; for example, ameliorating a movement disorder in an individual who is experiencing or displaying the pathology or symptomatology of the movement disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of movement disorder or reducing or alleviating one or more symptoms of the movement disorder. For example, when a mammal having, or at risk of developing, a movement disorder is administered a composition including CX-8998, the composition including CX-8998 can be effective to reduce or eliminate one or more symptoms of the movement disorder. Examples of symptoms of movement disorders include, without limitation, tremors (*e.g.*, rhythmic tremors), unsteady gait (*e.g.*, ataxia), dystonic movements, freezing (bradykinesia), tics, spasms, other dyskinetic movements, seizures, pain, sensory problems, psychiatric symptoms, cognitive impairment, hearing impairment, and mood changes. When a symptom is a tremor, the tremor can be any appropriate type of tremor (*e.g.*, a familial tremor, an action tremor, a postural tremor, a kinetic tremor, and/or a resting tremor). In some cases, a mammal having, or at risk of developing, a movement disorder can be administered a composition including CX-8998, to reduce or eliminate tremors in the mammal. When a symptom is a tremor, the tremor can affect any appropriate part of a mammal (*e.g.*, hands, head, voice, arms, fingers, legs, chin, and other parts of a mammal’s body). In some cases, a mammal having, or at risk of developing, a movement disorder can be administered a composition including CX-8998, to reduce or eliminate tremors in the mammal’s hand(s). For example, one or more T-type calcium channel antagonists can be administered to a mammal in need thereof (*e.g.*, a mammal having, or at risk of developing, a movement disorder) as described herein to reduce the severity of one or more symptoms of a movement disorder in the mammal by, for example, 10, 20,

30, 40, 50, 60, 70, 80, 90, 95, or more percent. Any appropriate method can be used to evaluate the severity of a movement disorder and/or a symptom of a movement disorder. In some cases, the severity of a movement disorder and/or a symptom of a movement disorder can include evaluating one or more global functional measures. In some cases, 5 the severity of a movement disorder and/or a symptom of a movement disorder can include evaluating one or more specific functional measures. Examples of methods that can be used to evaluate the severity of a movement disorder and/or a symptom of a movement disorder include, without limitation, measurements of activities of daily living (e.g., as measured using TETRAS), clinician global impression of improvement (e.g., as 10 measured using CGI-I), patient global impression of change (e.g., as measured using PGIC), tremor specific goal attainment (e.g., as measured using GAS), quality of life (e.g., as measured using QUEST tremor medication satisfaction sub-item), and archimedes spiral (e.g., as measured using pen and paper as in the TETRAS-PS sub-item and/or measured digitally using a tablet and stylus such as in iMotor). In some cases, 15 methods for measuring the severity of a movement disorder and/or a symptom of a movement disorder can be as described in the Examples section. For example, when using TETRAS to measure activities of daily living, the higher the score the worse the tremor such that a decrease in score is an improvement in tremor. In some cases, methods that can be used to evaluate the severity of a movement disorder and/or a symptom of a movement disorder can be as described elsewhere (see, e.g., Elble et al, 2013 *Movement 20 Disorders*, 28 1793; Fahn et al. “Clinical rating Scale for Tremor,” p. 225-34 In: Jankovic J and Tolosa E. *Parkinson’s Disease and Movement Disorders*. 1988 Baltimore-Milnich: Urban & Schwarzenberg; and Haubenberger et al, 2016 *Movement Disorders*, 31, No. 9; Fahn et al., “Members of the UPDRS Development Committee,” 25 pp 153-163 and 293-304 In: Fahn et al. (eds.) *Recent Developments in Parkinson’s Disease*, Vol 2. 1987 Florham Park, NJ. Macmillan Health Care Information; Treatment guidelines for essential tremor by the American academy of neurology such as those available at the website [aan.com/Guidelines/home/GuidelineDetail/492](http://aan.com/Guidelines/home/GuidelineDetail/492); and Treatment guidelines for Parkinson’s disease by the American academy of neurology such as those

available at the website [movementdisorders.org/MDS-Files1/Resources/PDFs/TreatmentsforMotorSymptomsofPD-2018.pdf](http://movementdisorders.org/MDS-Files1/Resources/PDFs/TreatmentsforMotorSymptomsofPD-2018.pdf).

In some cases, compositions (e.g., pharmaceutically acceptable compositions) including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) when the mammal is in a fasting state. For example, a mammal can have fasted (or have been instructed to fast) for at least 4 hours (e.g., about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours) prior to administering a composition including one or more T-type calcium channel antagonists.

In some cases, compositions (e.g., pharmaceutically acceptable compositions) including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) when the mammal is in a fed (e.g., non-fasting) state.

Any appropriate mammal having, or at risk of developing, a movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease) can be treated as described herein. Examples of mammals that can be treated as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998) include, without limitation, humans, non-human primates (e.g., monkeys), dogs, cats, horses, cows, pigs, sheep, mice, and rats. In some cases, a human having, or at risk of developing, a movement disorder can be treated with a composition containing one or more T-type calcium channel antagonists such as CX-8998 to reduce or eliminate one or more symptoms of the movement disorder.

When treating a mammal having one or more movement disorders as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998), the mammal can be any appropriate age. In some cases, appropriate humans for treatment are adults (e.g., young adults, middle-aged adults, and elderly adults). For example, an adult human can be 18 years of age or older (e.g., 20 years of age or older, 30 years of age or older, 40 years of age or older, 50 years

of age or older, 60 years of age or older, 65 years of age or older, 70 years of age or older, or 75 years of age or older). In some cases, an adult can be from about 18 years of age to about 100 years of age (e.g., from about 18 years to about 90 years, from about 18 years to about 80 years, from about 18 years to about 75 years, from about 18 years to about 70 years, from about 18 years to about 65 years, from about 18 years to about 60 years, from about 18 years to about 55 years, from about 18 years to about 50 years, from about 18 years to about 45 years, from about 18 years to about 40 years, from about 20 years to about 100 years, from about 30 years to about 100 years, from about 40 years to about 100 years, from about 50 years to about 100 years, from about 60 years to about 100 years, from about 65 years to about 100 years, from about 70 years to about 100 years, from about 75 years to about 100 years, from about 80 years to about 100 years, from about 20 years to about 55 years, from about 20 years to about 40 years, from about 22 years to about 39 years, from about 40 years to about 80 years, from about 40 years to about 66 years, from about 40 years to about 60 years, from about 50 years to about 80 years, from about 55 years to about 75 years, from about 57 years to about 75 years, or from about 57 years to about 70 years of age). In some cases, appropriate humans for treatment are adolescents (e.g., a human no more than 18 years old. For example, a human adolescents can be from about 1 year of age to about 18 years of age (e.g., from about 1 to about 17 years of age, from about 1 to about 16 years of age, from about 1 to about 15 years of age, from about 1 to about 14 years of age, from about 1 to about 13 years of age, from about 1 to about 12 years of age, from about 1 to about 11 years of age, from about 1 to about 10 years of age, from about 1 to about 8 years of age, from about 1 to about 5 years of age, from about 1 to about 3 years of age, from about 5 to about 18 years of age, from about 10 to about 18 years of age, from about 12 to about 18 years of age, from about 15 to about 18 years of age, from about 16 to about 18 years of age, from about 2 to about 16 years of age, from about 5 to about 15 years of age, from about 8 to about 12 years of age, from about 2 to about 8 years of age, or from about 5 to about 15 years of age). For examples, an adolescent can be about 16 years of age.

When treating a mammal having one or more movement disorders as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998), the mammal can be a female or a male.

When treating a mammal having one or more movement disorders as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998), a composition containing one or more T-type calcium channel antagonists such as CX-8998 can be administered at any appropriate time. In some cases, a composition containing one or more T-type calcium channel antagonists such as CX-8998 can be administered to a mammal in the morning. For example, a composition containing one or more T-type calcium channel antagonists such as CX-8998 can be administered to a mammal between from about 6 am to about noon (e.g., from about 6 am to about 11 am, from about 6 am to about 10 am, from about 6 am to about 9 am, from about 6 am to about 8 am, from about 6 am to about 7 am, from about 7 am to about noon, from about 8 am to about noon, from about 9 am to about noon, from about 10 am to about noon, from about 11 am to about noon, from about 7 am to about 11 am, from about 8 am to about 10 am, from about 7 am to about 9 am, from about 8 am to about 10 am, or from about 9 am to about 11 am). For example, a composition containing one or more T-type calcium channel antagonists such as CX-8998 can be administered to a mammal within about 4 hours (e.g., about 4 hours after waking, about 3 hours after waking, about 2 hours after waking, about 1 hour after waking, about 30 minutes after waking, or immediately after waking).

When treating a mammal having one or more movement disorders as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998), the mammal can have any appropriate movement disorder(s). In some cases, a movement disorder can include tremors. For example, the methods and materials provided herein can be used to treat a mammal having, or at risk of developing, tremors. Examples of movement disorders that can be treated by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998 include, without limitation, essential tremor, Parkinson's disease (e.g., tremor associated with Parkinson's disease), ataxias (e.g., spinocerebellar ataxia and

Friedreich's ataxia), epilepsies (e.g., idiopathic generalized epilepsy with absence seizures and pediatric epilepsies), dystonias (e.g., generalized dystonia, focal dystonia, pantothenate kinase-associated neurodegeneration (PKAN), and Hallervorden-Spatz disease), hemiballismus, cerebellar disorders, athetosis, spasticity, bradykinesia, tardive dyskinesia, Huntington's disease, myoclonus, Tourette's syndrome, chorea, tics, progressive supranuclear palsy, multiple system atrophy, corticobasal ganglionic degeneration, plasticity, restless legs/arms syndrome, orthostatic tremor, stiff person syndrome, hyperkinetic movement disorders, Rett syndrome, and Wilson's disease. In some cases, a mammal having, or at risk of developing, essential tremor can be treated by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998. In some cases, a mammal having, or at risk of developing, Parkinson's disease can be treated by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998.

In some cases, compositions (e.g., pharmaceutically acceptable compositions) including one or more T-type calcium channel antagonists (e.g., one or more Cav3 antagonists such as CX-8998) can be administered to a mammal having, or at risk of developing other conditions and/or disorders such as, but not limited to, neuropathic pain, psychiatric disorders, autism spectrum disorders, and obsessive compulsive disorder.

When treating a mammal having one or more movement disorders as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998), the mammal can be administered any appropriate amount of a composition (e.g., a pharmaceutically acceptable composition) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998). In some cases, a mammal having, or at risk of developing, one or more movement disorders can be administered a therapeutically effective amount a composition containing one or more T-type calcium channel antagonists such as CX-8998. The term "therapeutically effective amount" refers to the amount of active compound (e.g., one or more T-type calcium channel antagonists such as CX-8998) that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other

clinician. An effective amount of one or more T-type calcium channel antagonists described herein can vary depending on the severity of the movement disorder and/or one or more symptoms/complications associated with the movement disorder, the route of administration, the age and general health condition of the mammal, excipient usage, the 5 possibility of co-usage with other therapeutic treatments such as use of other agents, and the judgment of the treating physician. For example, a composition (e.g., a composition for use in a veterinary and/or research animal such as a dog or rat) can include a dose of one or more T-type calcium channel antagonists can be from about 1 mg/kg to about 1000 mg/kg of body weight per day (e.g., from about 5 mg/kg to about 1000 mg/kg, from 10 about 10 mg/kg to about 1000 mg/kg, from about 20 mg/kg to about 1000 mg/kg, from about 25 mg/kg to about 1000 mg/kg, from about 30 mg/kg to about 1000 mg/kg, from about 50 mg/kg to about 1000 mg/kg, from about 75 mg/kg to about 1000 mg/kg, from about 100 mg/kg to about 1000 mg/kg, from about 250 mg/kg to about 1000 mg/kg, from about 500 mg/kg to about 1000 mg/kg, from about 750 mg/kg to about 1000 mg/kg, from 15 about 1 mg/kg to about 750 mg/kg, from about 1 mg/kg to about 500 mg/kg, from about 1 mg/kg to about 300 mg/kg, from about 1 mg/kg to about 250 mg/kg, from about 1 mg/kg to about 200 mg/kg, from about 1 mg/kg to about 150 mg/kg, from about 1 mg/kg to about 125 mg/kg, from about 1 mg/kg to about 100 mg/kg, from about 1 mg/kg to about 75 mg/kg, from about 1 mg/kg to about 50 mg/kg, from about 1 mg/kg to about 30 20 mg/kg, from about 5 mg/kg to about 500 mg/kg, from about 10 mg/kg to about 300 mg/kg, from about 15 mg/kg to about 200 mg/kg, from about 20 mg/kg to about 100 mg/kg, from about 25 mg/kg to about 75 mg/kg, from about 10 mg/kg to about 30 mg/kg, from about 20 mg/kg to about 50 mg/kg, from about 30 mg/kg to about 60 mg/kg, or from about 50 mg/kg to about 75 mg/kg of body weight per day). For example, when a 25 composition includes CX-8998, the dose of CX-8998 can be about 10 mg/kg of body weight per day. For example, when a composition includes CX-8998, the dose of CX-8998 can be about 30 mg/kg of body weight per day. For example, when a composition includes CX-8998, the dose of CX-8998 can be about 60 mg/kg of body weight per day. For example, a composition (e.g., a composition for use in a human) can include a dose 30 of one or more T-type calcium channel antagonists can be from about 10  $\mu$ g/kg to about

1000  $\mu\text{g}/\text{kg}$  of body weight per day (*e.g.*, from about 10  $\mu\text{g}/\text{kg}$  to about 900  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 800  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 700  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 600  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 500  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 400  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 300  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 200  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 100  $\mu\text{g}/\text{kg}$ , from about 10  $\mu\text{g}/\text{kg}$  to about 50  $\mu\text{g}/\text{kg}$ , from about 50  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 100  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 200  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 300  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 400  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 500  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 600  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 700  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 800  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 900  $\mu\text{g}/\text{kg}$  to about 1000  $\mu\text{g}/\text{kg}$ , from about 50  $\mu\text{g}/\text{kg}$  to about 900  $\mu\text{g}/\text{kg}$ , from about 100  $\mu\text{g}/\text{kg}$  to about 800  $\mu\text{g}/\text{kg}$ , from about 200  $\mu\text{g}/\text{kg}$  to about 700  $\mu\text{g}/\text{kg}$ , from about 300  $\mu\text{g}/\text{kg}$  to about 600  $\mu\text{g}/\text{kg}$ , from about 100  $\mu\text{g}/\text{kg}$  to about 200  $\mu\text{g}/\text{kg}$ , from about 200  $\mu\text{g}/\text{kg}$  to about 300  $\mu\text{g}/\text{kg}$ , from about 300  $\mu\text{g}/\text{kg}$  to about 400  $\mu\text{g}/\text{kg}$ , from about 400  $\mu\text{g}/\text{kg}$  to about 500  $\mu\text{g}/\text{kg}$ , from about 500  $\mu\text{g}/\text{kg}$  to about 600  $\mu\text{g}/\text{kg}$ , from about 600  $\mu\text{g}/\text{kg}$  to about 700  $\mu\text{g}/\text{kg}$ , from about 700  $\mu\text{g}/\text{kg}$  to about 800  $\mu\text{g}/\text{kg}$ , or from about 800  $\mu\text{g}/\text{kg}$  to about 900  $\mu\text{g}/\text{kg}$  of body weight per day). For example, when a composition includes CX-8998, the dose of CX-8998 can be about 100  $\mu\text{g}/\text{kg}$  of body weight per day. For example, when a composition includes CX-8998, the dose of CX-8998 can be about 300  $\mu\text{g}/\text{kg}$  of body weight per day. For example, when a composition includes CX-8998, the dose of CX-8998 can be about 600  $\mu\text{g}/\text{kg}$  of body weight per day. In some cases, the dose can depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. In some cases, the dose can be increased over time. For example, a dose can be titrated up to a final dose over a period of time (*e.g.*, 1 week, 2 weeks, 3 weeks, or 4 weeks). In some cases, the dose can be decreased over time. For example, a dose can be decreased to a maintenance dose after one or more symptoms have been reduced or eliminated. The dose can be administered, *e.g.*, once a

day, twice a day, three times a day, or four times a day. In some cases, the dose can be administered once daily. In some cases, the dose can be administered twice daily.

In some cases, an effective amount of one or more T-type calcium channel antagonists in a composition (e.g., pharmaceutically acceptable compositions) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be extrapolated from dose-response curves derived from *in vitro* or *in vivo* model test systems. The effective amount (e.g., a therapeutically effective amount) can remain constant or can be adjusted as a sliding scale or variable dose depending on the mammal's response to treatment. Various factors can influence the actual effective amount used for a particular application. For example, a food effect (e.g., whether the mammal being administered the composition is in a fed state or a fasting state), the frequency of administration, duration of treatment, use of multiple treatment agents, route of administration, and severity of the movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease) may require an increase or decrease in the actual effective amount administered.

The frequency of administration can be any frequency that reduces the severity of movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease) without producing significant toxicity to the mammal. For example, the frequency of administration can be from about once a week to about three times a day, from about twice a month to about six times a day, or from about twice a week to about once a day. The frequency of administration can remain constant or can be variable during the duration of treatment. A course of treatment with a composition (e.g., pharmaceutically acceptable compositions) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can include rest periods. For example, a pharmaceutically acceptable composition containing a therapeutically effective amount of one or more T-type calcium channel antagonists can be administered daily over a two-week period followed by a two-week rest period, and such a regimen can be repeated multiple times. As with the effective amount, various factors can influence the actual frequency of administration used for a particular application. For example, the effective amount, duration of treatment, use of multiple treatment agents,

route of administration, and severity of the movement disorder (*e.g.*, essential tremor, epilepsy, and/or Parkinson's disease) may require an increase or decrease in administration frequency.

An effective duration for administering a composition (e.g., pharmaceutically acceptable compositions) described herein (e.g., a composition containing one or more T-type calcium channel antagonists such as CX-8998) can be any duration that that reduces the severity of movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease) without producing significant toxicity to the mammal. For example, the effective duration can vary from several days to several weeks, months, or years. In some cases, the effective duration for the treatment of movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease) can range in duration from about one month to about 10 years. In some cases, the effective duration for the treatment of movement disorder (e.g., essential tremor, epilepsy, and/or Parkinson's disease) can be indefinite (e.g., the lifespan of the mammal being treated). For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) for from about 1 week to about 9 weeks (e.g., from about 1 week to about 8 weeks, from about 1 week to about 7 weeks, from about 1 week to about 6 weeks, from about 1 week to about 5 weeks, from about 1 week to about 4 weeks, from about 1 week to about 3 weeks, from about 1 week to about 2 weeks, from about 2 weeks to about 9 weeks, from about 3 weeks to about 9 weeks, from about 4 weeks to about 9 weeks, from about 5 weeks to about 9 weeks, from about 6 weeks to about 9 weeks, from about 7 weeks to about 9 weeks, from about 8 weeks to about 9 weeks, from about 2 weeks to about 8 weeks, from about 3 weeks to about 7 weeks, from about 4 weeks to about 6 weeks, from about 2 weeks to about 4 weeks, from about 3 weeks to about 5 weeks, from about 4 weeks to about 6 weeks, from about 5 weeks to about 7 weeks, or from about 6 weeks to about 8 weeks). In some cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) for about 2 weeks (e.g., about 15 days). In some cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk

of developing, one or more movement disorders) for about 4 weeks (*e.g.*, about 28 days). For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (*e.g.*, a mammal having, or at risk of developing, one or more movement disorders) for about 8 weeks or longer. For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (*e.g.*, a mammal having, or at risk of developing, one or more movement disorders) for about 12 weeks or longer. For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (*e.g.*, a mammal having, or at risk of developing, one or more movement disorders) for about 2 months or longer. For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (*e.g.*, a mammal having, or at risk of developing, one or more movement disorders) for about 4 months or longer. For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (*e.g.*, a mammal having, or at risk of developing, one or more movement disorders) for about 6 months or longer. For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (*e.g.*, a mammal having, or at risk of developing, one or more movement disorders) for about 12 months or longer. For example, a composition including one or more T-type calcium channel antagonists can be administered to a mammal (*e.g.*, a mammal having, or at risk of developing, one or more movement disorders) for about 24 months or longer. Multiple factors can influence the actual effective duration used for a particular treatment. For example, an effective duration can vary with the frequency of administration, effective amount, use of multiple treatment agents, route of administration, and severity of the condition being treated.

In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including CX-8998, the composition can be effective to achieve a minimum effective concentration (MEC) of CX-8998 (*e.g.*, the minimum concentration of CX-8998 in a mammal's plasma required to produce a therapeutic effect described herein). For example, a MEC of CX-8998 can be from about 100 nM to about 1800 nM (*e.g.*, from about 200 nM to about 1800 nM, from about 300

nM to about 1800 nM, from about 400 nM to about 1800 nM, from about 500 nM to about 1800 nM, from about 700 nM to about 1800 nM, from about 1000 nM to about 1800 nM, from about 1200 nM to about 1800 nM, from about 1500 nM to about 1800 nM, from about 100 nM to about 1500 nM, from about 100 nM to about 1200 nM, from about 100 nM to about 1000 nM, from about 100 nM to about 800 nM, from about 100 nM to about 700 nM, from about 100 nM to about 600 nM, from about 100 nM to about 500 nM, from about 100 nM to about 400 nM, from about 100 nM to about 300 nM, from about 200 nM to about 1500 nM, from about 300 nM to about 1200 nM, from about 500 nM to about 1000 nM, from about 600 nM to about 800 nM, from about 200 nM to about 400 nM, from about 400 nM to about 600 nM, or from about 300 nM to about 500 nM).  
5 In some cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) to achieve a MEC of CX-8998 of about 200 nM. In some cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) to achieve a MEC of CX-8998 of about 209 nM. In some cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) to achieve a MEC of CX-8998 of about 215 nM.  
10  
15

In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including one or more Cav3 antagonists such as CX-8998, the composition can be effective to maintain a MEC of the Cav3 antagonist(s) (e.g., in the mammal's blood and/or in a blood sample obtained from the mammal such as a plasma sample) for any appropriate amount of time. For example, a MEC of CX-8998 can be maintained in the mammal for at least about 12 hours (e.g., about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, about 25 hours, or about 26 hours). For example, a MEC of CX-8998 can be maintained for from about 10 hours to about 15 hours (e.g., for from about 10 hours to about 14 hours, for from about 10 hours to about 13 hours, for from about 10 hours to about 12 hours, for from about 10 hours to about 11 hours, for from  
20  
25  
30

about 11 hours to about 15 hours, for from about 12 hours to about 15 hours, for from about 13 hours to about 15 hours, for from about 14 hours to about 15 hours, for from about 11 hours to about 14 hours, for from about 12 hours to about 13 hours, for from about 11 hours to about 12 hours, or for from about 13 hours to about 14 hours). In some 5 cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) to maintain a MEC of CX-8998 for about 12 hours. For example, a MEC of CX-8998 can be maintained for from about 22 hours to about 26 hours (e.g., for from about 22 hours to about 25 hours, for from about 22 hours to about 24 hours, for from about 22 hours to 10 about 23 hours, for from about 23 hours to about 26 hours, for from about 24 hours to about 26 hours, for from about 25 hours to about 26 hours, for from about 23 hours to about 25 hours, or for from about 23 hours to about 24 hours). In some cases, a 15 composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) to maintain a MEC of CX-8998 for about 24 hours.

In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including CX-8998, the composition can be effective to achieve a maximum safe concentration (e.g., the maximum concentration of CX-8998 that is well tolerated (e.g., result in minimal, reduced, or no side effects and/or adverse events such as dizziness, headache, euphoria, disturbance in attention, paresthesia, hallucination, insomnia, dry mouth, dysguesia, hypoesthesia, somnolence, lethargy, sleep disturbance, nausea, vomiting, akathisia, decreased level of consciousness, syncope, memory impairment, anxiety, restlessness, fatigue, irritability, constipation, tinnitus, anorexia, emotional disturbances, sexual impotency, diplopia, 20 nystagmus, drowsiness, morbilliform skin eruptions, granulocytopenia, agranulocytosis, red-cell hypoplasia, and aplasia) in a mammal's plasma) of CX-8998. For example, a maximum safe concentration of CX-8998 can be from about 1000 nM to about 1800 nM (e.g., from about 1100 nM to about 1800 nM, from about 1200 nM to about 1800 nM, 25 from about 1300 nM to about 1800 nM, from about 1400 nM to about 1800 nM, from about 1500 nM to about 1800 nM, from about 1600 nM to about 1800 nM, from about 30

1700 nM to about 1800 nM, from about 1000 nM to about 1700 nM, from about 1000 nM to about 1600 nM, from about 1000 nM to about 1500 nM, from about 1000 nM to about 1400 nM, from about 1000 nM to about 1300 nM, from about 1000 nM to about 1200 nM, from about 1000 nM to about 1100 nM, from about 1100 nM to about 1700 nM, from about 1200 nM to about 1600 nM, from about 1300 nM to about 1500 nM, from about 1100 nM to about 1300 nM, from about 1200 nM to about 1400 nM, from about 1300 nM to about 1500 nM, from about 1400 nM to about 1600 nM, or from about 1500 nM to about 1700 nM).

In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including one or more Cav3 antagonists such as CX-8998, the composition can be effective to maintain a  $C_{max}$  (e.g., the maximum concentration achieved in a mammal's plasma) below the tolerability threshold of Cav3 antagonist(s). For example, a  $C_{max}$  of CX-8998 can be less about 1800 nM (e.g., about 1700 nM, about 1600 nM, about 1500 nM, about 1400 nM, about 1300 nM, about 1200 nM, about 1100 nM, about 1000 nM, about 990 nM, about 980 nM, about 970 nM, about 960 nM, about 950 nM, about 940 nM, about 930 nM, about 920 nM, about 910 nM, or about 900 nM). For example, a  $C_{max}$  of CX-8998 can be from about 900 nM to about 1800 nM (e.g., from about 1000 nM to about 1800 nM, from about 1200 nM to about 1800 nM, from about 1400 nM to about 1800 nM, from about 1500 nM to about 1800 nM, from about 1600 nM to about 1800 nM, from about 900 nM to about 1700 nM, from about 900 nM to about 1500 nM, from about 900 nM to about 1400 nM, from about 900 nM to about 1300 nM, from about 900 nM to about 1200 nM, from about 900 nM to about 1100 nM, from about 1000 nM to about 1500 nM, or from about 1200 nM to about 1400 nM). In some cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) to achieve a  $C_{max}$  of CX-8998 of about 900 nM. In some cases, a composition including CX-8998 can be administered to a mammal (e.g., a mammal having, or at risk of developing, one or more movement disorders) to achieve a  $C_{max}$  of CX-8998 of about 1000 nM.

In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including one or more Cav3 antagonists such as CX-8998, the composition can be effective to maintain an area under the curve (AUC) of the Cav3 antagonist(s) from about 3,000 nM\*hour to about 10,000 nM\*hour. For example, an AUC of CX-8998 can be from about 3,000 nM\*hour to about 9,000 nM\*hour, from about 3,000 nM\*hour to about 8,000 nM\*hour, from about 3,000 nM\*hour to about 7,000 nM\*hour, from about 3,000 nM\*hour to about 6,000 nM\*hour, from about 3,000 nM\*hour to about 5,000 nM\*hour, from about 3,000 nM\*hour to about 4,000 nM\*hour, from about 4,000 nM\*hour to about 10,000 nM\*hour, from about 5,000 nM\*hour to about 10,000 nM\*hour, from about 6,000 nM\*hour to about 10,000 nM\*hour, from about 8,000 nM\*hour to about 10,000 nM\*hour, from about 9,000 nM\*hour to about 10,000 nM\*hour, from about 4,000 nM\*hour to about 9,000 nM\*hour, from about 5,000 nM\*hour to about 8,000 nM\*hour, from about 6,000 nM\*hour to about 7,000 nM\*hour, from about 4,000 nM\*hour to about 6,000 nM\*hour, from about 5,000 nM\*hour to about 7,000 nM\*hour, from about 6,000 nM\*hour to about 8,000 nM\*hour, or from about 7,000 nM\*hour to about 9,000 nM\*hour. An AUC can be measured at any appropriate time (e.g., any appropriate time after administration of a composition including CX-8998 to a mammal having, or at risk of developing, one or more movement disorders). An AUC can be measured for any appropriate time interval (e.g., any appropriate duration of time after administration of a composition including CX-8998 to a mammal having, or at risk of developing, one or more movement disorders). For example, an AUC can be measured for from about 12 hours (AUC<sub>0-24</sub> or AUC<sub>24</sub>) to about 36 hours (AUC<sub>0-36</sub> or AUC<sub>36</sub>; e.g., from about 12 hours to about 32 hours, from about 12 hours to about 28 hours, from about 12 hours to about 24 hours, from about 12 hours to about 20 hours, from about 12 hours to about 18 hours, from about 18 hours to about 36 hours, from about 22 hours to about 36 hours, from about 24 hours to about 36 hours, from about 15 hours to about 32 hours, from about 18 hours to about 24 hours, from about 12 hours to about 15 hours, from about 15 hours to about 18 hours, from about 18 hours to about 22 hours, from about 22 hours to about 26 hours, from about 26 hours to about 30 hours, or from about

30 hours to about 32 hours). In some cases, an AUC can be measured for about 24 hours (e.g.,  $AUC_{0-24}$  or  $AUC_{24}$ ).

In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including one or more Cav3 antagonists such as CX-8998, the composition can be effective to maintain a plasma concentration (e.g., a mean plasma concentration) of the Cav3 antagonist(s) in the mammal that is between a MEC of CX-8998 (e.g., about 400 nM CX-8998) and a  $C_{max}$  of CX-8998 (e.g., about 1000 nM). For example, when a composition including CX-8998 is administered to a mammal, the composition can be effective to maintain a mean plasma concentration of CX-8998 in the mammal that is from about 400 nM CX-8998 to about 1000 nM CX-8998. For example, when a composition including CX-8998 is administered to a mammal, the composition can be effective to maintain a mean plasma concentration of CX-8998 in the mammal as shown in Figure 74. In cases where a composition including CX-8998 includes a first component formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component formulated for immediate release of CX-8998, the first component formulated for delayed and/or sustained release of CX-8998 can be effective to maintain a plasma concentration (e.g., a mean plasma concentration) of CX-8998 that is between a MEC of CX-8998 (e.g., about 400 nM CX-8998) and a  $C_{max}$  of CX-8998 (e.g., about 1000 nM) such that the composition can be effective to maintain a concentration of CX-8998 that is between a MEC of CX-8998 and a  $C_{max}$  of CX-8998, and the second component formulated for immediate release of CX-8998, when present, can be effective to rapidly (e.g., in less than about 60 minutes) achieve a plasma concentration (e.g., a mean plasma concentration) that is at least a MEC of CX-8998 (e.g., at least about 400 nM CX-8998). For example, when a composition including CX-8998 that includes a first component formulated for delayed and/or sustained release of CX-8998 and, optionally, a second component formulated for immediate release of CX-8998 is administered to a mammal, the composition can be effective to achieve a mean plasma concentration of CX-8998 in less than about 60 minutes, and can be effective to maintain a mean plasma concentration of CX-8998 in the mammal that is from about 400 nM CX-8998 to about 1000 nM CX-8998.

8998. A mean plasma concentration of including CX-8998 achieved by a composition described herein including CX-8998 can be maintained for any appropriate amount of time (e.g., for any appropriate duration of time after administration of a composition including CX-8998 to a mammal having, or at risk of developing, one or more movement 5 disorders). For example, a mean plasma concentration of CX-8998 that is from about 400 nM to about 1000 nM can be maintained for at least about 12 hours (e.g., about 12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 24 hours, about 25 hours, or about 26 hours). In some cases, a mean plasma 10 concentration of from about 400 nM CX-8998 to about 1000 nM CX-8998 can be maintained for from about 12 hours to about 36 hours (e.g., from about 12 hours to about 32 hours, from about 12 hours to about 28 hours, from about 12 hours to about 24 hours, from about 12 hours to about 20 hours, from about 12 hours to about 18 hours, from 15 about 18 hours to about 36 hours, from about 22 hours to about 36 hours, from about 24 hours to about 36 hours, from about 15 hours to about 32 hours, from about 18 hours to about 24 hours, from about 12 hours to about 15 hours, from about 15 hours to about 18 hours, from about 18 hours to about 22 hours, from about 22 hours to about 26 hours, from about 26 hours to about 30 hours, or from about 30 hours to about 32 hours). For example, a mean plasma concentration of from about 400 nM CX-8998 to about 1000 20 nM CX-8998 can be maintained for about 18 hours. For example, a mean plasma concentration of from about 400 nM CX-8998 to about 1000 nM CX-8998 can be maintained for about 24 hours. For example, when a composition including CX-8998 is administered to a mammal, the composition can be effective to maintain a mean plasma concentration of CX-8998 in the mammal that is from about 400 nM CX-8998 to about 25 1000 nM CX-8998 for about 24 hours (e.g., can have an AUC of about 400 nM\*hour and about 1000 nM\*hour for about 24 hours).

In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including one or more Cav3 antagonists such as CX-8998, the composition can be effective to maintain a maximum concentration ( $C_{max}$ ) of the Cav3 antagonist(s) divided by a mean plasma concentration of 30

the Cav3 antagonist(s) at 24 hours after administration (e.g.,  $\frac{C_{max}}{\text{plasma concentration at 24 hours}}$ ) that is less than 5.0 (e.g., about 5, about 4.5, about 4, about 3.5, about 3, about 2.5, about 2, about 1.5, or about 1.0). For example, when a composition including CX-8998 is administered to a mammal, the composition can be effective to maintain a

5  $\frac{C_{max}}{\text{plasma concentration at 24 hours}}$  of CX-8998 in the mammal that is from about 1.0 to about 5.0 (e.g., from about 1.0 to about 4.5, from about 1.0 to about 4.0, from about 1.0 to about 3.5, from about 1.0 to about 3.0, from about 1.0 to about 2.5, from about 1.0 to about 2.0, from about 1.5 to about 5.0, from about 2.0 to about 5.0, from about 2.5 to about 5.0, from about 3.0 to about 5.0, from about 3.5 to about 5.0, from about 4.0 to about 5.0, from about 1.5 to about 4.5, from about 2.0 to about 4.0, from about 1.5 to about 2.5, from about 2.5 to about 3.5, or from about 3.5 to about 4.5).

10 In some cases, when a mammal having, or at risk of developing, one or more movement disorders is administered a composition including one or more Cav3 antagonists such as CX-8998, the composition can be effective to achieve a  $C_{max}$  that is lower than a  $C_{max}$  achieved from an immediate release composition including one or more Cav3 antagonists such as CX-8998 (e.g., an immediate release composition including one or more Cav3 antagonists of the same dose). For example, when a composition including CX-8998 is administered to a mammal, the composition can be effective to maintain a  $C_{max}$  of CX-8998 that is from about 30% to about 70% (e.g., from about 30% to about 60%, from about 30% to about 50%, from about 30% to about 40%, from about 40% to about 70%, from about 50% to about 70%, from about 60% to about 70%, or from about 40% to about 60%) lower than a  $C_{max}$  achieved from an immediate release composition including CX-8998.

15 In some cases, methods of treating a mammal having, or at risk of developing, one or more movement disorders as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998), also can include identifying the mammal as having, or as being at risk of developing, one or more movement disorders. Any appropriate method can be used to identify a mammal as having a movement disorder. Methods of identifying a mammal as

having, or at risk of developing a movement disorder can include, without limitation, reviewing the mammal's medical history, reviewing the mammal's family history, conducting a physical examination (e.g., neurological examinations including checking tendon reflexes, muscle strength and tone, ability to feel certain sensations, posture and coordination, and/or gait), laboratory tests (e.g., laboratory tests including checking the mammal's blood and/or urine for thyroid disease, metabolic problems, drug side effects, alcohol levels, and/or levels of chemicals that may cause tremor), imaging (e.g., functional imaging), performance tests (e.g., performance tests to evaluate the tremor itself including drinking from a glass, holding arms outstretched, writing, and/or drawing a spiral), and/or a dopamine transporter scan. In some cases, identifying a mammal as having, or at risk of developing a movement disorder can include genetic testing. For example, testing for the presence or absence of one or more genetic variants that associated with movement disorders, can be used for identifying a mammal as having, or at risk of developing a movement disorder (e.g., essential tremor). For example, genetic variants associate with a movement disorder (e.g., essential tremor) can be as described elsewhere (see, e.g., Odgerel et al, 2018 *bioRxiv* doi: <http://dx.doi.org/10.1101/248443>).

In some cases, when treating a mammal having, or at risk of developing, one or more movement disorders (e.g., essential tremor, epilepsy, and/or Parkinson's disease) as described herein (e.g., by administering a composition containing one or more T-type calcium channel antagonists such as CX-8998), the treatment also can include one or more additional therapies. A therapy can be any appropriate therapy (e.g., a therapy used to treat one or more movement disorders and/or one or more symptoms associated with a movement disorder) such as administering one or more pharmaceuticals, administering one or more nutraceuticals, physical therapies, occupational therapies, surgeries, ultrasound thalamotomy, neurostimulation techniques, digital therapeutics, and alternative medicines. Examples of therapies that can be used to treat a mammal having, or at risk of developing, essential tremor and/or one or more symptoms associated with essential tremor include, without limitation, administering one or more beta blockers (e.g., propranolol), administering one or more anti-seizure medications (e.g., primidone, gabapentin, topiramate, pregabalin, zonisamide, and ethosuximide), administering one or

more tranquilizers (*e.g.*, alprazolam and clonazepam), injections of onabotulinumtoxinA (botox), physical therapy, occupational therapy, surgery (*e.g.*, deep brain stimulation), ultrasound thalamotomy (*e.g.*, focused/guided ultrasound thalamotomy), neurostimulation (*e.g.*, transcranial magnetic stimulation), and digital therapeutics (*e.g.*, devices such as

5 tremor canceling wearables and utensils such as tremor spoons). In some cases, a therapy that can be used to treat a mammal having, or at risk of developing, essential tremor and/or one or more symptoms associated with essential tremor can be as described elsewhere (see, *e.g.*, Treatment guidelines for essential tremor by the American academy of neurology such as those available at [aan.com/Guidelines/home/GuidelineDetail/492](http://aan.com/Guidelines/home/GuidelineDetail/492)).

10 Examples of therapies that can be used to treat a mammal having, or at risk of developing, Parkinson's disease and/or one or more symptoms associated with Parkinson's disease include, without limitation, administering one or more dopamine agonists (*e.g.*, carbidopa-levodopa, pramipexole, ropinirole, rotigotine, and apomorphine), administering one or more monoamine oxidase B (MAO B) inhibitors (e.g., selegiline, rasagiline, and safinamide), administering one or more catechol O-methyltransferase (COMT) inhibitors (*e.g.*, entacapon, and tolcapone), administering one or more anticholinergics (*e.g.*, benztrapine and trihexyphenidyl), administering amantadine, physical therapy, occupational therapy, and surgery (*e.g.*, deep brain stimulation). In some cases, a therapy that can be used to treat a mammal having, or at 15 risk of developing, Parkinson's disease and/or one or more symptoms associated with Parkinson's disease can be as described elsewhere (see, *e.g.*, Treatment guidelines for Parkinson's disease by the American academy of neurology such as those available at the website [movementdisorders.org/MDS-Files1/Resources/PDFs/TreatmentsforMotorSymptomsofPD-2018.pdf](http://movementdisorders.org/MDS-Files1/Resources/PDFs/TreatmentsforMotorSymptomsofPD-2018.pdf)).

20 In some cases, a therapy that can be used to treat a mammal having, or at risk of developing, Parkinson's disease and/or one or more symptoms associated with Parkinson's disease can be as described elsewhere (see, *e.g.*, Treatment guidelines for Parkinson's disease by the American academy of neurology such as those available at the website [movementdisorders.org/MDS-Files1/Resources/PDFs/TreatmentsforMotorSymptomsofPD-2018.pdf](http://movementdisorders.org/MDS-Files1/Resources/PDFs/TreatmentsforMotorSymptomsofPD-2018.pdf)).

25 In cases where a mammal having, or at risk of developing, one or more movement disorders is treated with a composition containing one or more T-type calcium channel antagonists (*e.g.*, one or more Cav3 antagonists such as CX-8998) and is treated with one or more additional therapies, the one or more additional therapies can be administered at the same time or independently. For example, a composition containing one or more T-type calcium

channel antagonists (*e.g.*, CX-8998) can be administered first, and the one or more additional therapies administered second, or vice versa.

This document also provides methods for identifying the presence, absence, or amount of total active moiety (TAM) in a composition (*e.g.*, a pharmaceutically acceptable composition) described herein (*e.g.*, a composition containing one or more T-type calcium channel antagonists such as CX-8998). The term “TAM” as used herein refers to the sum of the active components present in a composition. For example, when a composition includes CX-8998, the TAM can include one or more of CX 8998, M01, M02, M03, and/or M04. For example, when a composition includes CX-8998, the methods can include identifying the presence, absence, or amount of CX 8998 and metabolites M01, M02, M03, and M04. In some cases, mass spectrometry (MS) methods can be used for the quantitation (*e.g.*, simultaneous quantitation) of CX-8998, M01, M02, M03, and/or M04. Any appropriate MS method can be used. In some cases, a liquid chromatography-tandem MS (LC/MS/MS) bioanalytical method can be used for the simultaneous quantitation of CX-8998 and metabolites M01, M02, M03, and M04. For example, LC/MS/MS can be used to quantifying the TAM associated with CX-8998. In some cases, identifying the presence, absence, or amount of TAM (*e.g.*, of CX 8998, M01, M02, M03, and/or M04) in a composition can be effective to determine acceptance criteria for system performance suitability, quantitation range, calibration linearity, assay accuracy and precision, and/or assay recovery. For example, when a composition includes CX-8998, identifying the presence, absence, or amount of CX 8998, M01, M02, M03, and/or M04 can be effective to determine acceptance criteria for system performance suitability, quantitation range, calibration linearity, assay accuracy and precision, and assay recovery.

This document also provides kits containing one or more materials described herein. For example, materials provided in kits described herein can be used for treating mammals (*e.g.*, humans) having, or at risk of developing, one or more movement disorders (*e.g.*, essential tremor, epilepsy, and/or Parkinson’s disease) as described herein. In some cases, a composition (*e.g.*, a pharmaceutically acceptable composition) including one or more T-type calcium channel antagonists (*e.g.*, one or more Cav3 antagonists such

as CX-8998) can be combined with packaging material and sold as a kit. For example, a kit can include a composition including one or more T-type calcium channel antagonists described herein presented in unit-dose or multi-dose containers. A container can be any appropriate size (e.g., a 60 cc container). A container can be any appropriate material

5 (e.g., high-density polyethylene (HDPE) such as a white HDPE). A container can include a closure (e.g., a child-resistant closure). A close can be any appropriate material (e.g., polypropylene such as a white, 33-mm polypropylene). In some cases, no desiccant is included in the bottles. In some cases, no cotton is included in the bottles. In some cases, a kit can include a pharmaceutically acceptable composition including CX-8998

10 described herein in the form of tablets or capsules (e.g., tablets or capsules for oral administration) having a component (e.g., a first component) that is a sustained release composition, and, optionally, a component (e.g., a second component) that is an immediate release composition. In some cases, the packaging material included in such a kit typically contains instructions or a label describing how the composition can be used, for example, to treat mammal (e.g., a human) having, or at risk of developing, one or

15 more movement disorders (e.g., essential tremor, epilepsy, and/or Parkinson's disease) as described herein. For example, a kit can include instructions or a label instructing a mammal to not eat for at least about 4 hours (e.g., about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours) prior to taking the composition. For example, a kit can include

20 instructions or a label instructing a mammal to take the composition with food. For example, a kit can include instructions or a label instructing a mammal to take the composition within about 4 hours (e.g., about 4 hours after waking, about 3 hours after waking, about 2 hours after waking, about 1 hour after waking, about 30 minutes after waking, or immediately after waking) of waking. In some cases, the packaging material included in such a kit typically contains instructions or a label describing how the composition can be stored (e.g., to be stored between from about 15°C to about 30°C, or from about 20°C to about 25°C).

25

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

## EXAMPLES

### **The Essential Tremor Rating Assessment Scale (TETRAS)**

The Tremor Research Group first published the TRG Essential Tremor Rating Assessment Scale (TETRAS) in 2008 (Elble *et al.*, 2008 *Mov Disord.* 23(Suppl 1):S1-6).

5 TETRAS consists of a 9-item performance subscale and a 12-item activities of daily living (ADL) subscale. TETRAS was developed as a rapid clinical assessment of ET that requires no equipment other than pen and paper. Administration of the performance subscale takes less than 10 minutes. The scale employs objective metrics to reduce experiential rater bias.

10 To evaluate the inter-rater reliability of TETRAS, Elble *et al.* (2012 *Mov Disord.* 27(12):1567-1569) videotaped 50 TETRAS exams, including assessments of 44 patients with ET and 6 controls. The severity of ET ranged from mild to severe. Ten specialists rated the patients in the videos 2 times with an interval of 1 to 2 months separating the ratings. Of the 10 raters, 6 had been involved in the development of TETRAS, and 4 had 15 never used the scale.

20 Inter-rater reliability of the scale was calculated using a two-way random effects intraclass correlation (ICC) with an absolute agreement definition. The inter- and intra-rater ICC for head and upper limb tremor ranged from 0.86 to 0.96, and the ICC for the total score were 0.94 and 0.96. The ICC for voice, face, trunk and leg were less robust (Elble *et al.* 2012 *Mov Disord.* 27(12):1567-1569).

25 The TETRAS Performance subscale is widely used in clinical practice and has high content validity and strong inter-rater reliability. The TETRAS ADL and performance scores are highly correlated, and the TETRAS ratings of upper extremity function correlate strongly with transducer measures (accelerometry) of upper limb tremor (Mostile *et al.*, 2010 *Mov Disord.* 25(12):1938-1943). TETRAS is also shown to be sensitive to change in tremor over time (Voller *et al.*, 2014 *Mov Disord.* 29(4):555-558).

The higher the score the worse the tremor – a decrease in score is an improvement in tremor.

**Example 1. Significant Change from Baseline to Day 28 in the TETRAS-PS as Rated by Investigator**

**TETRAS Performance Subscale**

The Performance subscale quantifies tremor in the head, face, voice, limbs and trunk. Each item is rated on a 0 to 4 rating scale, with scoring of upper limb tremor allowing for 0.5-point increments. Specific amplitude ranges (measured in centimeters) define the tremor rating. Raters first estimate the maximum amplitude of tremor and then assign the corresponding rating. The sum of the individual rating scores provides the overall Performance score, ranging from 0 to 64. The complete TETRAS Performance Subscale is as shown below.

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.

0 = no tremor  
 1 = slight tremor (< 0.5 cm)  
 2 = mild tremor (0.5- < 2.5 cm)  
 3 = moderate tremor (2.5-5 cm)  
 4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

0 = no tremor  
 1 = slight; barely perceptible tremor  
 2 = mild; noticeable tremor  
 3 = moderate; obvious tremor, present in most voluntary facial contractions  
 4 = severe; gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended "aah" sound and eee" sound for 5 seconds each. Then assess speech during normal conversation by asking patients "How do you spend your average day?"

0 = no tremor  
 1 = slight: tremor during aah, and eee and no tremor during speech  
 2 = mild: tremor in "aah" and "eee" and minimal tremor in speech  
 3 = moderate: obvious tremor in speech that is fully intelligible  
 4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds. The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

- Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground. The wrist should also be straight and the fingers abducted so that they do not touch each other.
- Lateral "wing beating" postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.
- Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

For all three hand tremor ratings 0 = no tremor

1 = tremor is barely visible  
 1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude  
 2.5 = tremor is 3- < 5 cm amplitude  
 3 = tremor is 5- < 10 cm amplitude  
 3.5 = tremor is 10- < 20 cm amplitude  
 4 = tremor is > 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds each. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

0 = no tremor  
 1 = slight, barely perceptible  
 2 = mild, less than 1 cm at any point  
 3 = moderate tremor, less than 3 cm at any point  
 4 = severe tremor, greater than 3 cm

6. Archimedes spiral: Demonstrate how to draw Archimedes spiral that approximately fills 1/4 of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

0 = normal  
 1 = slight: tremor barely visible.  
 2 = mild: obvious tremor  
 3 = moderate: portions of figure not recognizable.  
 4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

0 = normal  
 1 = slight: unidy due to tremor that is barely visible. 2 = mild: legible, but with considerable tremor.  
 3 = moderate: some words illegible.  
 4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an X) without touching it, (ideally approximately 1 mm) for 10 seconds". Each hand is score separately.

0 = no tremor  
 1 = tremor is barely visible  
 1.5 = tremor is visible, but less than 1 cm 2 = tremor is 1- < 3 cm amplitude

2.5 = tremor is 3- < 5 cm amplitude  
 3 = tremor is 5- < 10 cm amplitude  
 3.5 = tremor is 10- < 20 cm amplitude  
 4 = tremor is > 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk

0 = no tremor  
 1 = barely perceptible tremor  
 2 = obvious but mild tremor, does not cause instability 3 = moderate tremor, impairs stability of stance  
 4 = severe tremor, unable to stand without assistance

The principal investigator (or sub-principal investigator) scored the TETRAS performance subscale, the TETRAS Performance Subscale scores provided by the 5 investigator were utilized in the statistical analyses of efficacy.

The efficacy analysis of the TETRAS performance subscale was conducted using an analysis of covariance (ANCOVA) model with fixed effects for treatment, concomitant anti-tremor medication use, site type, and Baseline value of the TETRAS performance subscale. The mean change from Baseline in TETRAS performance scale 10 indicates that the CX-8998 arm is different from placebo (Figure 1 and Table 1). All testing is performed using the least square (LS) means from the ANCOVA model and a two-sided test at the alpha=0.05 level of significance. If the data indicate a departure from the normal distribution, a corresponding rank test is performed.

Table 1. Change from Baseline to Day 15 and Day 28 in the TETRAS-PS as Rated by Physician.

|                           | CX-8998 |                        |    |                    | Placebo |                        |        |
|---------------------------|---------|------------------------|----|--------------------|---------|------------------------|--------|
|                           | LS mean | standard error of mean | N  | p value vs placebo | LS mean | standard error of mean | N      |
| <b>Day 15 (8 mg BID)</b>  | -3.1    | 0.78                   | 39 | 0.378              | -2.4    | 0.75                   | 4<br>4 |
| <b>Day 28 (10 mg BID)</b> | -4.6    | 0.8                    | 37 | 0.027              | -2.9    | 0.77                   | 4<br>2 |

5 **Example 2. Significant Change from Baseline to Day 15 and Day 28 in the TETRAS-  
ADL**

**TETRAS Activities of Daily Living Subscale**

The ADL subscale includes many of the items assessed in the scales described elsewhere (see, *e.g.*, Fahn *et al.*, “Clinical rating scale for tremor,” pages 225–234 in 10 *Parkinson’s Disease and Movement Disorders* (Jankovic *et al.*, eds.), Baltimore: Williams & Wilkins, 1993; Louis, 2000 *Arch Neurol.* 57(10): 1522-1524; and Bain *et al.*, 1993 *J Neurol Neurosurg Psychiatry* 56(8):868-873), including eating and drinking, dressing and personal hygiene, carrying items and finer motor skills. Each item is rated on a 0 to 4 scale, with 0 representing normal activity and 4 representing severe 15 abnormality. The sum of the individual scores provides the overall score, ranging from 0 to 48. The complete TETRAS ADL Subscale is as follows.

**Activities of Daily Living Subscale**

Rate tremor's impact on activities of daily living (0 - 4 scoring).

**1. Speaking**0 = **Normal**.

1 = Slight voice tremor/hoarseness, only when "nervous".

2 = Mild voice tremor. All words easily understood.

3 = Moderate voice tremor. Some words difficult to understand.

4 = Severe voice tremor. Most words difficult to understand.

**2. Feeding with a spoon**0 = **Normal**.

1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.

2 = Mildly abnormal. Spills a little.

3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.

4 = Severely abnormal. Cannot feed with a spoon.

**3. Drinking from a glass**0 = **Normal**.

1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.

2 = Mildly abnormal. Spills a little.

3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.

4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

**4. Hygiene**0 = **Normal**.

1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.

2 = Mildly abnormal. Some difficulty but can complete task.

3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy such as using two hands or using the less affected hand.

4 = Severely abnormal. Cannot complete hygiene activities independently.

**5. Dressing**0 = **Normal**.

1 = Slightly abnormal. Tremor is present but does not interfere with dressing.

2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.

3 = Moderately abnormal. Unable to do most dressing unless uses strategy such as using Velcro, buttoning shirt before putting it on or avoiding shoes with laces.

4 = Severely abnormal. Cannot dress independently.

**6. Pouring**

0 = Normal

1 = Slightly abnormal. Tremor is present but does not interfere with pouring.  
 2 = Mildly abnormal. Must be very careful to avoid spilling but may spill accidentally.  
 3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.  
 4 = Severely abnormal. Cannot pour.

**7. Carrying food trays, plates or similar items**

0 = Normal

1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.  
 2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.  
 3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.  
 4 = Severely abnormal. Cannot carry food trays or similar items.

**8. Using Keys**

0 = Normal

1 = Slightly abnormal. Tremor is present but can open key with one hand without difficulty.  
 2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.  
 3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.  
 4 = Severely abnormal. Cannot put key in lock.

**9. Writing**

0 = Normal

1 = Slightly abnormal. Tremor present but does not interfere with writing.  
 2 = Mildly abnormal. Difficulty writing due to the tremor.  
 3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.  
 4 = Severely abnormal. Cannot write.

**10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as if relates to housework.**

0 = Normal

1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.  
 2 = Mildly abnormal. Tremor interferes with work, able to do everything, but with errors.  
 3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.  
 4 = Severely abnormal. Cannot perform any job or household work.

**11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)**

Task \_\_\_\_\_

0 = Normal

1 = Slightly abnormal. Tremor present but does not affect task.  
 2 = Mildly abnormal. Tremor interferes with task but is still able to perform task.  
 3 = Moderately abnormal. Can do task but must use strategies.  
 4 = Severely abnormal. Cannot do the task.

**12. Social Impact**

0 = None

1 = Aware of tremor, but it does not affect lifestyle or professional life.  
 2 = Feels embarrassed by tremor in some social situations or professional meetings.  
 3 = Avoids participating in some social situations or professional meetings because of tremor.  
 4 = Avoids participating in most social situations or professional meetings because of tremor.

Analyses of the TETRAS-ADL was conducted using the same type of ANCOVA

5 model as described for the TETRAS-PS, using two-sided tests at the alpha=0.05 level of significance (Figure 2 and Table 2).

Table 2. Change from Baseline to Day 15 and Day 28 in the TETRAS-ADL.

|                           | CX-8998 |                        |    |                    | Placebo |                        |    |
|---------------------------|---------|------------------------|----|--------------------|---------|------------------------|----|
|                           | LS mean | standard error of mean | N  | p value vs placebo | LS mean | standard error of mean | N  |
| <b>Day 15 (8 mg BID)</b>  | -4.5    | 0.87                   | 39 | 0.005              | -1.4    | 0.85                   | 43 |
| <b>Day 28 (10 mg BID)</b> | -4.5    | 1.12                   | 37 | 0.049              | -1.6    | 1.08                   | 42 |

**Example 3. Significant Change from Baseline to Day 15 and Day 28 in the TETRAS Total score**

5 **TETRAS Total Score**

The Total TETRAS score was defined as the sum of the TETRAS performance subscale total score and the TETRAS ADL subscale score. TETRAS TOTAL score combines both patient reported outcome and objective measurement of tremor amplitude in a single score. Analyses of the TETRAS-ADL was conducted using the same type of 10 ANCOVA model as described for the TETRAS-PS, using two-sided tests at the alpha=0.05 level of significance (Figure 3 and Table 3).

Table 3. Change from Baseline to Day 15 and Day 28 in the TETRAS-Total

|                           | CX-8998 |                        |    |                    | Placebo |                        |    |
|---------------------------|---------|------------------------|----|--------------------|---------|------------------------|----|
|                           | LS mean | standard error of mean | N  | p value vs placebo | LS mean | standard error of mean | N  |
| <b>Day 15 (8 mg BID)</b>  | -7.5    | 1.42                   | 39 | 0.04               | -3.7    | 1.38                   | 43 |
| <b>Day 28 (10 mg BID)</b> | -9      | 1.66                   | 37 | 0.029              | -4.2    | 1.6                    | 42 |

**Example 4. Significant Change from Baseline to Day 28 in the TETRAS-PS spiral task (item 6)**

5 The Archimedes spiral item of the TETRAS-PS subscale (Item 6) incorporates a routine clinical assessment of functional tremor impact into the TETRAS scoring of tremor severity. The investigator demonstrates how to draw an Archimedes spiral that approximately fills 1/4 of an unlined page of standard (letter) paper using a ballpoint pen. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. The investigator 10 then asks the subject to copy the spiral. Each hand is tested and scored separately. The pen is held such that no part of the limb touches the table and the paper is secured on the table in a location that is suitable for the patient's style of drawing. The tremor in the spiral is scored, not the movement of the limb.

15 0 = normal; 1 = slight: tremor barely visible; 2 = mild: obvious tremor; 3 = moderate: portions of figure not recognizable; 4 = severe: figure not recognizable

Scores for TETRAS-PS subscale item 6 were summed for both hands and the mean change from baseline was calculated for Day 15 and Day 28 (Figure 4 and Table 4). Statistical significance was calculated by Mann-Whitney non-parametric t-test (two tailed).

Table 4. Change from Baseline to Day 15 and Day 28 in the TETRAS-PS Spiral Item.

|  | CX-8998 |                        |    |                    | Placebo |                        |    |
|--|---------|------------------------|----|--------------------|---------|------------------------|----|
|  | Mean    | standard error of mean | N  | p value vs placebo | Mean    | standard error of mean | N  |
| <b>Day 15 (8 mg BID)</b>                                   | -0.41   | 0.141                  | 39 | 0.19               | -0.205  | 0.168                  | 44 |
| <b>Day 28 (10 mg BID)</b>                                  | -0.658  | 0.137                  | 39 | 0.0031             | -0.116  | 0.174                  | 43 |
| p-value by Mann Whitney non-parametric t-test (two tailed) |         |                        |    |                    |         |                        |    |

**Example 5. Significant Change from baseline to day 15 and day 28 in functional tremor frequency measured by digital spirography (imotor)**

5 iMotor, developed by Apptomics, Inc., is an application specifically designed to objectively quantify motor function in patients with movement disorders (see, *e.g.*, Mitsi *et al.*, 2017 *Front. Neurol.* 8:273). The application requires the patient to complete a cycle of evaluations measuring motor function.

10 For the Archimedes spiral item of iMotor, subjects are asked to draw a spiral using a digital stylus on a tablet-based application. Prompts instruct the subject to trace a dotted grey mid-line that begins at the start of the spiral without lifting the stylus off the screen. The test is not timed. Subjects are asked to complete the task twice – one with the right and one with the left hand.

15 Functional tremor frequency (in Hz) is calculated by the iMotor algorithm based on the number and timing of stylus crosses of the mid-line. The mean change from baseline to Day 15 and Day 28 was calculated for the dominant hand. Statistical significance was calculated by Mann-Whitney non-parametric t-test (two tailed) (Figure 5 and Table 5).

Table 5. Change from Baseline to Day 15 and Day 28 in Functional Tremor Frequency by iMotor.

|  | CX-8998 |                        |   |                    | Placebo |                        |   |
|--|---------|------------------------|---|--------------------|---------|------------------------|---|
|  | Mean    | standard error of mean | N | p value vs placebo | Mean    | standard error of mean | N |
| <b>Day 15 (8 mg BID)</b>                                   | -2.66   | 0.604                  | 3 | 0.012              | -0.196  | 0.169                  | 3 |
| <b>Day 28 (10 mg BID)</b>                                  | -2.41   | 0.477                  | 3 | 0.012              | -0.0384 | 0.906                  | 3 |
| p-value by Mann Whitney non-parametric t-test (two tailed) |         |                        |   |                    |         |                        |   |

**Example 6. Significant difference from placebo in Clinical global impression of improvement (CGI-I) at day 28**

**Clinical Global Impression Scale**

The Clinical Global Impressions Scale (CGI) was developed for use in NIMH-sponsored clinical trials to provide a brief, stand-alone assessment of the clinician's view of a patient's global functioning before and after initiating a study medication (Guy (ed.), 10 *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration; 1976). The CGI is a summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. The CGI has two forms—the CGI-Severity, which rates 15 illness severity at baseline, and the CGI-Improvement, which rates change from baseline.

**CGI-Improvement (CGI-I)**

The CGI-I consists of a single 7-point rating of total improvement or change from baseline CGI-S, regardless of whether or not the change is due entirely to drug treatment. 20 Raters select one response based on the following question, "Compared to your subject's condition at the beginning of treatment, how much has your subject changed?" Scores

are: 1 = Very much improved; 2 = Much improved; 3 = Minimally improved; 4 = No change; 5 = Minimally worse; 6 = Much worse; 7 = Very much worse.

Treatment success as measured by CGI-I was summarized using descriptive statistics. Differences between treatment groups were assessed using an ANCOVA model with fixed effects for treatment, anti-tremor medication use, and site type (Figure 6 and Table 6).

Table 6. Mean CGI-I Score at Day 28 by Treatment Group.

|                           | CX-8998 |            | Placebo |            |
|---------------------------|---------|------------|---------|------------|
|                           | number  | percentage | number  | percentage |
| <b>Worsened</b>           | 0       | 0          | 2       | 4.76       |
| <b>No Change</b>          | 13      | 35.14      | 30      | 71.43      |
| <b>Improved</b>           | 24      | 64.86      | 10      | 23.81      |
| <b>Total</b>              | 37      | 100        | 42      | 100        |
| <b>p value vs placebo</b> | 0.001   |            |         |            |

10 **Example 7. Significant Difference from placebo in patient global impression of change (PGIC) at day 15 and day 28**

Global rating of change (GRC) scales were designed to quantify a patient's improvement or deterioration over time, usually either to determine the effect of an intervention or to chart the clinical course of a condition. GRC scales ask a patient to assess his or her current health status, recall that status at the beginning of treatment, and then calculate the difference between the two. The simplicity of GRC scales makes them easy to administer and applicable to a wide range of patients (see, *e.g.*, Kamper *et al.*, 2009 *The Journal of Manual & Manipulative Therapy* 17(3):163-170).

20 The Patient Global Impression of Change (PGIC) is a 7-point GRC consisting of one question: "With respect to your essential tremor, how would you describe yourself now, as compared to when you started taking the study drug?" Subjects will choose one

of the following answers: “very much worse, much worse, minimally worse, no change, minimally improved, much improved, very much improved.”

Treatment success as measured by PGIC was summarized using descriptive statistics. Differences between treatment groups were assessed using an ANCOVA model with fixed effects for treatment, anti-tremor medication use, and site type (Figure 7 and Table 7).

Table 7. Mean PGIC Score at Day 15 and Day 28 by Treatment Group.

|                           | Day 15  |         |         |         | Day 28  |         |         |         |
|---------------------------|---------|---------|---------|---------|---------|---------|---------|---------|
|                           | CX-8998 |         | Placebo |         | CX-8998 |         | Placebo |         |
|                           | number  | percent | number  | percent | Number  | percent | Number  | percent |
| <b>Worsened</b>           | 2       | 5.12    | 5       | 11.36   | 3       | 8.11    | 3       | 7.14    |
| <b>No Change</b>          | 11      | 28.2    | 27      | 61.36   | 14      | 37.84   | 29      | 69.05   |
| <b>Improved</b>           | 26      | 66.67   | 12      | 27.27   | 20      | 54.05   | 10      | 23.81   |
| <b>Total</b>              | 39      | 100     | 44      | 100     | 37      | 100     | 42      | 100     |
| <b>p value vs placebo</b> | 0.003   |         |         |         | 0.089   |         |         |         |

#### 10 Example 8. Significant difference from placebo in goal attainment scale (GAS)

Goal Attainment Scaling (GAS) is a tool that involves the development of a written set of goals between a physician and patient and was used for monitoring patient progress. GAS was developed in 1968 (see, e.g., Kiresuk & Sherman, 1968 *Community Mental Health Journal* 4:443–453) and has been employed in patients with physical disorders including spasticity (see, e.g., Ashford *et al.*, 2006 *Physiother Res Int.* 11(1):24-34) and multiple sclerosis (Khan *et al.*, 2008 *Arch Phys Med Rehabil.* 89(4):652-9).

GAS frames the discussion in terms of individual patient-desired goals rather than universally applied health states. Goal-oriented care prompts patients to articulate which

health goals are most important to them. Patients and clinicians can then monitor progress in reaching them.

Subjects identify 3 health goals at Baseline. Examples of goals are drinking from a cup, buttoning a shirt or ability to write. Goals may be either active or passive. All goals will be specifically tailored to the individual, with each subject required to rate each goal at baseline on the level of importance, based on a 3-point scale (1 = fairly important; 2 = very important; 3 = extremely important). For the investigator, the feasibility of attaining each goal must be considered before the goals are set and adjusted accordingly if needed. Once each goal is set, the investigator is asked to rate the degree of difficulty in achieving each of the set goals, based on another 3-point scale (1 = probable; 2 = possible; 3 = doubtful.)

Progress towards each goal is scored on a 5-point scale: -2 = Worse than Baseline (unfavorable outcome); -1 = No change from Baseline; 0 = Achieved the defined goal (expected outcome); +1 = Better than expected outcome; +2 = Best anticipated outcome.

GAS is mapped to the values -2 to 2, from the worst outcome to the best outcome, respectively. Differences between treatment groups were assessed using an ANCOVA model with fixed effects for treatment, anti-tremor medication use, and site type (Figure 8 and Table 8).

Overall GAS Score =  $50 + (10 * \text{sum of weights})/\text{square root} (0.7 * \text{sum of weights}^{**2}) + [0.3 * (\text{sum of weights})^{**2}]$ .

Table 8. Mean Difference From Placebo in Goal Attainment Score.

|                               | <b>LS Mean Difference from Placebo</b> | <b>Confidence Interval</b> | <b>p value</b> | <b>N</b> |
|-------------------------------|--|----------------------------|----------------|----------|
| <b>Day 15<br/>(8 mg BID)</b>  | 2.9                                    | (-0.6, 6.4)                | 0.103          | 39       |
| <b>Day 28<br/>(10 mg BID)</b> | 4.8                                    | (0.4, 9.3)                 | 0.034          | 37       |

**Example 9. Significant increase vs placebo in Percentage of subjects satisfied with anti-tremor medication at day 15 and day 28 (QUEST sub-item)**

The QUEST is a 30-item questionnaire that contributes to 5 sub-scales (physical, psychosocial, communication, hobbies/leisure and work/finance) and a total score, plus 3 additional items relating to sexual function and satisfaction with tremor control and medication side effects within the last month of treatment. Initial reports provide preliminary support of its reliability and validity. The internal consistency was very good to excellent for 4 scales and the total score, and moderately high for the Work/Finance scale (see, e.g., Tröster *et al.*, 2005 *Parkinsonism Relat Disord.* 11(6):367-373). These reliability coefficients are also supportive of the QUEST's construct validity.

Percentage of subjects responding affirmatively to the following question were summarized at baseline, Day 15 and Day 28: "In the past month are you satisfied with tremor control by your anti-tremor medications? (Y/N)". Statistical significance compared to placebo was calculated using Fisher's exact test (Figure 9 and Table 9).

15

Table 9. Patient satisfaction when asked: In the past month are you satisfied with tremor control by your anti-tremor medications? (Y/N).

|          | CX-8998 |    | Placebo |    | p-value Fishers Exact Test |
|----------|---------|----|---------|----|----------------------------|
|          | % Yes   | N  | % Yes   | N  |                            |
| Baseline | 3       | 39 | 7       | 44 | 0.619                      |
| Day 15   | 38      | 39 | 11      | 44 | 0.005                      |
| Day 28   | 38      | 37 | 14      | 42 | 0.011                      |

**Example 10. CX-8998 Plasma concentrations resulting in clinical efficacy at day 15 and day 28**

CX-8998 efficacy in rat models of CNS disease have demonstrated CX-8998 efficacy at human equivalent concentrations of 300 – 700 nM. Dose response analyses of human pharmaco-EEG data confirmed that reductions of alpha power of about 25% or

greater (and indirect marker of CNS target engagement) occurred in a dose- and concentration- dependent manner at plasma CX 8998 concentrations greater than 200 to 300 nM (4 mg BID). Modeling suggested a single dose of 8 mg would result in reduction of 25% or greater in alpha power for approximately 12 hours post-dose. Dose response analysis of adverse event data suggested that incidence of CNS and psychiatric adverse events is increased at concentrations greater than 800 nM. Based on human PK profiles from healthy volunteers, final steady state concentrations of CX-8998 between 200 and 800 nM were targeted in T-CALM with a 10 mg BID dose under fed conditions.

All T-CALM subjects had blood sample drawn prior to administration of CX-8998 at Visits 2 (trough concentration at 4 mg BID dose), 3 (trough concentration at 8 mg BID), and 4 (trough concentration at 10 mg BID). Additionally, at Visit 4, a post-dose sample will be collected as close to 4 hours post-dose as possible, but within the window of 4-6 hours post-dose (i.e., a total of two PK samples are collected at Visit 4.)

Cavion has developed and validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) bioanalytical methods for the simultaneous quantitation of CX-8998 and metabolites (M01, M02, M03, and M04) in rat, dog, and human plasma as per recent FDA guidance (FDA, Guidance for Industry: Bioanalytical Method Validation, May 2018, available at: [fda.gov/downloads/drugs/guidances/ucm070107.pdf](https://fda.gov/downloads/drugs/guidances/ucm070107.pdf)). Assay performances were satisfactory and met acceptance criteria for system performance suitability, quantitation range, calibration linearity, assay accuracy and precision, and assay recovery. These “5-in-1” bioanalytical methods were used to quantitate CX-8998 and its 4 metabolites in samples that were collected in T-CALM (Figure 10 and Table 10).

Table 10. CX-8998 Plasma Concentration (nM).

|                 | Dose Level | Sample Time | Mean | STD | 95% CI     | Min, Max  | N  |
|-----------------|------------|-------------|------|-----|------------|-----------|----|
| Visit 2 (Day 8) | 4 mg BID   | trough      | 304  | 161 | (254, 354) | (23, 883) | 43 |

|                  |           |                   |     |     |             |            |    |
|------------------|-----------|-------------------|-----|-----|-------------|------------|----|
| Visit 3 (Day 15) | 8 mg BID  | trough            | 568 | 262 | (484, 651)  | (85, 1280) | 40 |
| Visit 4 (Day 28) | 10 mg BID | trough            | 707 | 355 | (589, 826)  | (18, 1806) | 37 |
|                  |           | 4 hours post-dose | 866 | 371 | (773, 1007) | (18, 1793) | 36 |

### Example 11. CX-8998 Metabolite exposure following BID dosing of CX-8998

CX-8998 metabolites M01 – M04 are active Cav3 antagonists. The “5-in-1” bioanalytical methods were used to quantitate CX-8998 metabolites M01, M02, M03 and M04 in samples that were collected in T-CALM (Figure 11 and Table 11).

Table 11. CX-8998 Plasma Concentrations (nM).

| M01 Plasma Concentration (nM) |            |                   |      |     |             |            |    |
|-------------------------------|------------|-------------------|------|-----|-------------|------------|----|
|                               | Dose Level | Sample Time       | Mean | STD | 95% CI      | Min, Max   | N  |
| Visit 2 (Day 8)               | 4 mg BID   | trough            | 398  | 152 | (351, 444)  | (122, 732) | 43 |
| Visit 3 (Day 15)              | 8 mg BID   | trough            | 812  | 352 | (700, 925)  | (73, 1966) | 40 |
| Visit 4 (Day 28)              | 10 mg BID  | trough            | 1023 | 501 | (856, 1191) | (84, 2933) | 37 |
|                               |            | 4 hours Post-dose | 976  | 383 | (847, 1106) | (84, 2286) | 36 |
| M02 Plasma Concentration (nM) |            |                   |      |     |             |            |    |
|                               | Dose Level | Sample Time       | Mean | STD | 95% CI      | Min, Max   | N  |
| Visit 2 (Day 8)               | 4 mg BID   | trough            | 168  | 75  | (145, 192)  | (15, 353)  | 43 |
| Visit 3 (Day 15)              | 8 mg BID   | trough            | 325  | 134 | (282, 368)  | (38, 658)  | 40 |
| Visit 4 (Day 28)              | 10 mg BID  | trough            | 406  | 168 | (350, 462)  | (31, 888)  | 37 |
|                               |            | 4 hours Post-dose | 438  | 141 | (390, 486)  | (31, 769)  | 36 |
| M03 Plasma Concentration (nM) |            |                   |      |     |             |            |    |
|                               | Dose Level | Sample Time       | Mean | STD | 95% CI      | Min, Max   | N  |
| Visit 2 (Day 8)               | 4 mg BID   | trough            | 11   | 5.9 | (7.9, 14)   | (7, 29)    | 16 |
| Visit 3 (Day 15)              | 8 mg BID   | trough            | 16   | 6.6 | (13, 18)    | (8, 34)    | 28 |
| Visit 4 (Day 28)              | 10 mg BID  | trough            | 20   | 13  | (16, 25)    | (8, 65)    | 35 |
|                               |            | 4 hours Post-dose | 22   | 13  | (18, 27)    | (8, 68)    | 34 |

| M04 Plasma Concentration (nM) |            |                   |      |      |            |            |    |
|-------------------------------|------------|-------------------|------|------|------------|------------|----|
|                               | Dose Level | Sample Time       | Mean | STD  | 95% CI     | Min, Max   | N  |
| Visit 2 (Day 8)               | 4 mg BID   | trough            | 4.5  | 0.38 | (1.1, 7.8) | (4.2, 4.7) | 2  |
| Visit 3 (Day 15)              | 8 mg BID   | trough            | 4.9  | 1.9  | (3.8, 6.0) | (3.0, 9.0) | 14 |
| Visit 4 (Day 28)              | 10 mg BID  | trough            | 5.6  | 5.3  | (3.3, 7.8) | (2.6, 28)  | 24 |
|                               |            | 4 hours Post-dose | 6.4  | 3.8  | (4.9, 7.9) | (2.7, 16)  | 27 |

These data demonstrate that a composition including a combination of more than one Cav3 antagonist (e.g. CX-8998 plus its active metabolites) is relevant to the treatment of movement disorders.

5

### Example 12. Responder analysis for tetras and CGI-I

Responder analysis was utilized to describe the proportion of subjects demonstrating a certain threshold of response to treatment based on a cut-off value for a particular scale. Table 12 summarizes the proportion of subjects who achieved an improvement from baseline of at least 5 points in the three TETRAS scales (performance subscale, activities of daily living and total score) and the proportion of subjects scored as improved (minimally improved, much improved and very much improved) using the CGI-I. Statistical analysis was conducted by Fisher's exact test.

15 Table 12. CX-8998 Plasma Concentrations (nM).

| Summary of CX-8998 Responder Analysis   |         |            |         |            |         |
|---|---------|------------|---------|------------|---------|
| Question  | CX-8998 |            | Placebo |            | P-value |
|   | N       | Number (%) | N       | Number (%) |         |
| What proportion of subjects had improvement of at least 5 points by TETRAS Total score at Day 28? | 37      | 21 (56.8%) | 42      | 13 (31%)   | 0.025   |
| What proportion of subject had improvement of at least 5 points by TETRAS Total score at Day 15?  | 39      | 22 (56.4%) | 43      | 13 (30.2%) | 0.025   |

|  |    |               |    |                |        |
|--|----|---------------|----|----------------|--------|
| <b>What proportion of subjects had improvement of at least 5 points by TETRAS-PS score at Day 28?</b>  | 37 | 16<br>(43.2%) | 42 | 8<br>(19.1%)   | 0.027  |
| <b>What proportion of subjects had improvement of at least 5 points by TETRAS-PS score at Day 15?</b>  | 39 | 12<br>(30.8%) | 44 | 10<br>(22.7%)  | ns     |
| <b>What proportion of subjects had improvement of at least 5 points by TETRAS-ADL score at Day 28?</b> | 37 | 11<br>(29.7%) | 42 | 10<br>(23.81%) | ns     |
| <b>What proportion of subjects had improvement of at least 5 points by TETRAS-ADL score at Day 15?</b> | 39 | 18<br>(46.2%) | 43 | 8<br>(18.6%)   | 0.009  |
| <b>What proportion of subjects showed improvement by CGI-I at Day 28?</b>                              | 37 | 24<br>(64.9%) | 41 | 9<br>(22.0%)   | <0.001 |
| <b>What proportion of subjects showed improvement by CGI-I at Day 15?</b>                              | 39 | 25<br>(64.1%) | 44 | 20<br>(45.5%)  | ns     |

5 Proportion of subjects achieving a response as defined by at least 5 points of improvement on a TETRAS endpoint or any level of improvement by Clinical Global Impression. Statistical analysis by Fishers Exact Test. Following tables show granular data for each endpoint.

| TETRAS Total Score at Day 15          |                 |                 |
|---------------------------------------|-----------------|-----------------|
| Change from Baseline                  | Placebo<br>N=43 | CX-8998<br>N=39 |
| <b>&gt;20 point improvement</b>       | 2 (4.7%)        | 2 (5.1%)        |
| <b>&gt;10 to 20 point improvement</b> | 6 (14.0%)       | 12 (30.8%)      |
| <b>&gt;5 to 10 point improvement</b>  | 4 (9.3%)        | 6 (15.4%)       |
| <b>&gt;2.5 to 5 point improvement</b> | 9 (20.9%)       | 7 (17.9%)       |
| <b>&gt;1 to 2.5 point improvement</b> | 5 (11.6%)       | 2 (5.1%)        |
| <b>&gt;0 to 1 point improvement</b>   | 3 (7.0%)        | 2 (5.1%)        |
| <b>0 change</b>                       | 2 (4.7%)        | 1 (2.6%)        |
| <b>&gt;0 to 1 point worsening</b>     | 0               | 2 (5.1%)        |
| <b>&gt;1 to 2.5 point worsening</b>   | 0               | 1 (2.6%)        |
| <b>&gt;2.5 to 5 point worsening</b>   | 8 (18.6)        | 4 (10.3%)       |
| <b>&gt; 5 to 10 point worsening</b>   | 2 (4.7%)        | 0               |
| <b>&gt;10 point worsening</b>         | 1 (2.3%)        | 0               |

| TETRAS Total Score at Day 28          |                 |                 |
|---------------------------------------|-----------------|-----------------|
| Change from Baseline                  | Placebo<br>N=42 | CX-8998<br>N=37 |
| <b>&gt;20 point improvement</b>       | 2 (4.8%)        | 5 (13.5%)       |
| <b>&gt;10 to 20 point improvement</b> | 6 (14.3%)       | 8 (21.6%)       |
| <b>&gt;5 to 10 point improvement</b>  | 3 (7.1%)        | 7 (18.9%)       |
| <b>&gt;2.5 to 5 point improvement</b> | 6 (14.3%)       | 5 (13.5%)       |
| <b>&gt;1 to 2.5 point improvement</b> | 4 (9.5%)        | 2 (5.4%)        |
| <b>&gt;0 to 1 point improvement</b>   | 6 (14.3%)       | 2 (5.4%)        |
| <b>0 change</b>                       | 1 (2.4%)        | 0               |
| <b>&gt;0 to 1 point worsening</b>     | 2 (4.8%)        | 4 (10.8%)       |
| <b>&gt;1 to 2.5 point worsening</b>   | 6 (14.3%)       | 2 (5.4%)        |
| <b>&gt;2.5 to 5 point worsening</b>   | 2 (4.6%)        | 1 (2.7%)        |
| <b>&gt; 5 to 10 point worsening</b>   | 2 (4.6%)        | 0               |
| <b>&gt;10 point worsening</b>         | 2 (4.6%)        | 0               |

| TETRAS-PS Score at Day 15             |                 |                 |
|---------------------------------------|-----------------|-----------------|
| Change from Baseline                  | Placebo<br>N=44 | CX-8998<br>N=39 |
| <b>&gt;10 point improvement</b>       | 3 (6.8%)        | 3 (7.7%)        |
| <b>&gt;5 to 10 point improvement</b>  | 7 (15.9%)       | 8 (20.5%)       |
| <b>&gt;2.5 to 5 point improvement</b> | 6 (13.6%)       | 10 (25.6%)      |
| <b>&gt;1 to 2.5 point improvement</b> | 7 (15.9%)       | 4 (10.3%)       |
| <b>&gt;0 to 1 point improvement</b>   | 6 (13.6%)       | 3 (7.7%)        |
| <b>0 change</b>                       | 5 (11.4%)       | 2 (5.1%)        |
| <b>&gt;0 to 1 point worsening</b>     | 5 (11.4%)       | 2 (5.1%)        |
| <b>&gt;1 to 2.5 point worsening</b>   | 4 (9.1%)        | 5 (12.8%)       |
| <b>&gt;2.5 to 5 point worsening</b>   | 1 (2.3%)        | 2 (5.1%)        |
| <b>&gt; 5 to 10 point worsening</b>   | 0               | 0               |
| <b>&gt;10 point worsening</b>         | 0               | 0               |

| TETRAS-PS Score at Day 28             |                 |                 |
|---------------------------------------|-----------------|-----------------|
| Change from Baseline                  | Placebo<br>N=42 | CX-8998<br>N=37 |
| <b>&gt;10 point improvement</b>       | 2 (4.5%)        | 4 (10.3%)       |
| <b>&gt;5 to 10 point improvement</b>  | 5 (11.4%)       | 8 (20.5%)       |
| <b>&gt;2.5 to 5 point improvement</b> | 15 (34%)        | 11 (28.2%)      |
| <b>&gt;1 to 2.5 point improvement</b> | 5 (11.4%)       | 5 (12.8%)       |
| <b>&gt;0 to 1 point improvement</b>   | 6 (13.6%)       | 6 (15.4%)       |
| <b>0 change</b>                       | 0               | 1 (2.6%)        |
| <b>&gt; 0 to 1 point worsening</b>    | 3 (6.8%)        | 2 (5.1%)        |
| <b>&gt;1 to 2.5 point worsening</b>   | 5 (11.4%)       | 1 (2.6%)        |
| <b>&gt;2.5 to 5 point worsening</b>   | 3 (6.8%)        | 1 (2.6%)        |
| <b>&gt; 5 to 10 point worsening</b>   | 0               | 0               |
| <b>&gt;10 point worsening</b>         | 0               | 0               |

| TETRAS-ADL Score at Day 15            |                 |                 |
|---------------------------------------|-----------------|-----------------|
| Change from Baseline                  | Placebo<br>N=43 | CX-8998<br>N=39 |
| <b>&gt;10 point improvement</b>       | 2 (4.7%)        | 5 (12.8%)       |
| <b>&gt;5 to 10 point improvement</b>  | 4 (9.3%)        | 11 (28.2%)      |
| <b>&gt;2.5 to 5 point improvement</b> | 8 (18.6%)       | 7 (17.9%)       |
| <b>&gt;1 to 2.5 point improvement</b> | 9 (20.9%)       | 2 (5.1%)        |
| <b>&gt;0 to 1 point improvement</b>   | 6 (14.0%)       | 5 (12.8%)       |
| <b>0 change</b>                       | 6 (14.0%)       | 2 (5.1%)        |
| <b>&gt;0 to 1 point worsening</b>     | 4 (9.3%)        | 1 (2.6%)        |
| <b>&gt;1 to 2.5 point worsening</b>   | 2 (4.7%)        | 3 (7.7%)        |
| <b>&gt;2.5 to 5 point worsening</b>   | 6 (14.0%)       | 3 (7.7%)        |
| <b>&gt; 5 to 10 point worsening</b>   | 1 (2.3%)        | 0               |
| <b>&gt;10 point worsening</b>         | 1 (2.3%)        | 0               |

| TETRAS-ADL Score at Day 28            |                 |                 |
|---------------------------------------|-----------------|-----------------|
| Change from Baseline                  | Placebo<br>N=42 | CX-8998<br>N=37 |
| <b>&gt;10 point improvement</b>       | 4 (9.5%)        | 5 (13.5%)       |
| <b>&gt;5 to 10 point improvement</b>  | 2 (4.8%)        | 6 (16.2%)       |
| <b>&gt;2.5 to 5 point improvement</b> | 7 (16.7%)       | 7 (18.9%)       |
| <b>&gt;1 to 2.5 point improvement</b> | 3 (7.1%)        | 3 (8.1%)        |
| <b>&gt;0 to 1 point improvement</b>   | 4 (9.5%)        | 2 (5.4%)        |
| <b>0 change</b>                       | 5 (11.9%)       | 5 (13.5%)       |
| <b>&gt;0 to 1 point worsening</b>     | 6 (14.3%)       | 3 (8.1%)        |
| <b>&gt;1 to 2.5 point worsening</b>   | 2 (4.8%)        | 3 (8.1%)        |
| <b>&gt;2.5 to 5 point worsening</b>   | 5 (11.9%)       | 3 (8.1%)        |
| <b>&gt; 5 to 10 point worsening</b>   | 3 (7.1%)        | 0               |
| <b>&gt;10 point worsening</b>         | 1 (2.4%)        | 0               |

| CGI-I Score at Day 15         |                 |                 |
|-------------------------------|-----------------|-----------------|
| Change from Baseline          | Placebo<br>N=44 | CX-8998<br>N=39 |
| <b>3 – very much improved</b> | 1 (2%)          | 0               |
| <b>2 – much improved</b>      | 5 (11%)         | 6 (15%)         |
| <b>1 – minimally improved</b> | 14 (32%)        | 19 (49%)        |
| <b>0 – no change</b>          | 21 (48%)        | 14 (36%)        |
| <b>-1 – minimally worse</b>   | 2 (5%)          | 0               |
| <b>-2 – much worse</b>        | 1 (2%)          | 0               |
| <b>-3 – very much worse</b>   | 0               | 0               |
| CGI-I Score at Day 28         |                 |                 |
| Change from Baseline          | Placebo<br>N=44 | CX-8998<br>N=39 |
| <b>3 – very much improved</b> | 1 (2%)          | 0               |
| <b>2 – much improved</b>      | 2 (5%)          | 9 (23%)         |
| <b>1 – minimally improved</b> | 7 (16%)         | 15 (38%)        |
| <b>0 – no change</b>          | 30 (68%)        | 13 (33%)        |
| <b>-1 – minimally worse</b>   | 2 (5%)          | 0               |
| <b>-2 – much worse</b>        | 0               | 0               |
| <b>-3 – very much worse</b>   | 0               | 0               |

| PGIC Score at Day 15          |                 |                 |
|-------------------------------|-----------------|-----------------|
| Change from Baseline          | Placebo<br>N=44 | CX-8998<br>N=39 |
| <b>3 – very much improved</b> | 1 (2%)          | 1 (3%)          |
| <b>2 – much improved</b>      | 3 (7%)          | 8 (21%)         |
| <b>1 – minimally improved</b> | 8 (18%)         | 17 (44%)        |
| <b>0 – no change</b>          | 27 (61%)        | 11 (28%)        |
| <b>-1 – minimally worse</b>   | 1 (2%)          | 1 (3%)          |
| <b>-2 – much worse</b>        | 4 (9%)          | 1 (3%)          |
| <b>-3 – very much worse</b>   | 0               | 0               |
| PGIC Score at Day 28          |                 |                 |
| Change from Baseline          | Placebo<br>N=44 | CX-8998<br>N=39 |
| <b>3 – very much improved</b> | 2 (5%)          | 3 (8%)          |
| <b>2 – much improved</b>      | 2 (5%)          | 7 (18%)         |
| <b>1 – minimally improved</b> | 6 (14%)         | 10 (26%)        |
| <b>0 – no change</b>          | 29 (66%)        | 14 (36%)        |
| <b>-1 – minimally worse</b>   | 2 (5%)          | 1 (3%)          |
| <b>-2 – much worse</b>        | 1 (2%)          | 1 (3%)          |
| <b>-3 – very much worse</b>   | 0               | 1 (3%)          |

### Example 13. Relationship between cx-8998 plasma concentration and response

Evaluation of the relationship between the  $C_{min}$  exposure level of CX-8998 and response (E) as measured by change from baseline in TETRAS-PS using the Hill Equation:

$$\text{Response} = E_{max} * C_{min}^b / (C_{min}^b + EC_{50}^b)$$

The  $E_{max}$  and  $EC_{50}$  values were estimated to be approximately -4.1 and 250 nM; however, the value for "b" was not statistically significant.

Summary of PK/PD Findings: The evaluation was done under steady state conditions, using concentration values ( $C_{min}$ ) for CX-8998, combinations of analytes or total active moiety (TAM; the sum of the exposures to all measured Cav3 antagonists, *e.g.* total exposure of CX-8998 and all of its metabolites) and using either trough (T=0 hours) or post dose (T=4 hours; day 28 only) concentration samples for each study visit. 5 Pharmacodynamic variables (Response) evaluated included change from baseline in TETRAS performance subscale, TETRAS activities of daily living, TETRAS total score.

The analysis found that concentration ranges were not low enough to fully define the PK/PD relationship, which suggests that the full pharmacological effect has been 10 reached within the anticipated therapeutic range of 200 to 800 nM.

Change in TETRAS PS is shown in Figure 12 and is representative of similar results obtained with other PD markers (*e.g.*, change in total TETRAS score).

#### Example 14. Patient population

The patient population enrolled in T-CALM had a mean baseline TETRAS-PS 15 score of 28.4 points, mean baseline TETRAS-ADL score of 26 points and mean time from ET diagnosis of 23 years. In addition, the majority of patients (64%) were also taking concomitant anti-tremor medications and those who were not taking ET medications were refractory to or intolerant of first and second line ET therapies. Thus 20 efficacy was observed on top of standard of care in a moderate to severe ET population refractory to existing therapies.

Table 13. Patient Demographics.

|                               |                     | CX-8998<br>n=48 | Placebo<br>n=47 | Total<br>n=95 |
|-------------------------------|---------------------|-----------------|-----------------|---------------|
| Demographics<br>-well matched | Age, years (SD)     | 64 (9.6)        | 63 (10.8)       | 63 (10.2)     |
|                               | Age Group (%>65yrs) | 26 ( 54%)       | 25 ( 53%)       | 51 ( 54%)     |
|                               | Male, n (%)         | 25 (52%)        | 25 (53%)        | 50 (53%)      |

|   |                                      |                  |                  |                  |
|---|--------------------------------------|------------------|------------------|------------------|
|   | White, n (%)                         | 45 (94%)         | 46 (98%)         | 91 (96%)         |
|   | Weight, kg* (SD)                     | 88.8 (19.25)     | 84.8 (20.72)     | 86.8 (19.98)     |
| <b>Baseline characteristics</b><br><b>-moderate to severe</b><br><b>-on tremor meds</b> | <b>Years Since Tremor Onset (SD)</b> | <b>24 (16.3)</b> | <b>21 (15.7)</b> | <b>23 (16.0)</b> |
|   | Alcohol Response (%Yes)              | 23 (48%)         | 16 (34%)         | 39 (41%)         |
|   | <b>On Anti-Tremor Meds (%)</b>       | <b>28 (58%)</b>  | <b>33 (70%)</b>  | <b>61 (64%)</b>  |
|   | TETRAS-PS - Central (SD)             | 23.1 (6.27)      | 22.8 (5.67)      | 22.9 (5.95)      |
|   | TETRAS-PS - Investigator (SD)        | 28.3 (5.95)      | 28.5 (6.35)      | 28.4 (6.13)      |
|   | TETRAS-ADL                           | 26 (6.0)         | 26 (7.0)         | 26 (6.5)         |

### Example 15. Adverse Event profile

5 This is a summary of the most common (>2%) treatment-emergent adverse events related to study drug by system organ class and preferred term that confirms the benign nature of CX-8998 safety and tolerability profile.

Table 14. Summary of adverse events.

| MedDRA System Organ Class/<br>Preferred Term <sup>1</sup>              | CX-8998<br>(n = 48) | Placebo<br>(n = 47) |
|--|---------------------|---------------------|
| Subjects with at least 1 treatment-emergent adverse event <sup>2</sup> | <b>28 (58%)</b>     | <b>23 (49%)</b>     |
| Nervous System Disorders   | <b>20 (42%)</b>     | <b>10 (21%)</b>     |
| Dizziness  | 10 (21%)            | 3 (6%)              |
| Headache   | 4 (8%)              | 2 (4%)              |

|                                    |                 |                |
|------------------------------------|-----------------|----------------|
| Disturbance in attention           | 2 (4%)          | 1 (2%)         |
| Dysgeusia                          | 2 (4%)          | 0              |
| Paraesthesia                       | 2 (4%)          | 1 (2%)         |
| Somnolence                         | 1 (2%)          | 2 (4%)         |
| Hypesthesia                        | 0               | 2 (4%)         |
| <b>Psychiatric Disorders</b>       | <b>12 (52%)</b> | <b>1 (2%)</b>  |
| Euphoric mood                      | 3 (6%)          | 0              |
| Insomnia                           | 3 (6%)          | 0              |
| Abnormal dreams                    | 2 (4%)          | 1 (2%)         |
| Hallucination                      | 2 (4%)          | 0              |
| <b>Gastrointestinal Disorders</b>  | <b>9 (19%)</b>  | <b>7 (15%)</b> |
| Dry mouth                          | 2 (4%)          | 1 (2%)         |
| Nausea                             | 1 (2%)          | 3 (6%)         |
| Vomiting                           | 0               | 2 (4%)         |
| <b>Infections and Infestations</b> | <b>4 (8%)</b>   | <b>3 (6%)</b>  |
| Urinary Tract Infection            | 2 (4%)          | 1 (2%)         |
| <b>Ear and Labyrinth Disorders</b> | <b>2 (4%)</b>   | <b>0</b>       |
| Tinnitus                           | 2 (4%)          | 0              |

#### **Example 16. Toleration to adverse events with dose titration**

T-CALM employed the following dose titration scheme: Week 1 at 4 mg BID (8 mg/day), Week 2 at 8 mg BID (16 mg/day) and Weeks 3 & 4 at 10 mg BID (20 mg/day). Adverse event reports decrease after the first week of dosing despite the fact that dose was being increased at the beginning of Weeks 2 and 3. This shows that patients tolerate quickly to CX-8998 related CNS and psychiatric adverse events (Figure 13). Adverse Events were coded using MedDRA V20.0. Only treatment emergent adverse events with an onset date and time after the initiation of study drug until 30 days after discontinuation of drug were reported. For subjects who experience the same coded event more than once, a single event was presented. Adverse events were attributed to a study week based

on the onset date, i.e. events that started on or after Visit 1 and prior to Visit 2 were classified as Study Week 1.

Table 15. Adverse events in other system organ classes.

| System Organ Class  | CX-8998     |             |            |           |           | Placebo    |            |            |           |           |
|---|-------------|-------------|------------|-----------|-----------|------------|------------|------------|-----------|-----------|
|   | 1           | 2           | 3          | 4         | >4        | 1          | 2          | 3          | 4         | >4        |
| <b>Any Event</b>  | 19<br>(40%) | 10<br>(21%) | 8<br>(17%) | 2<br>(4%) | 1<br>(2%) | 9<br>(19%) | 7<br>(15%) | 9<br>(19%) | 4<br>(9%) | 1<br>(2%) |
| <b>Central Nervous System Disorders</b>                     | 16<br>(33%) | 4<br>(8%)   | 1<br>(2%)  | 0         | 1<br>(2%) | 2<br>(4%)  | 3<br>(6%)  | 5<br>(11%) | 1<br>(2%) | 1<br>(2%) |
| <b>Psychiatric Disorders</b>                                | 8<br>(17%)  | 2<br>(4%)   | 3<br>(6%)  | 2<br>(4%) | 0         | 1<br>(2%)  | 1<br>(2%)  | 0          | 0         | 0         |
| <b>Gastrointestinal Disorders</b>                           | 7<br>(15%)  | 1<br>(2%)   | 1<br>(2%)  | 0         | 0         | 4<br>(9%)  | 3<br>(6%)  | 0          | 0         | 0         |
| <b>Infections and Infestations</b>                          | 0           | 2<br>(4%)   | 2<br>(4%)  | 0         | 0         | 2<br>(4%)  | 0          | 0          | 1<br>(2%) | 0         |
| <b>Investigations</b>                                       | 1<br>(2%)   | 1<br>(2%)   | 1<br>(2%)  | 1<br>(2%) | 0         | 1<br>(2%)  | 0          | 1<br>(2%)  | 0         | 0         |
| <b>General Disorders and Administration Site Conditions</b> | 3<br>(6%)   | 0           | 0          | 0         | 0         | 0          | 0          | 0          | 0         | 0         |
| <b>Metabolism and Nutrition Disorders</b>                   | 1<br>(2%)   | 0           | 1<br>(2%)  | 1<br>(2%) | 0         | 0          | 0          | 1<br>(2%)  | 0         | 0         |
| <b>Musculoskeletal and Connective Tissue Disorders</b>      | 1<br>(2%)   | 1<br>(2%)   | 1<br>(2%)  | 0         | 0         | 0          | 0          | 0          | 0         | 0         |
| <b>Ear and Labyrinth Disorders</b>                          | 2<br>(4%)   | 0           | 0          | 0         | 0         | 0          | 0          | 0          | 0         | 0         |
| <b>Injury, Poisoning and Procedural Complications</b>       | 1<br>(2%)   | 0           | 1<br>(2%)  | 0         | 0         | 1<br>(2%)  | 0          | 0          | 0         | 0         |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      | 1<br>(2%)   | 0           | 1<br>(2%)  | 0         | 0         | 0          | 1<br>(2%)  | 0          | 0         | 0         |
| <b>Eye Disorders</b>  | 1<br>(2%)   | 0           | 0          | 0         | 0         | 0          | 0          | 0          | 0         | 0         |
| <b>Neoplasms</b>  | 1<br>(2%)   | 0           | 0          | 0         | 0         | 0          | 0          | 0          | 0         | 0         |
| <b>Skin and Subcutaneous Tissue Disorders</b>               | 1<br>(2%)   | 0           | 0          | 0         | 0         | 1<br>(2%)  | 1<br>(2%)  | 0          | 2<br>(4%) | 0         |
| <b>Vascular Disorders</b>                                   | 0           | 1<br>(2%)   | 0          | 0         | 0         | 0          | 0          | 0          | 0         | 0         |

### **Example 17. No cardiovascular safety findings at efficacious doses**

An integrated analysis of electrocardiogram outliers revealed no CVS safety signals. Electrocardiogram results were calculated as the average of the triplicate records at each time point. Baseline was defined as the mean of the triplicate values obtained pre-dose at Day 1. If this value was not available, the mean of the triplicate records obtained at screening were used. A summary of electrocardiogram outliers is shown in Figure 14. No difference was seen between CX-8998 and Placebo (Figure 15).

### **Example 18. Subgroup analysis**

Exploratory subgroup analyses of the primary and secondary efficacy endpoints includes the following subgroups formed from baseline parameters:

1. Sex: male and female
2. Age at the time of informed consent as defined by: subjects up to 65 years of age and subjects >65 years of age
3. Baseline severity as assessed by centrally rated TETRAS performance score baseline values: greater than and less than the median value.
4. Baseline tremor asymmetry defined as a >1 point difference between the right and left side on any one of the TETRAS performance subscale items 4A (postural tremor), 4B (wingbeating tremor) or 4C (kinetic tremor): asymmetry present and asymmetry absent
5. Baseline ratio of TETRAS performance postural tremor (subscale item 4A) versus kinetic tremor (subscale item 4C) as defined by the ratio of total postural tremor (sum of left and right hand) divided by total kinetic tremor (sum of left and right hand): greater than and less than the median ratio
6. Baseline ratio of Kinesia ONE postural tremor versus kinetic tremor defined and grouped similarly to the ratio above
7. Baseline rest tremor as defined as total rest score (sum of rest for left and right hand) measured by Kinesia ONE at baseline of greater than (presence) or less than

(absence) the median total rest tremor score: presence of rest tremor and absence of rest tremor

8. Concurrent essential tremor medication at Day 1: yes and no, also a subgroup on subjects taking beta-blockers will be examined

5 9. Primidone use at study start as defined as subjects who discontinued primidone use within two weeks prior to or during the screening period: taking primidone and not taking primidone

10 Individual endpoints including TETRAS-PS (Figure 16) and TETRAS-ADL (Figure 17) representative of the results are shown. Subsets that may show increase improvement with Cav3 antagonist treatment include females, patients with higher severity of tremor, and subjects not concurrently taking antitremor medications. Subjects with lower levels of rest tremor and a lower ration of postural to kinetic tremor may also achieve greater level of improvement.

15

**Example 19. Analytical methods for measuring CX-8998 and metabolites in human plasma with a single bioanalytical assay separating M02 & M04**

20 A liquid chromatography tandem mass spectrometry (LC/MS/MS) method was developed, qualified and validated for the simultaneous quantitation of CX-8998 and M01, M02, M03, and M04 concentrations in human plasma K2EDTA. To develop a 5-in-1 assay for the simultaneous quantitation of analytes CX-8998, M01, M02, M03 and M04 in human plasma, an HPLC method which is capable to retain and separate all 25 compounds within a reasonable run time was necessary. Furthermore, due to the isobaric nature of M02 and M04, baseline separation was required for accurate quantitation of these metabolites.

With MW around 400 g/mol and calculated logP values between 3 and 5, all 5 compounds were prime candidates to be analyzed by reverse phase chromatography. Based on the structural differences between the analytes, separation between CX-8998,

M01, M03 and either M02 or M04 was not difficult. The challenge was to develop a condition which can achieve baseline resolution between M02 and its isobaric positional isomer, M04. Various early screenings using Agilent Zorbax extended C18, Agilent Eclipse XDB C18, and Phenomenex Synergi MaxRP columns were tested (data not shown); however, none were able to satisfactorily separate M02 and M04. Eventually, the Phenomenex Luna C18 column showed the highest resolving power between M02 and M04 and was selected for further HPLC method optimization.

Phenomenex Luna C18 Chromatography was initially investigated. During initial trials using the Luna C18 (30x2.0mm, 3 $\mu$ m) column, only partial separation was achieved between M02 and M04 and peak widths for M01 and M03 were suboptimal (Figure 18).

Optimizations to reduce peak width and increase peak resolution involved adjustments in:

- sample solvent compositions (lower organic content for enhanced retention)
- mobile phase modifiers (reduce secondary interactions)
- 15 ion-pairing (alter retention behaviour to improve peak shape)
- solvent strength of organic mobile phases (lowering strength to enhance retention and change in selectivity)

However, none resulted in satisfactory separation between M02 and M04. Furthermore, peak widths were still suboptimal.

20 Phenomenex Luna Phenyl-Hexyl Chromatography: A chromatography based mainly on hydrophobic interactions (e.g., C18) was concluded not strong enough to achieve the required separation. The introduction of additional interaction types can enhance selectivity. A phenyl-hexyl column provides unique electrostatic, hydrogen bonding, and dipole-dipole interactions based on its electron rich aromatic phenyl-hexyl phase. It was hypothesized these unique chemistries can generate sufficient specificity to 25 separate M02 and M04. Slightly better peak resolution between the analytes compared to a C18-based system was observed, however, this column type (30x2mm, 3 $\mu$ m) exhibited unwanted secondary interactions resulting in poor peak shapes (Figure 19).

Phenomenex Kinetex PFP Chromatography: The highly electronegative pentafluorophenyl (PFP) bonded phase offers alternative selectivity (hydrophobic, pi-pi interactions, dipole-dipole, hydrogen-bonding, and shape selectivity) compared to traditional C18-based or phenyl-hexyl reverse-phase columns in part due to the electron deficient phenyl ring and high retention for halogen related compounds. Near baseline separation of all five analytes from a plasma sample was achieved using this column chemistry type (100x2.1mm, 2.6 $\mu$ m, and Figure 20).

An excessively long run time was necessary to provide sufficient separation of all analytes, thus this method was prohibitively long and would be logistically challenging for the analysis of prospective clinical plasma test samples. The ideal run time should be 15 minutes or less. Several chromatographic optimizations were investigated to further reduce runtime:

increasing column temperatures to enable the use of higher flow rates without hampering column efficiency

shorter column length

Unfortunately, these changes resulted in deteriorated resolution between M02 and M04. Shortening of the method run time was not possible.

Sample Derivatization Development: Analyte derivatization was investigated as an alternative to chromatographically separate M02 and M04 while maintaining a reasonable method run time. Since the structural difference between M02 and M04 was only by the position of one hydroxyl group (3°-OH in M02; 1°-OH in M04), it should be possible to selectively react with the 1°-OH group while the sterically hindered 3°-OH group remain non-reacted. This should provide stronger structural difference to allow separation during chromatography. Various OH-group derivatization methods from the literature were reviewed and 4, involving selective acylation and dansylation of the primary alcohol moiety, were selected and tested.

Table 16. Chromatographic optimization parameters.

| Condition         | 1                       | 2                   | 3                      | 4                          |
|-------------------|-------------------------|---------------------|------------------------|----------------------------|
| Reagent           | Acetic anhydride        | Acetic anhydride    | TFA                    | Dansyl Chloride            |
| Donating Group    | Acetate, MW 42          | Acetate, MW 42      | Acetate, MW 42         | Dansyl, MW 176             |
| Temperature       | 50°C                    | 50°C                | RT                     | 60°C                       |
| pH                | Acidic (in acetic acid) | Basic (in pyridine) | Acidic (TFA)           | Basic (sodium bicarbonate) |
| Time (h)          | 1.5                     | 0.5                 | 0.25                   | 0.42                       |
| Reaction with M02 | No                      | No                  | No                     | No                         |
| Reaction with M04 | various forms detected  | No                  | various forms detected | Yes                        |

Acetylation under acidic conditions was selective but appeared to form a complex mixture of M04 reaction products with low reaction yield. Minimal derivatization was observed with dansylation and reaction with TFA resulted in complex mixture of M04 reaction products (data not shown). Acetylation with acetic anhydride under basic conditions appeared to be selective for M04 and showed high reaction yield (Figure 21). Signal intensity for M04 appeared to be 100- fold lower than that of other analytes due to its reaction with the reagent. Formation of a M04 product peak at 8.48 minute (compared to the unreacted M04 peak at 7 minutes) was detected with a m/z of 439.4, which corresponded to the mass of singly acetylated M04 (M04-Ac) entity. This was confirmed by the observation of a daughter fragment at 204 m/z, in line with the daughter fragment observed for all other analytes.

Kinetics of the M04 Acetylation Reaction: A plasma reaction and stability time course experiment was subsequently performed to determine reaction kinetics up to 2 hours at 50°C. Reaction kinetics was evaluated for M04 at 2.5 µg/mL independently and as a mixture containing the other analytes, in equal volumes with acetic anhydride and pyridine, to verify efficiency of the reaction. The derivatization reaction reached a plateau in the formation of M04-Ac between ~30 to 60 minutes of reaction at 50°C with or without the presence of other analytes. Approximately 6% of M04 remained unreacted after ~30 minutes of reaction (Figure 22).

Table 17. M04 Acetylation Reaction.

| Reaction Time (min) | % M04 Peak Area Remaining |
|---------------------|---------------------------|
| 0                   | 100.0                     |
| 25                  | 5.9                       |
| 38                  | 4.6                       |
| 78                  | 2.8                       |
| 130                 | 2.3                       |

To reduce the amounts of unreacted M04 remaining, pyridine and acetic anhydride volumes were increased by up to 2.5-fold and 5-fold, respectively (Figure 23).

5 The best yield was achieved when the plasma:pyridine:acetic anhydride volume ratio was at 1:2.5:5 (% M04 unreacted ~2.2%). This condition was selected for method validation. Increase in reaction temperature as a means to improve reaction yield was not investigated due to potential concerns of analyte instability. Stability was also evaluated for CX-8998, M01, M02, and M03 at 2.5 µg/mL in the presence of equal volumes of 10 acetic anhydride and pyridine at 50°C. Overall, CX-8998, M01, M02, and M03 appeared to be stable up to 130 minutes of reaction at 50°C (Figure 24).

Following optimization of the chromatography, the following 5-in-1 LC/MS/MS assay for the quantitation of CX-8998, M01, M02, M03, and M04 concentrations from 1 to 2000 ng/mL in human plasma K2EDTA was performed.

15 Sample preparation procedures: With reference to a previously validated method for CX-8998, M01, and M02 involving protein precipitation (Merck, West Point, SBP 261), the following procedure was adopted and qualified:

1. Prepare serial dilutions of reference and internal standard solutions in 1:1 diH<sub>2</sub>O:ACN
- 20 2. Add 10µL each of the reference standard and internal standard solutions to 0.2 mL of human plasma K2EDTA
3. Precipitate plasma proteins with 0.6 mL of ACN
4. Centrifuge and obtain supernatant
5. Evaporate dry supernatant at 50°C

6. Reconstitute samples in 0.1 mL of dichloromethane with sonication for 5 minutes
7. Derivatization with 20  $\mu$ L\* each of acetic anhydride and pyridine at 50°C for 30 minutes
8. Evaporate dry at 50°C
- 5 9. Reconstitute samples in 0.1% formic acid in 1:1 diH<sub>2</sub>O:ACN with sonication for 10 minutes

\*Volumes were optimized subsequent to method qualification to use 100  $\mu$ L of acetic anhydride and 50  $\mu$ L of pyridine. This was a minor modification with no anticipated impact to assay performance aside from higher reaction yields for M04-Ac.

10 Therefore, these volume ratios were not re-qualified.

#### Chromatographic Parameters

|                     |  |
|---------------------|--|
| MPA                 | 0.1% (v/v) FA in diH <sub>2</sub> O                                |
| MPB                 | 0.1% (v/v) FA in ACN   |
| Column              | Phenomenex Kinetex PFP (50 x 2.1 mm, 100 $\text{\AA}$ , 5 $\mu$ m) |
| 15 Injection volume | 10 $\mu$ L   |
| Run time            | 14 min   |
| Autosampler temp    | 2°C to 8°C   |
| Column temp         | 30°C   |
| Needle wash         | 0.1% (v/v) FA in CAN   |

20 Table 18. HPLC Gradient Time Table.

| Time | %B | Flow (mL/min) |
|------|----|---------------|
| 0.00 | 20 | 0.5           |
| 0.10 | 20 | 0.5           |
| 0.11 | 25 | 0.5           |
| 4.50 | 29 | 0.5           |
| 4.51 | 36 | 0.5           |
| 8.50 | 40 | 0.5           |

|       |    |     |
|-------|----|-----|
| 8.51  | 98 | 0.5 |
| 10.00 | 98 | 0.5 |
| 10.01 | 98 | 0.8 |
| 11.50 | 98 | 0.8 |
| 11.51 | 20 | 0.8 |
| 13.90 | 20 | 0.8 |
| 13.91 | 20 | 0.8 |
| 14.00 | 20 | 0.8 |

Mass Spectrometry Parameters: The analytes were monitored using Micromass Quattro®-LC tandem triple quadrupole mass spectrometer, controlled by Micromass MassLynx® software Version 4.0. Representative MS parameters (ESI positive, MRM mode) were as follows:

Table 19. Mass Spectrometry Parameters.

| Analyte                       | MRM     | Cone (V) | Collision Energy (eV) |
|-------------------------------|---------|----------|-----------------------|
| CX-8998                       | 381>204 | 40       | 24                    |
| M01                           | 379>204 | 40       | 23                    |
| M02                           | 397>204 | 38       | 23                    |
| M03                           | 411>204 | 40       | 22                    |
| M04-Ac                        | 439>204 | 45       | 21                    |
| d <sub>3</sub> -CX-8998 (ITS) | 384>207 | 40       | 25                    |
| d <sub>3</sub> -M01 (ITS)     | 382>207 | 40       | 24                    |
| d <sub>3</sub> -M02 (ITS)     | 400>207 | 38       | 24                    |
| d <sub>3</sub> -M03 (ITS)     | 414>207 | 40       | 22                    |
| d <sub>3</sub> -M04-Ac (ITS)  | 442>207 | 40       | 23                    |

Chromatography. A representative chromatographic performance following an injection of a 10 ng/mL of CX-8998, M01, M02, M03, and M04 in human plasma sample is shown in Figure 25.

In this study, a 5-in-1 LC/MS/MS assay was developed for the simultaneous quantitation of CX- 8998 and its metabolites M01, M02, M03 and M04 in human plasma

K2EDTA. Due to the isobaric nature of M02 and M04, full separation could not be achievable via hydrophobic interactions by traditional C18-based reverse-phase systems. A variety of other alternative reverse-phase columns were evaluated and near complete separation was achieved utilizing a pentafluorophenyl (PFP) bonded column, albeit with 5 prohibitively long run times. Consequently, an acetylation derivatization approach specific for M04 was successfully developed which enabled satisfactory chromatographic separation for all five analytes in reasonable assay runtimes.

The LC/MS/MS assay for the simultaneous quantitation of all five analytes was subsequently qualified with a calibration range of 1 to 2000 ng/mL for all analytes in 10 human plasma. Assay performances were satisfactory and met acceptance criteria for system performance suitability, quantitation range, calibration linearity, assay accuracy and precision, and assay recovery. Slight chromatographic carryover was observed for CX-8998. Some reference standard impurities were observed; however, levels were negligible and have minimal impact on calibration. Low residual levels of unreacted M04 15 was observed resulting in interference in M02 detection. Overall, this is expected to have minimal impact as only a total bias of ~7.1% to M02 quantitation resulting from the sum of all interferences. The accuracy limit of the assay for quantitation of M02 at varying ratios of M04 in samples was ascertained during method validation.

**20 Example 20. Wide safety margins between human therapeutic exposures and toxicology findings in nonclinical studies**

Safety margins for CX-8998 and its metabolites M01 and M02 were calculated from exposures in the 90-day repeat-dose toxicology studies in rats and dogs at the 25 NOAEL doses (300 mg/kg/day and 30 mg/kg/day, respectively) for total (bound and unbound) CX-8998, M01, and M02, based on estimated human plasma concentration ( $C_{ss}$ ) and area under the curve (AUC<sub>24</sub>) values at steady state for 10 mg BID dosing. In addition, safety margins for the sum of the exposures of the active components (CX-8998, M01 and M02) or so called “total active moiety” (TAM) was also calculated.

Calculated safety margins for total CX-8998 AUC<sub>24</sub> in males and females were 19-fold and 41-fold respectively in rats and 24-fold and 26-fold in dogs. Calculated total

margins for CX-8998  $C_{ss}$  in males and females were 39- and 91-fold respectively in rats and 68- and 74-fold in dogs. In rat, margins were approximately 2-fold lower in males than in females while in dog margins were similar across the 2 sexes.

5 The calculated safety margins for total  $AUC_{24}$  (female/male) are 41-/19-, 13-/6.8-, and 62-/31-fold for CX-8998, M01, and M02, respectively, in rat and 26-/24-, 5.6-/6.5, and 25-/26-fold, respectively, in dog (Table 20). The calculated safety margins for total  $C_{ss}$  (female/male) are 91-/39-, 21-/13-, and 104-/56-fold for CX-8998, M01, and M02 respectively in rats, and 74-/68-, 8-/10-, and 46-fold, respectively, in dogs.

10 The calculated safety margins for total  $AUC_{24}$  TAM are 32- and 16-fold in female and male rats respectively and 17- and 16-fold in both female and male dogs. The calculated safety margins for total  $C_{ss}$  TAM are 62- and 31-fold in female and male rats respectively and 39- and 37-fold in female and male dogs respectively.

15 Table 20. Total Margins (in Fold) Based on Rat and Dog Day 90 TK Assessments and Human Estimated Exposures at Steady State

| NOAEL<br>Dose       | Parameter      | Total Margins for Human 10 mg BID at Steady State |      |        |      |        |      |
|---------------------|----------------|---|------|--------|------|--------|------|
|                     |                | CX-8998   |      | M01    |      | M02    |      |
|                     |                | Female  | Male | Female | Male | Female | Male |
| Rat<br>300<br>mg/kg | $C_{ss}^a$     | 91  | 39   | 21     | 13   | 104    | 56   |
|                     | $AUC_{24hr}^b$ | 41  | 19   | 13     | 6.8  | 62     | 31   |
|                     | $TAM C_{ss}^c$ | 62  | 31   |        |      |        |      |
|                     | $TAM AUC^d$    | 32  | 16   |        |      |        |      |
| Dog<br>30 mg/kg     | $C_{ss}^a$     | 74  | 68   | 8.0    | 10   | 46     | 46   |
|                     | $AUC_{24hr}^b$ | 26  | 24   | 5.6    | 6.5  | 25     | 26   |
|                     | $TAM C_{ss}^c$ | 39  | 37   |        |      |        |      |
|                     | $TAM AUC^d$    | 17  | 16   |        |      |        |      |

$C_{ss}$  margin calculated from rat and dog  $C_{max}$  and human estimated  $C_{ss}$  at steady state for each analyte.

$AUC$  margin calculated from rat and dog  $AUC$  and human estimated  $AUC$  at steady state for each analyte.

$C_{ss}$  total active moiety (TAM) margin calculated from rat and dog  $C_{max}$  TAM and human estimated  $C_{ss}$  TAM at steady state (1,967 nM).  $^d$   $AUC$  TAM margin calculated from rat and dog  $AUC$  TAM and human estimated  $AUC$  TAM at steady state (40,728 nM\*hr).

### Example 21. CX-8998 formulation development

CX-8998 was formulated into 1 mg, 2 mg, 3 mg, 4 mg, 8 mg, 12 mg, and 18 mg capsules and used as single morning doses. Capsules with varied doses provide highly flexible titration schedules, and allow ideal dosing regimens.

5 The performance of CX-8998 immediate release capsules was evaluated in human subjects and in a simulated gastrointestinal tract where 900 mL of acidic medium was used to mimic the stomach.

10 Rapid release of CX-8998 from the immediate release formulation in the acid medium is shown in Figure 26. Overall, the plasma profiles followed a 2 compartment PK model that was dose proportional in the 2-18 mg dose range. Slight shifts in both 15 terminal elimination rate and redistribution were seen in elderly patients (Figure 29).

15 *In silico* models were developed to generate theoretical release profiles that would yield desired plasma concentration values at steady-state between minimum effective concentration and maximum tolerated concentration. Models were validated against independent data sets to predict CX-8998 behavior in GI tract and systemically in young and elderly males.

Optimizations were carried out with 2 mg, 4 mg, 8 mg, 12 mg and 18 mg single morning doses in elderly males. PK parameters in elderly males are as shown below.

| Parameter | 2-compartments |
|-----------|----------------|
| CL (L/h)  | 2.6576         |
| Vc (L/kg) | 0.18219        |
| K12 (1/h) | 1.495          |
| K21 (1/h) | 0.28064        |

20 Plasma concentrations of CX-8998 in elderly patients following a single morning dose of 2 mg, 4 mg, 8 mg, 12 mg, or 18 mg capsules are shown in Figure 31. Predicted and observed output correlations for elderly patients are shown in Figure 32.

Optimizations were carried out simultaneously with 1 mg, 3 mg, 8 mg, and 12 mg single morning doses in healthy males. PK parameters in young males are as shown below.

| Parameter | 2-compartments |
|-----------|----------------|
| CL (L/h)  | 3.9515         |
| Vc (L/kg) | 0.32511        |
| K12 (1/h) | 0.21431        |
| K21 (1/h) | 0.13625        |

5 Maximum CX-8998 exposures associated with different doses in healthy volunteers are as follows:

| Study                      | PN001<br>Part 1 | PN001<br>Part 2 | PN002<br>Part 1 | PN002<br>Part 2 | Average | PN002<br>Part 2 |
|----------------------------|-----------------|-----------------|-----------------|-----------------|---------|-----------------|
| Dose                       | 16 mg           | 18 mg           | 18 mg           | 12 mg           | 16      | 12 mg           |
| # of Doses                 | 1               | 1               | 1               | 1               | 1       | 7               |
| C <sub>max</sub> (nM)      | 940<br>(259)    | 1180<br>(352)   | 1330<br>(325)   | 798<br>(167)    | 1062    | 895<br>(271)    |
| t <sub>1/2</sub> (h)       | 14.3            | 14.8            | 26.1            | 18.4            | 18.4    | 14.2            |
| AUC <sub>0-24</sub> (h*nM) | 8520<br>(2380)  | 9930<br>(1340)  | 9440<br>(1720)  | 4990<br>(1100)  | 8220    | 6100<br>(604)   |
| AUC <sub>inf</sub> (h*nM)  | 12500<br>(5000) | 14600<br>(3120) | 18500<br>(6620) | 7310<br>(1110)  | 13200   | NC              |

10 Plasma concentrations of CX-8998 in young patients following a single morning dose of 1 mg, 3 mg, 8 mg, and 12 mg capsules are shown in Figure 33. Predicted and observed output correlations for young patients are shown in Figure 34. Plasma

concentrations of CX-8998 in young patients following multiple single morning doses of 1 mg, 3 mg, 8 mg, and 12 mg capsules are shown in Figure 35.

A comparison of Simulated release profiles for a single daily dose and for multiple daily doses of 12 mg/day in young and elderly subjects is shown in Figure 28.

5 Release profiles from different matrices were evaluated using the *in silico* model to determine target release profiles by optimization of matrix or by combining beads of different release profiles (e.g. immediate release (IR) + sustained release (SR) or IR + delayed release (DR)). Zero order release from an osmotic pump tablet is shown in Figure 38. First order release from a matrix tablet having coated beads in a capsule is shown in Figure 39. Burst and zero order release from an osmotic pump tablet with an IR release coating is shown in Figure 40. Burst and first order release from a mixture of IR and slow release beads in a matrix tablet with an IR coating is shown in Figure 41. A double burst with a 3 hour delay from a mixture of IR beads and pH 6 enteric-coated beads from an IR tablet with enteric coating and an IR coating is shown in Figure 42. A double burst with a 6 hour delay from a mixture of IR beads and pH 7 enteric-coated beads from an IR tablet with enteric coating and an IR coating is shown in Figure 10. Based on model an ideal release profile for young adult males is about a 6 mg burst followed by ~12 mg at an almost constant rate over 12 hours (Figure 36), and an ideal release profile for elderly males is about a 7 mg burst followed by ~12 mg at a slightly diminishing rate over 12 hours (Figure 37).

10

15

20

Sustained release (SR) beads were developed with multiple types of sustained release and enteric coatings. Some SR matrix beads were developed using typical polymers (e.g, hydroxypropyl methylcellulose or carbopol) to achieve sustained release. Some SR matrix beads were developed using pH independent sustained release osmotic pumps to achieve zero order release from the tablet. Some SR matrix beads were developed using a delayed release (DR) coating of IR beads to obtain release at pH 6 or 7, and to take advantage of poor solubility of CX-8998 at higher pH values to provide sustained release. Some SR matrix beads were developed using Eudragit RS/RL30D

25

coating of IR beads to achieve an approach that depends on slow erosion of coating thereby sustaining the release of the drug from an IR matrix.

### **Example 22. Twice daily (BID) CX-8998**

A randomized, double-blind, placebo-controlled, parallel-group study (NCT03101241) of 95 patients with ET that have an inadequate response to anti-tremor medication (e.g., propranolol) was performed. Following consent and screening, subjects were randomized to receive oral doses of either CX-8998 (titrated up to 10 mg BID) or placebo for 28 days. Clinical rating scales, patient-reported outcomes and accelerometer recordings of tremor and digital spirography were collected at baseline (visit 1), day 15 (visit 3) and day 28 (visit 4).

Plasma concentrations of CX-8998 showed predictable steady state exposure that achieved target levels from multiple different dosages delivered twice daily (Figure 10).

Investigator-rated TETRAS (The Essential Tremor Rating Assessment Scale) Performance Subscale ( $p=0.027$ ), TETRAS ADL ( $p=0.049$ ), TETRAS total score ( $p=0.007$ ) and Clinician Global Impression of Improvement ( $p=0.001$ ) significantly improved (Figure 44). There were no major safety and tolerability concerns.

Upper Dose Limits Based on Tolerability Profile: up to 10 mg BID Yields Concentrations Associated with Lower Occurrence of CNS AEs. The sigmoidal relationship suggests that the frequency of CNS AEs may begin to increase substantially at CX-8998 plasma concentrations of approximately 700-800 nM (Figure 45).

The study achieved proof-of-concept in ET and identified key pivotal study design parameters including primary and secondary efficacy endpoints, patient population and titration scheme. CX-8998 was safe and well tolerated in ET patients. These results are expected to enable late-stage development of CX-8998 in ET.

CX-8998 formulations were developed that include a total active moiety (TAM) of CX-8998 and CX-8998 metabolites. For example a TAM can be the sum of CX-8998, M01, and M02 concentrations adjusted for plasma protein binding (fu) and potency relative to CX-8998 ( $C_{u,ss\_TAM}$ ) as shown in Table 21.

Table 21. Css of CX-8998, M01, M02, and Total Active Moiety (TAM) Simulated from CX-8998 10 mg BID.

| PK Parameter   | CX-8998 | M01  | M02  | Total Active Moiety<br>(CX-8998 + M01 + M02) |
|----------------|---------|------|------|--|
| Cp,ss (nM)     | 583     | 771  | 343  | -  |
| fU (%)         | 0.4     | <0.1 | 14   | -  |
| Potency        | 1.0     | 1.37 | 0.21 | -  |
| Cu,ss (nM)     | 2.3     | <0.8 | 48   | -  |
| Cu,ss_adj (nM) | 2.3     | <1.2 | 10.1 | 14.4   |

5 Target exposure levels and PK profiles of total and unbound CX-8998 in plasma and TAM following administration of CX-8998 10 mg BID are shown in Figure 46.

### Example 23. Target CX-8998 concentrations

Exemplary target concentrations for CX-8998 were established as shown in Appendix A.

### 10 Example 24. Study Design and Methodology for Efficacy Endpoint and Digital Biomarker Selection

The T-CALM study assesses the efficacy of CX-8998, at doses up to 10mg BID, for reduction of severity (amplitude) of ET. An optional/additional component of the main T-CALM study is the T-CALM digital substudy that evaluates the feasibility of 3 different digital monitoring platforms for accurate quantification of changes in motor function in ET patients. An exemplary T-CALM design is shown in Figure 47.

15 The T-CALM study is a proof of concept, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. The screening period is up to 4 weeks. Before any study procedures are conducted, patients read and sign informed consents. Primidone (a strong CYP3A4 inducer) use is excluded due to the potential of CX-8998 to be subject

to CYP3A metabolism. Thus, patients taking primidone are given 6 weeks of screening to allow for safe discontinuation of the drug. Stable doses of a single anti-tremor medication other than primidone as a standard of care are allowed during the study. Patients that meet screening criteria are randomized to treatment group A or B. Group A receives 5 titrated doses of CX-8998 up to 10 mg BID. Group B receives matching placebo. Randomized study participants enter a 4-week, double-blind, dose titration period followed by a 1-week safety follow up after the last dose of study medication. At baseline (day 1), patients have safety and tremor evaluations prior to administration of study treatments. During the first week, patients receive 4 mg of study drug or matching 10 placebo twice daily. On day 8 (week 2), patients are assessed at the clinic for safety and dose titration to 8 mg (or matching placebo) twice daily. On day 15 (week 3), patients report to clinic for safety and efficacy evaluations and final dose titration to 10mg (or matching placebo) twice daily. The final efficacy visit is day 28 (week 4). The final safety visit takes place on day 35 (week 5). Blood samples are collected pre-dose on days 15 8, 15 and 28 and at approximately 4 hours post-dose on day 28 for plasma concentration measurements of CX-8998. If intolerable adverse events (AEs) are evident at any of the doses, the dose may be decreased to the next lowest dose at day 8 or 15 or at any time 20 prior to those scheduled visits. If the lowest scheduled dose (4mg BID) is intolerable, it can be decreased to 2 mg BID. After dose reduction, an increase in dose is not be allowed. If patients do not tolerate dose reduction, they are withdrawn from treatment.

Patients that have been screened and met the eligibility criteria for the main T-CALM study have the option to additionally participate in the T-CALM digital substudy. Enrollment of patients in the substudy is randomized to CX-8998 or placebo in the same proportion (1:1) as the main study. After informed consent is signed, patients are given 25 the option to use one or both of two digital tools, iMotor or Kinesia 360, or to conduct additional testing with Kinesia One for objective measurement of motor function. The dosing regimen and schedule of safety assessments for the substudy are identical to that of the main study. At the screening visit, patients in the iMotor arm of the substudy have evaluations completed in the presence of a study staff member. Patients in the Kinesia 30 360 arm of the substudy wear the device to collect data for 2 days after screening and

then return the device to the study site. Data collected for these 2 days serve as baseline motor assessments for Kinesia 360. At baseline (day 1), baseline iMotor evaluations are taken prior to dosing and after completion of the main T-CALM safety and tremor assessments. At the end of weeks 1 and 2, safety and Kinesia 360 and iMotor evaluations are collected. The final efficacy measurements for both devices are collected at the end of week 4 visit. The final safety visit is at the end of week 5.

The study enrolls a population of moderate to severe ET patients inadequately treated with standard of care approaches. Key eligibility criteria for the main T-CALM study are as follows:

- 10 1. Signed, informed consent are obtained for all study participants
2. Males and females 18-75 years of age are enrolled
3. Patients with moderate to severe ET and initial diagnosis prior to age 65 are included
4. Tremor severity score of at least 2 in at least one upper limb of the 3 maneuvers
- 15 5. TETRAS-PS score of at least 15 at screen
6. On stable doses of up to one concurrent anti-tremor medication permitted; use of strong CYP inducer primidone is excluded
7. Surgical intervention excluded

20

A complete list of inclusion/exclusion criteria for the main T-CALM study is available online at ClinicalTrials.gov under registration number NCT03101241.

Eligibility criteria for the optional T-CALM digital substudy are as follows:

1. Patients must meet all eligibility criteria of the main T-CALM study protocol
- 25 2. Patients must be able to comply with user requirements as assessed by site personnel

3. Patients are not issued digital devices/downloads until they have consented to participate in the optional T-CALM digital substudy

5 The primary, secondary and exploratory efficacy endpoints for the main T-CALM study are listed below:

The primary endpoint is the change from baseline to day 28 of the TETRAS performance subscale. The secondary endpoints are the change from baseline to day 28 for the TETRAS Activity of Daily Living Schedule and for the Kinesia One score. There are several exploratory endpoints. The change from baseline to days 15 and 28 for Total 10 TETRAS score (independent video rater) and for Kinesia One is measured. The change from baseline to day 15 for the TETRAS performance subscale (independent video rater) and Kinesia One Score is evaluated. Treatment success at the end of therapy will be measured by Patient Global Impression of Change (PGIC), Clinical Global Impression of Improvement (CGI-I), Goal Attainment Scaling (GAS) and Quality of Life in Essential 15 Tremor Questionnaire (QUEST).

There are 2 exploratory endpoints for the T-CALM digital substudy. Kinesia 360 measures the change in tremor amplitude from baseline to days 15 and 28. The iMotor test evaluates 5 simple motor functions including digital spirography from baseline to days 15 and 28.

20 Several performance scales and an objective biometric monitoring are utilized in the main T-CALM study. These tools generate relevant and convergent efficacy data that may more accurately define the response of patients to ET therapies.

The Essential Tremor Rating Assessment Scale (TETRAS; see, e.g., Elble et al., 2012 *Mov Disord.* 27:1567-1569) and is composed of a 9-item performance subscale and 25 a 12-item activities of daily living (ADL) subscale. These subscales provide a rapid clinical evaluation (< 10 minutes) of ET using pen and paper methodology. The performance subscale measures tremor amplitude (severity) in the head, face, voice, limbs and trunk as well as functional tests including handwriting, drawing a spiral and

holding a pen over a dot on a 5-point rating scale where 0 represents no tremor and 4 indicates severe tremor. The sum of the individual scores generates an overall performance subscale score from 0 to 64. The TETRAS performance subscale is scored by both investigators at the clinical site and independent video raters. The scores of the 5 independent video rater are statistically analyzed as the change from baseline to day 28 and serve as the primary efficacy endpoint. The most optimal rating methodology (investigator vs independent video rated TETRAS performance subscale) is selected for late-stage development. The performance subscale data is also used for exploratory analysis of efficacy on day 15. The ADL subscale evaluates activities of daily living such 10 as speaking, eating, drinking, dressing, personal hygiene, writing and carrying items. The patient scores each item from 0 (normal activity) to 4 (severe abnormality). The overall score ranges from 0 to 48 and are analyzed as the change from baseline to day 28 as a secondary efficacy endpoint. The total TETRAS score (sum of the performance subscale and ADL) on the change from baseline to days 15 and 28 is evaluated as an exploratory 15 endpoint.

Kinesia One platform is deployed in T-CALM as a digital marker of tremor severity. Kinesia One is FDA cleared for monitoring Parkinson's motor symptom severity with only limited data on assessment of tremor in ET patients. The 20 algorithmically derived score was developed primarily in Parkinson's disease algorithms and has limited validation in ET (see, e.g., Hoffman et al., 2011 *Conf Proc IEEE Eng Med Biol Soc.* 2011:4378-81). The Kinesia One device is placed on the index finger of each ET patient and worn in the clinic after completion of the TETRAS Performance subscale. Four tasks are performed by the patient on the left and right sides to assess resting, postural, kinetic and lateral wing beating tremor. The Kinesia One score change 25 in score from baseline to day 28 is evaluated as a secondary efficacy endpoint. The Kinesia One data is also utilized for exploratory analysis of efficacy on the change from baseline to day 15 for accelerometry score and for change from baseline on amplitude measures for days 15 and 28. Consistent finger sensor placement and consistent task execution are critical factors for valid Kinesia One scores.

Due to the deleterious effects of ET on daily activities and well-being, several quality of life assessments are conducted to more accurately assess the patient's perception of the disorder and the effects of pharmacotherapy from baseline to the conclusion of treatment (day 28). Each of these questionnaires and scales requires 5 substantial input from the ET patient and the data is used to address exploratory efficacy endpoints.

The Quality of Life in Essential Tremor Questionnaire (QUEST) (see, e.g., Tröster et al., 2005 *Parkinsonism Relat Disord.* 11:367-373) is used to evaluate the consequences of ET on daily life of ET patients from baseline to day 28. The 10 questionnaire contains 30 items that involve 5 subscales (physical, psychosocial, communication, hobbies/leisure and work/finance) and a total score. There are also 3 additional items that pertain to sexual capability, satisfaction with tremor control and side effects of pharmacotherapy. If the treatment program for ET is beneficial, whether symptomatic or curative, patients are likely respond in a positive manner to QUEST. The 15 QUEST includes questions that are not expected to change within a 28-days timeframe. However, some items such as the satisfaction with tremor control may generate insightful data.

The Clinical Global Impressions Scale (CGI) generates a clinician's perception of a patient's functioning prior to and after study medication (see, e.g., Guy, *Assessment 20 Manual for Psychopharmacology*. Rockville, MD: Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976). The CGI overall score considers patient history, psychosocial situations, symptoms and behavior with respect to the ability to function. The CGI-Improvement (CGI-I) will involve a single 7-point rating of total improvement or change from baseline 25 CGI-Severity (CGI-S). The clinician rater will select one response (from 1 = very much improved to 7 = very much worse) based upon the question, "Compared to your patient's condition at the onset of treatment, how much has your patient changed?"

The Patient Global Impression of Change (PGIC) will quantify a patient's impression of improvement or decline over time with respect to ET treatment (see, e.g.,

Guy, *Assessment Manual for Psychopharmacology*. Rockville, MD: Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976). The patient will use the PGIC scale to assess current health status versus initiation of treatment and calculate the difference. The 7-point scale will 5 ask the question, "With respect to your ET, how would you describe yourself now compared to when you started taking the study drug?" The patient replies with one of 7 answers from very much worse to very much improved.

The Goal Attainment Scaling (GAS) (see, e.g., Kiresuk et al., 1968 *Community 10 Mental Health J.* 4:443-453) requires interaction between the physician and ET patient for development of a written set of individual patient-desired goals to track progress of treatment. At baseline, each patient establishes 3 individual health goals and rates each 15 goal as fairly important = 1, very important = 2 or extremely important = 3. The clinician rates the degree of difficulty for each goal as probable = 1, possible = 2 or doubtful = 3. During the study, progress is scored on a 5-point scale from worse than baseline = -2 to best anticipated outcome = +2.

Two additional biometric monitoring tools are employed in the T-CALM digital substudy to explore their ability to measure changes in motor function of ET patients. The data is used for exploratory efficacy endpoints.

The Kinesia 360 (Great Lakes NeuroTechnologies, Cleveland, OH, USA) (see, 20 e.g., Pullam et al., 2014 *Parkinsonism Relat Disord.* 20:37-40) is a home monitoring system that utilizes wrist and ankle sensors to objectively and continuously tabulate motion data. The Kinesia 360 kit contains a smartphone with the installed Kinesia 360 application, two wearable sensors and charging equipment. The sensors capture 3-dimensional linear acceleration and angular velocity from the wrist and ankle of each ET 25 patient throughout each day. At the end of each day, the motion data are uploaded from the smartphone to a central server. The data are processed to detail the occurrence and severity of tremor as well as the patient's level of daily activity.

The iMotor (Apptomics, Inc., Wellesley Hills, MA, USA) (see, e.g., Mitsi et al., 2017 *Front. Neurol.* 13:273) is a tablet-based application that objectively measures motor

function in patients with abnormal movement. The iMotor test is only conducted during scheduled visits. Each ET patient is required to conduct 5 simple tasks (finger tapping, hand tapping, hand pronation and supination, reaction to a mild stimulus, and a spiral drawing with a digital stylus) on a tablet. Each task has a time limit of 30 seconds and 5 will be done twice (once with each hand).

10 All treatment-emergent adverse events are coded into the Medical Dictionary for Regulatory Activities (MedDRA) version 20 with system organ classes and preferred terms and displayed in frequency tables by treatment group. Adverse events are characterized by maximum severity, drug-related adverse events, serious adverse events and adverse events leading to discontinuation of study.

15 Other safety assessments include physical examination, neurological examination, vital signs, clinical laboratory tests (hematology, chemistry and urinalysis), urine drug screen, pregnancy tests, electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (C-SSRS), Epworth Sleepiness Scale (ESS) and University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ) (see, e.g., Papapetropoulos et al., 2008 *BMC Neurol.* 8:21).

20 All statistical analyses are performed with the SAS system, version 9.4 or higher based on a prespecified statistical analysis plan. Based upon phase 2 studies of comparable design, a sample size of approximately 92 patients are appropriately powered to provide proof-of-concept safety and efficacy data on CX-8998 in the main T-CALM study.

There is not a formal sample size determination. It is proposed that at least 30 patients are randomized to CX-8998 or placebo.

25 **Example 25. Safety and efficacy of CX-8998, a selective modulator of the T-Type calcium channel, in patients with essential tremor**

Essential tremor (ET) is a debilitating disorder that significantly impairs quality of life (QOL). Current pharmacotherapies are not optimal. T-CALM evaluated safety and efficacy of a selective T-type calcium channel modulator, CX-8998, in ET patients.

This Example describes a phase 2, randomized, double-blind, proof-of-concept trial (T-CALM) that evaluated CX-8998, titrated to 10 mg twice daily, in ET patients, age 18-75. Patients had moderate to severe ET and were allowed stable dosages of up to 1 concurrent anti-tremor medication (excluding primidone). Study participants were 5 randomized (1:1) to receive CX-8998 or placebo for 28 days. Primary and secondary endpoints were change from baseline to Day 28 on TETRAS-performance scale (PS) and TETRAS-activities of daily living (ADL) scores, respectively. Exploratory endpoints included global impression of change (CGI), global goal attainment (GAS), and QOL scores. Safety and tolerability were monitored. T-CALM is registered with 10 ClinicalTrials.gov, NCT03101241.

T-CALM was designed to be adequately powered to enable decision making for further development of CX-8998 in inadequately treated ET. Eligibility criteria were carefully defined to ensure selection of a well-defined cohort of ET patients. Clinically meaningful and convergent clinician-measured and patient-reported outcomes with 15 validated performance scales, objective biometric tools, and quality of life questionnaires were utilized as key endpoints to assess drug efficacy. The results of the T-CALM trial demonstrated that CX-8998 reduced tremor severity on the basis of several clinically relevant and confluent efficacy endpoints, and CX-8998 had a favorable safety and tolerability profile.

## 20 **Methods**

### *Study Design and Participants*

T-CALM was designed as a phase 2, proof-of-concept, multicenter (22 U.S. sites), double-blind, randomized, placebo-controlled trial to evaluate efficacy, safety, and tolerability of CX-8998, after titration to a target dosage of 10 mg BID for 28 days, in 25 patients with moderate to severe ET.

Key eligibility criteria for the T-CALM study were signed, informed consent, males and females 18-75 years of age, initial diagnosis of ET prior to age 65, tremor severity score of at least 2 in at least one upper limb during any of the three maneuvers of

TETRAS-PS item 4 (upper limbs held forward and horizontally, upper limbs extended laterally and horizontally with elbows flexed and hands positioned close to each other near chin and finger-nose or chin-nose movements), TETRAS-PS total score of at least 15 at screening, either no anti-tremor medications, or a stable dosage of only one concurrent anti-tremor medication. Primidone was excluded because it is a strong CYP inducer that could impact the metabolism of CX-8998. Patients with surgical interventions for ET were also excluded. A complete list of inclusion/exclusion criteria is available online at ClinicalTrials.gov under registration number NCT03101241.

#### *Randomization and Masking*

10 Patients were randomized in a 1:1 ratio to receive CX-8998 or placebo. Randomization was stratified by concomitant use of anti-tremor medication and study site (sub study participation or non-participation). The randomization code was prepared by an unblinded statistician who was not involved in conduct of the study.

15 The sponsor, patients, investigators, and any others involved in conduct of the study or analysis of data were unaware of treatment assignments until after study completion and unblinding. CX-8998 was formulated in capsules of the active drug mixed with a blend of excipients. Matched placebo was formulated in identical capsules with a blend of comparable excipients.

#### *Procedures*

20 A study schematic is shown in Figure 47A. After informed consent, eligible subjects were randomized to receive titrated dosages of CX-8998 up to 10 mg BID or matching placebo during a 4-week double-blind dosing period followed by a 1-week safety follow-up. Subjects received CX-8998 4 mg BID (or matching placebo BID) during week 1 followed by an assessment in clinic for safety and dosage increase to 8 mg BID or matching placebo BID on day 8. On day 15 (week 3), patients were evaluated at the clinic for safety and efficacy and for final dose titration to 10 mg BID or matching placebo BID. The final efficacy visit occurred on day 28 (week 4). Reduction to the next lowest dosage was allowed, if needed, during weeks 1 and 2, and only 1 reduction was

permitted. Patients who could not tolerate dosage reduction were withdrawn from the study. Reescalation of dose was not allowed.

Safety procedures involved collection of all TEAEs (treatment-emergent adverse events) coded into the Medical Dictionary for Regulatory Activities (MedDRA) version 20. Adverse events were classified by maximum severity, drug-related adverse events, serious adverse events, and adverse events leading to patient discontinuation. Other safety assessments were physical examination, neurological examination, vital signs, clinical laboratory tests (hematology, chemistry and urinalysis), urine drug test at screen, pregnancy tests, electrocardiogram (ECG), Columbia Suicide Severity Rating Scale (C-SSRS), Epworth Sleepiness Scale (ESS), and University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ).

### *Outcomes*

An overview of the methods for T-CALM efficacy and safety endpoints is presented in Table 22. The Essential Tremor Rating Assessment Scale (TETRAS) consists of a 9-item performance subscale (PS) and a 12-item activities of daily living (ADL) subscale. The primary endpoint was the change from baseline to Day 28 on the TETRAS-PS score. The TETRAS-PS was scored by investigators of each patient (in real time) at the clinical site and by five independent video raters who reviewed and scored videotapes of each patient. Both sets of scores were statistically analyzed. In the absence of precedent, the objective of this dual approach was to select the optimal rating methodology (investigator versus independent video rater TETRAS-PS) for late-stage clinical development. The secondary endpoints were change from baseline to Day 28 on the TETRAS-ADL subscale score, change from baseline to Day 28 on accelerometry score measured by Kinesia ONE, and safety and tolerability: change from baseline in electrocardiogram (ECG) parameters, clinical safety laboratory assessments, Columbia Suicide Severity Rating Scale (C-SSRS), Epworth Sleepiness Scale (ESS), University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-PDHQ), vital signs, number (%) of study dropouts, and number (%) of study dropouts due to AEs. The following exploratory endpoints were also included: change from baseline to Day 15 and

28 on TETRAS total score; change from baseline to Day 15 on TETRAS-PS score, TETRAS-ADL subscale score and Kinesia ONE; score and treatment success at Day 15 and Day 28 measured by Patient Global Impression of Change (PGIC), Clinical Global Impressions (CGI) scale, Goal Attainment Scale (GAS), and Quality of Life in Essential Tremor (QUEST) questionnaire.

5

Table 22. Methods for Evaluation of T-CALM Efficacy and Safety Endpoints

| Methods  | Endpoints (Primary, Secondary, Exploratory)  | Data Collection (Clinician-Rated, Patient-Rated, Digital Biomarker) | Overview of Scoring Systems   |
|--|--|---|---|
| The Essential Tremor Rating Assessment Scale-Performance Scale (TETRAS-PS) <sup>1,2</sup>  | Primary-baseline to day 28 (investigator and central video-rated)<br>Exploratory-baseline to day 15 (investigator and central video-rated) | Clinician-Rated   | 9 performance items rated for tremor severity in head, face, voice limbs, and trunk and 3 functional tests (writing, drawing, and holding pen over dot); each item scored 0 (no tremor) to 4 (severe tremor) with total score of 0 to 64. |
| The Essential Tremor Rating Assessment Scale-Activities of Daily Living (TETRAS-ADL) <sup>1,2</sup>  | Secondary-baseline to day 28<br>Exploratory-baseline to day 15   | Clinician-Rated   | 12 daily activities scored from 0 (normal) to 4 (severe abnormality) with total score of 0 to 48  |
| The Essential Tremor Rating Assessment Scale-Total Score = Performance Scale Plus Activities of Daily Living (TETRAS-TS = PS + ADL) <sup>1,2</sup> | Exploratory-baseline to day 15 and day 28<br>PS (investigator and central video-rated) plus ADL  | PS-Clinician-Rated<br>ADL-Clinician-Rated                           | Sum of PS and ADL scores  |
| Kinesia ONE <sup>3</sup>   | Secondary-baseline to day 28<br>Exploratory-baseline to day 15   | Digital Biomarker   | Algorithmic score of four 15 second tasks to measure amplitude of resting, postural, kinetic and lateral wing tremor  |

|  |   |                                   |  |
|--|---|-----------------------------------|--|
| Quality of Life in Essential Tremor (QUEST) <sup>4</sup>                                     | Exploratory-day 15 and day 28                       | Patient-Rated                     | 30 QOL items scored as never, rarely, sometimes, frequently, always, NA  |
| Clinical Global Impressions (CGI) <sup>5</sup>   | Exploratory-baseline to day 15 and day 28           | Clinician-Rated                   | 7-point rating scale of total improvement or change in tremor severity scored as 1 (very much improved) to 7 (very much worse)   |
| Patient Global Impression of Change (PGIC) <sup>5</sup>                                      | Exploratory-baseline to day 15 and day 28           | Patient-Rated                     | 7-point rating scale of total improvement or change in tremor severity scored as 1 (very much improved) to 7 (very much worse)   |
| Goal Attainment Scale (GAS) <sup>6</sup>   | Exploratory-day 15 and day 28                       | Clinician-Rated and Patient-Rated | 3 health goals developed and rated by patient (3-point importance scale of fairly to extremely important) and clinician (3-point goal attainment scale of probable to doubtful); patient progress toward goals rated by 5-point scale from -2 (unfavorable outcome) to +2 (best anticipated outcome) |
| Columbia Suicide Severity Rating Scale (C-SSRS) <sup>7</sup>                                 | Secondary-baseline and all subsequent clinic visits | Patient-Rated                     | 6 questions on suicidal ideation and behavior rated by yes or no answers   |
| Epiworth Sleepiness Scale (EPS) <sup>8</sup>   | Secondary-baseline and all subsequent clinic visits | Patient-Rated                     | 8 daytime sleepiness situations rated from 0 (no chance of dozing) to 3 (high chance of dozing); total score ranged from 0 (lower normal sleepiness) to 24 (severe excessive sleepiness)   |
| University of Miami Parkinson's Disease Hallucinations Questionnaire (UM-1PDHQ) <sup>9</sup> | As needed   | Patient-Rated                     | 6 quantitative hallucination items (modality, frequency, duration, insight, sensation, and emotional burden) with total score from 0 (minimum) to 14 (maximum) and 14 qualitative hallucination items with most scored as yes or no  |

<sup>1</sup>Elble et al., *Mov. Disord.* 2008; **23** (Suppl 1): S1-6.

<sup>2</sup>Elble et al., *Mov Disord.* 2012; **27** (12): 1567-1569.

<sup>3</sup>Mostile et al., *Mov Disord.* 2010; **25** (12): 1938-1943.

<sup>4</sup>Tröster et al., *Parkinsonism Relat Disord.* 2005; **11** (6): 367-373.

<sup>5</sup>Guy, *Assessment Manual for Psychopharmacology*. Rockville, MD: Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration, 1976.

<sup>6</sup>Kiresuk et al., *Community Ment Health J.* 1968; **4** (6): 443-453.

<sup>7</sup>Posner et al., *Am J Psychiatry* 2011; **168** (12): 1266-1277.

<sup>8</sup>Kenderska et al., Sleep Med Rev. 2014; **18** (4): 321-331.

<sup>9</sup>Papapetropoulos et al., BMC Neurol. 2008; **8**: 21.

### *Statistical Analysis*

All statistical analyses were performed with the SAS system, version 9.4 or higher. A sample size of 43 patients per treatment group had at least 90% power to detect at least a 5.5-point difference between CX-8998 and placebo for the primary endpoint of the change from baseline to Day 28 on the TETRAS-PS score assuming a standard deviation of 7.5 and alpha = 0.05. This calculation was based on the Wilcoxon-Mann-Whitney test for two independent means and assumed normal distributions for each treatment group with a common, but unconfirmed, standard deviation. Approximately 92 patients were planned for enrollment to ensure 86 patients were available for inclusion in the efficacy analyses. The Intent to Treat (ITT) analysis set contained all randomized patients and was used for patient disposition and demographics. The Safety Analysis Set (SAS) had all randomized patients who received at least 1 dose of study drug. The Full Analysis Set (FAS) included all patients who received at least 1 dose of study drug and had both baseline and at least 1 post-baseline efficacy assessment. FAS was utilized for all efficacy assessments.

The primary efficacy endpoint was analyzed with FAS and analysis of covariance (ANCOVA) model, with fixed effects for treatment, anti-tremor medication use, study site, and baseline TETRAS-PS score. Testing was performed with least square (LS) means from the ANCOVA model and a two-sided test at the alpha = 0.05 level of significance. Multiple imputation was used to estimate missing data for patients who were missing a TETRAS-PS score on Day 28. Secondary and exploratory efficacy endpoints were similarly analyzed. P-values for secondary and exploratory analysis were considered nominal.

## **Results**

The T-CALM study period was 2017-2018 with August 29, 2017 as the date of the first patient visit and July 16, 2018 as the date of the last patient visit. Disposition of patients is presented in Figure 47B. The ITT analysis set included 95 patients randomized

to receive CX-8998 (N=48) or placebo (N=47). The study was completed by 37 (77%) patients in the CX-8998 group and 42 (89%) patients on placebo. Discontinuation due to adverse events took place in 8 (17%) of CX-8998-treated patients and 3 (6%) of placebo-treated patients. The primary efficacy analysis set (prespecified mITT) comprised 37 subjects in the CX-8998 group and 44 subjects in the placebo group who received at least one dose of study drug and completed a baseline and at least one post-baseline efficacy assessment.

Demographic characteristics at baseline are shown in Table 23. Male and female patients were almost equally distributed among CX-8998 and placebo groups. Age, race, and ethnicity were similar between CX-8998 and placebo groups. ET characteristics at baseline are shown in Table 24. CX-8998 and placebo groups were matched for most ET baseline characteristics. The only exception was the use of beta-blocker medication by 62% of the placebo-group compared to 44% of CX-8998 group.

15 Table 23. Demographic Characteristics at Baseline (ITT Analysis Set)

| Parameter                      | CX-8998<br>(N=48) | Placebo<br>(N=47) | Total<br>(N=95) |
|--------------------------------|-------------------|-------------------|-----------------|
| Sex                            |                   |                   |                 |
| Male                           | 25 (52%)          | 25 (53%)          | 50 (53%)        |
| Female                         | 23 (48%)          | 22 (47%)          | 45 (47%)        |
| Age at informed consent, years |                   |                   |                 |
| Mean (SD)                      | 64 (9.6)          | 63 (10.8)         | 63 (10.2)       |
| Median                         | 66                | 66                | 66              |
| Minimum, maximum               | 28, 75            | 21, 75            | 21, 75          |
| Age group                      |                   |                   |                 |
| ≤65 years                      | 22 (46%)          | 22 (47%)          | 44 (46%)        |
| >65 years                      | 26 (54%)          | 25 (53%)          | 51 (54%)        |
| Race                           |                   |                   |                 |
| White                          | 45 (94%)          | 46 (98%)          | 91 (96%)        |
| Black or African American      | 3 (6%)            | 1 (2%)            | 4 (4%)          |
| Ethnicity                      |                   |                   |                 |
| Not Hispanic or Latino         | 48 (100%)         | 45 (96%)          | 93 (98%)        |
| Hispanic or Latino             | 0 (0%)            | 1 (2%)            | 1 (1%)          |
| Not reported                   | 0 (0%)            | 1 (2%)            | 1 (1%)          |

ITT = intent to treat.

Table 24. Essential Tremor Characteristics at Baseline (ITT Analysis Set)

| Parameter   | CX-8998<br>(N=48) | Placebo<br>(N=47) | Total<br>(N=95) |
|---|-------------------|-------------------|-----------------|
| Time since onset of essential tremor, years <sup>1</sup>            |                   |                   |                 |
| Mean (SD)   | 24 (16.3)         | 21 (15.7)         | 23 (16.0)       |
| Median  | 20                | 18                | 19              |
| Minimum, maximum  | 3, 63             | 1, 62             | 1, 63           |
| Essential tremor improves with alcohol                              |                   |                   |                 |
| Yes   | 23 (48%)          | 16 (34%)          | 39 (41%)        |
| No  | 11 (23%)          | 13 (28%)          | 24 (25%)        |
| Unknown   | 14 (29%)          | 18 (38%)          | 32 (34%)        |
| Baseline TETRAS-PS total score <sup>2</sup>                         |                   |                   |                 |
| Mean (SD)   | 23.1 (6.27)       | 22.8 (5.67)       | 22.9 (5.95)     |
| Median  | 22.3              | 22.5              | 22.5            |
| Minimum, maximum  | 11.5, 46.5        | 12.5, 43.5        | 11.5, 46.5      |
| Baseline TETRAS-ADL subscale score <sup>2</sup>                     |                   |                   |                 |
| Mean (SD)   | 26 (6.0)          | 26 (7.0)          | 26 (6.5)        |
| Median  | 26                | 26                | 26              |
| Minimum, maximum  | 13, 38            | 9, 42             | 9, 42           |
| Baseline TETRAS-ADL total score <sup>2</sup>                        |                   |                   |                 |
| Mean (SD)   | 49.2 (10.59)      | 48.9 (10.46)      | 49.1 (10.47)    |
| Median  | 47.0              | 48.5              | 47.5            |
| Minimum, maximum  | 28.0, 81.5        | 28.5, 85.5        | 28.0, 85.5      |
| Anti-tremor medication at study entry                               |                   |                   |                 |
| Yes   | 22 (46%)          | 21 (45%)          | 43 (45%)        |
| No  | 26 (54%)          | 26 (55%)          | 52 (55%)        |
| Baseline TETRAS-PS severity group <sup>2,3</sup>                    |                   |                   |                 |
| ≤ Median at baseline  | 25 (52%)          | 24 (51%)          | 49 (52%)        |
| > Median at baseline  | 23 (48%)          | 23 (49%)          | 46 (48%)        |
| Tremor asymmetry group <sup>3,4</sup>                               |                   |                   |                 |
| Asymmetry absent  | 42 (88%)          | 35 (74%)          | 77 (81%)        |
| Asymmetry present   | 6 (13%)           | 12 (26%)          | 18 (19%)        |
| Postural-to-kinetic tremor ratio group:<br>TETRAS-PS <sup>3,5</sup> |                   |                   |                 |
| ≤ Median at baseline  | 23 (48%)          | 26 (55%)          | 49 (52%)        |

|  |          |          |          |
|--|----------|----------|----------|
| > Median at baseline                                       | 25 (52%) | 21 (45%) | 46 (48%) |
| Concurrent essential tremor medication on Day 1 (baseline) |          |          |          |
| No   | 20 (42%) | 14 (30%) | 34 (36%) |
| Yes  | 28 (58%) | 33 (70%) | 61 (64%) |
| Using beta-blocker at Day 1 (baseline)                     | 21 (44%) | 29 (62%) | 50 (53%) |
| Primidone use at screening                                 |          |          |          |
| Yes  | 5 (10%)  | 6 (13%)  | 11 (12%) |
| No   | 43 (90%) | 41 (87%) | 84 (88%) |

ADL = activities of daily living; ITT = intent to treat; TETRAS = The Essential Tremor Rating Assessment Scale; TETRAS-PS = TETRAS performance subscale.

<sup>1</sup> Time since onset of essential tremor was estimated by subtracting age at onset of essential tremor from age at informed consent.

<sup>5</sup> <sup>2</sup> Baseline was defined as the last non-missing value that was obtained before or  $\leq$ 15 minutes after initiation of study drug.

<sup>3</sup> This subgroup was used in the exploratory analyses.

<sup>4</sup> Tremor asymmetry was defined as a >1-point difference between the right and left side on any of the following TETRAS-PS items: 4A (postural tremor), 4B (wing-beating tremor), or 4C (kinetic tremor).

<sup>10</sup> <sup>5</sup> The ratio of postural tremor (subscale item 4A) to kinetic tremor (subscale item 4C) was defined as the ratio of the total postural tremor (sum of left and right hand) score divided by the total kinetic tremor (sum of left and right hand) score as provided by TETRAS-PS.

Except for primidone, patients were allowed use of up to a single concomitant anti-tremor drug during the study. These medications were used by 28 patients (58%) in the CX-8998 group and 33 patients (70%) in placebo group. Some patients in the CX-8998 (10%) and placebo (17%) groups were taking more than 1 concomitant anti-tremor medication (e.g. benzodiazepines, beta-blockers) to treat comorbid conditions such as anxiety, insomnia, and hypertension. Non-selective beta-blockers, such as propranolol, were the most frequently used anti-tremor medications in both CX-8998 (29%) and placebo (36%) groups. Concomitant anti-tremor medications were not used by 20 CX-8998 and 14 placebo patients, and 11 of these patients (12%) were reported by investigational sites as having tried and discontinued standard-of-care medications (propranolol, primidone, or both) for either efficacy or tolerability reasons. The remaining 23 patients had either no history of anti-tremor medication use, or information was not attainable. Compliance with study drug administration was comparable for CX-8998 (99.3%) and placebo (97.7%).

The LS mean ( $\pm$  SE) change from baseline to Day 28 in TETRAS-PS as the primary endpoint, scored by independent video raters, was  $-1.8 \pm 0.81$  for CX-8998 and  $2.3 \pm 0.78$  for placebo and the difference was not significant ( $p = 0.696$ ) (Table 25). When the same endpoint was scored by investigators (in person), the mean score was 5 significantly improved ( $p = 0.017$ ) by CX-8998 ( $-4.8 \pm 0.80$ ) compared to placebo ( $-2.8 \pm 0.77$ ), as shown in Figure 48A and Table 25. Sensitivity analyses confirmed the findings for the primary endpoint (measured by both independent video raters and investigators). A prespecified subgroup analysis of the primary endpoint scored by the investigators showed a more robust response in patients with more severe ET (Figure 48B and Table 10 26). Prespecified subgroup analysis based on concurrent anti-tremor medication use showed significantly greater improvement compared to placebo in subgroups not taking concurrent anti-tremor medications at baseline. (Figures 48C and 48D and Table 26).

Table 25. TETRAS-PS Subscale Primary Endpoint

| TETRAS-PS Total Score <sup>1</sup>       | Independent Video Raters <sup>2</sup> |                   | Investigator Rated <sup>2</sup> |                   |
|--|---------------------------------------|-------------------|---------------------------------|-------------------|
|  | CX-8998<br>(N=39)                     | Placebo<br>(N=44) | CX-8998<br>(N=39)               | Placebo<br>(N=44) |
| Baseline, N                              | 39                                    | 44                | 39                              | 44                |
| Mean (SD)                                | 22.7 (6.44)                           | 22.8 (5.84)       | 28.3 (5.95)                     | 28.5 (6.35)       |
| Median (minimum, maximum)                | 22.0 (11.5, 46.5)                     | 22.8 (12.5, 43.5) | 27.5 (20.5, 42.5)               | 27.8 (19.5, 45.0) |
| Day 28, N                                | 38                                    | 43                | 37                              | 42                |
| Mean (SD)                                | 21.1 (6.71)                           | 20.7 (7.96)       | 23.6 (5.50)                     | 25.8 (7.65)       |
| Median (minimum, maximum)                | 20.0 (10.5, 49.0)                     | 20.5 (0.0, 44.5)  | 22.5 (14.0, 37.0)               | 25.8 (0.0, 45.5)  |
| Change from baseline to Day 28, N        | 38                                    | 43                | 37                              | 42                |
| Mean (SD)                                | -1.6 (4.36)                           | -2.0 (4.98)       | -4.4 (4.16)                     | -2.8 (5.13)       |
| Median (minimum, maximum)                | -1.5 (-11.0, 7.0)                     | -1.5 (-23.0, 7.5) | -4.0 (-13.5, 4.5)               | -2.5 (-26.0, 4.5) |
| Analysis Results <sup>3,4</sup>          |                                       |                   |                                 |                   |
| LS mean (SE)                             | -1.8 (0.81)                           | -2.3 (0.78)       | -4.8 (0.80)                     | -2.8 (0.77)       |
| LS mean difference from placebo (95% CI) | 0.5 (-1.5, 2.5)                       |                   | -2.0 (-4.0, 0.0)                |                   |
| p-value <sup>5</sup>                     | 0.696                                 |                   | <b>0.017</b>                    |                   |

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; TETRAS = The Essential Tremor Rating Assessment Scale; TETRAS-PS = TETRAS performance subscale.

<sup>1</sup> TETRAS-PS quantifies tremor in the head, face, voice, limbs, and trunk. The overall subscale score ranges from 0 to 64. A decrease in score is indicative of improvement.

<sup>2</sup> The change from baseline to Day 28 on the TETRAS-PS total score, as scored by the independent video raters, was the protocol-specified primary efficacy endpoint. TETRAS-PS was also scored in real time by the investigators and was analyzed post hoc (using the same methodology that was used for the independent video rater assessments) as if it were the primary endpoint.

<sup>3</sup> Missing values were replaced by multiple imputation. LS means, standard errors, difference from placebo, 95% CIs, and p-values were estimated using an ANCOVA model, with effects for treatment, anti-tremor medication use, site type, and baseline value of TETRAS-PS total score.

<sup>4</sup> Missing items on the subscale at Day 28 were imputed using PROC MI, and 10 datasets were produced for analysis. The results of the ANCOVA model of the 10 datasets were combined using PROC MIANALYZE to produce the LS means, difference from placebo, 95% CI, and p-value.

<sup>5</sup> The analysis was performed on ranked data; LS means, standard errors, the difference from placebo, and 95% CIs were estimated using unranked data, and the p-value was calculated using ranked data.

Table 26. TETRAS-PS Prespecified Subset Analysis

| TETRAS-PS Total Score <sup>1</sup>             | Independent Video Raters <sup>2</sup> |                   | Investigator Rated <sup>2</sup> |                   |
|--|---------------------------------------|-------------------|---------------------------------|-------------------|
|  | CX-8998<br>(N=39)                     | Placebo<br>(N=44) | CX-8998<br>(N=39)               | Placebo<br>(N=44) |
| Baseline TETRAS-PS Severity <=Median, N        | 22                                    | 22                | 22                              | 22                |
| Mean (SD)                                      | -0.1 (3.98)                           | -1.6 (3.34)       | -3.4 (3.74)                     | -2.5 (3.95)       |
| Median (minimum, maximum)                      | 0 (-9.5, 7.0)                         | -1.0 (-10, 4.5)   | -3.0 (-13.5, 1.0)               | -1.8 (-11.5, 4.5) |
| LS mean (SE)                                   | -0.6 (0.82)                           | -1.8 (0.79)       | -3.8 (0.67)                     | -2.5 (0.65)       |
| LS mean difference from placebo (95% CI)       | 1.2 (-1.1, 3.4)                       |                   | -1.2 (-3.1, 0.6)                |                   |
| p-value  | 0.296                                 |                   | 0.166                           |                   |
| Baseline TETRAS-PS Severity > Median, N        | 16                                    | 21                | 15                              | 20                |
| Mean (SD)                                      | -3.6 (4.14)                           | -2.5 (6.31)       | -5.8 (4.48)                     | -3.1 (6.27)       |
| Median (minimum, maximum)                      | -3.0 (-11, 2.5)                       | -1.5 (-23.0, 7.5) | -6.0 (-13, 4.5)                 | -3.3 (-26, 4.5)   |
| LS mean (SE)                                   | -3.5 (1.47)                           | -2.2 (1.57)       | -5.6 (1.60)                     | -2.1 (1.70)       |
| LS mean difference from placebo (95% CI)       | -1.3 (-4.8, 2.3)                      |                   | -3.5 (-7.4, 0.4)                |                   |
| p-value  | 0.266                                 |                   | <b>0.011</b>                    |                   |
| Using Concurrent Tremor Medication at Day 1, N | 24                                    | 30                | 23                              | 29                |
| Mean (SD)                                      | -1.1 (3.71)                           | -2.6 (5.06)       | -3.9 (4.31)                     | -3.3 (5.55)       |
| Median (minimum, maximum)                      | -1.3 (-9.5, 5.5)                      | -1.5 (-23, 4.5)   | -3.5 (-13.5, 4.5)               | -3.0 (-26, 4.5)   |
| LS mean (SE)                                   | -1.6 (1.14)                           | -3.4 (1.05)       | -3.5 (1.29)                     | -3.0 (1.15)       |
| LS mean difference from placebo (95% CI)       | 1.8 (-0.7, 4.3)                       |                   | -0.5 (-3.2, 2.3)                |                   |
| p-value  | 0.202                                 |                   | 0.570                           |                   |
| No Concurrent Tremor Medication at Day 1, N    | 14                                    | 13                | 14                              | 13                |
| Mean (SD)                                      | -2.5 (5.33)                           | -0.7 (4.69)       | -5.0 (3.97)                     | -1.7 (3.99)       |
| Median (minimum, maximum)                      | -3.3 (-11, 7.0)                       | -0.5 (-10, 7.5)   | -4.5 (-12.5, 1.0)               | -1.5 (-11.5, 4.5) |
| LS mean (SE)                                   | -4.3 (2.05)                           | -2.3 (2.08)       | -6.2 (1.60)                     | -1.8 (1.59)       |
| LS mean difference from placebo (95% CI)       | -2.0 (-5.8, 1.8)                      |                   | -4.4 (-7.4, -1.3)               |                   |
| p-value  | 0.312                                 |                   | <b>0.005</b>                    |                   |
| Using Beta-blocker at Day 1, N                 | 18                                    | 26                | 18                              | 26                |
| Mean (SD)                                      | -1.5 (3.68)                           | -3.0 (5.34)       | -4.2 (4.55)                     | -3.4 (5.85)       |
| Median (minimum, maximum)                      | -1.3 (-9.5, 4.0)                      | -2.3 (-23, 4.5)   | -4.0 (-13.5, 4.5)               | -3.3 (-26, 4.5)   |
| LS mean (SE)                                   | -2.5 (1.36)                           | -3.9 (1.14)       | -3.6 (1.56)                     | -3.3 (1.27)       |
| LS mean difference from placebo (95% CI)       | 1.4 (-1.4, 4.3)                       |                   | -0.3 (-3.6, 3.0)                |                   |
| p-value  | 0.333                                 |                   | 0.527                           |                   |

| No Beta-blocker Use at Day 1, N          | 20              | 17               | 19                | 16                |
|--|-----------------|------------------|-------------------|-------------------|
| Mean (SD)                                | -1.6 (4.99)     | -0.6 (4.09)      | -4.5 (3.89)       | -1.8 (3.65)       |
| Median (minimum, maximum)                | -2.0 (-11, 7.0) | -0.5 (-10, 7.5)  | -4.0 (-12.4, 1.0) | -1.8 (-11.5, 4.5) |
| LS mean (SE)                             | -1.3 (1.10)     | -0.1 (1.31)      | -5.6 (0.97)       | -1.3 (1.11)       |
| LS mean difference from placebo (95% CI) |                 | -1.2 (-4.3, 1.8) |                   | -4.3 (-7.0, -1.7) |
| p-value                                  |                 | 0.425            |                   | <b>0.003</b>      |

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; TETRAS = The Essential Tremor Rating Assessment Scale; TETRAS-PS = TETRAS performance subscale.

<sup>1</sup> TETRAS-PS quantifies tremor in the head, face, voice, limbs, and trunk. The overall subscale score ranges from 0 to 64. A decrease in score is indicative of improvement.

<sup>2</sup> The change from baseline to Day 28 on the TETRAS-PS total score, as scored by the independent video raters, was the protocol-specified primary efficacy endpoint. TETRAS-PS was also scored in real time by the investigators and was analyzed post hoc (using the same methodology that was used for the independent video rater assessments) as if it were the primary endpoint.

<sup>5</sup> The analysis was performed on ranked data; LS means, standard errors, the difference from placebo, and 95% CIs were estimated using unranked data, and the p-value was calculated using ranked data.

The TETRAS-ADL subscale score was evaluated at Day 15 (exploratory endpoint) and at Day 28 (secondary endpoint), and the difference between treatment groups for the change from baseline showed a significant decrease (improvement) for the CX-8998 group compared to placebo at both time points. As presented in Figure 49A, the LS mean ( $\pm$  SE) was  $-4.5 \pm 0.87$  and  $-1.4 \pm 0.85$  ( $p = 0.005$ ) at Day 15 and  $-4.5 \pm 1.12$  and  $-1.6 \pm 1.08$  ( $p = 0.049$ ) at Day 28 for CX-8998 and placebo, respectively.

Prespecified subgroup analysis of the secondary endpoint at Day 28 showed greater responses in CX-8998 patients with more severe ET (Figure 49B). In contrast to the TETRAS-PS, prespecified subgroup analysis of TETRAS-ADL scores based on concurrent anti-tremor medication use showed significantly greater improvement compared to placebo in the subgroup taking concurrent anti-tremor medications at baseline (Figure 49C).

<sup>25</sup> To estimate the clinical detectable change of the TETRAS-ADL improvement, a post-hoc analysis of TETRAS-ADL scores was conducted on the subset of patients who achieved a score of minimally improved as measured by CGI-I or PGIC as anchors. This analysis revealed that a 3- to 4-point reduction from baseline in the TETRAS-ADL score

represented a detectable change to clinicians, whereas a 2- to 4-point reduction in score from baseline represented a noticeable change to patients (Table 27).

5 Table 27. Post-hoc Analysis of TETRAS-ADL Meaningful Difference Based on CGI-I and PGIC

| TETRAS-ADL Score <sup>1</sup>  | Day 15            |                   | Day 28            |                   |
|--------------------------------|-------------------|-------------------|-------------------|-------------------|
|                                | CX-8998<br>(N=39) | Placebo<br>(N=44) | CX-8998<br>(N=39) | Placebo<br>(N=44) |
| Minimally Improved by CGI-I, N | 19                | 14                | 15                | 7                 |
| Mean (SD)                      | -3.7 (4.21)       | -3.1 (3.77)       | -4.4 (8.10)       | -3.3 (4.61)       |
| Median (minimum, maximum)      | -2.0 (-11, 3)     | -3.0 (-9, 3)      | -1.0 (-24, 3)     | -2.0 (-11, 2)     |
|                                |                   |                   |                   |                   |
| Minimally Improved by PGIC, N  | 17                | 8                 | 10                | 6                 |
| Mean (SD)                      | -3.3 (4.27)       | -1.5 (6.16)       | -1.6 (3.84)       | -3.2 (5.19)       |
| Median (minimum, maximum)      | -4.0 (-13, 4)     | -2.5 (-9, 12)     | -1.0 (-7, 3)      | -1.5 (-11, 2)     |

ADL = activities of daily living; SD = standard deviation; TETRAS = The Essential Tremor Rating Assessment Scale; CGI-I = clinical global impression of improvement; PGIC = patient global impression of improvement.

10 <sup>1</sup> TETRAS-ADL subscale assesses items such as eating and drinking, dressing and personal hygiene, carrying items, and finer motor skills. Each item is rated on a scale for 0 to 4 on which 0 = normal activity and 4 = severe abnormality. The sum of the individual scores provides an overall score, which ranges from 0 to 48.

15 The LS mean ( $\pm$  SE) total TETRAS score (TETRAS-PS score rated by investigators plus TETRAS-ADL subscale score rated by patients) significantly improved at Day 15 ( $-7.5 \pm 1.42$  and  $-3.7 \pm 1.38$ ,  $p = 0.040$ ) and at Day 28 ( $-9.0 \pm 1.66$  and  $-4.2 \pm 1.60$ ,  $p = 0.029$ ) for CX-8998 compared to placebo, respectively (Figure 49D). When the TETRAS-PS score was rated by independent video raters, the total TETRAS score trended toward improvement for the CX-8998 group but was not statistically significant at either Day 15 or 28.

20 Kinesia ONE score (triaxial accelerometry and gyroscopy) at Day 15 (exploratory endpoint) and Day 28 (secondary endpoint) did not show a significant difference between CX-8998 and placebo at either time point. (Table 28)

Table 28. Kinesia ONE Score

| Kinesia ONE Total Score <sup>1</sup>        | Day 15               |                      | Day 28               |                      |
|---|----------------------|----------------------|----------------------|----------------------|
|   | CX-8998<br>(N=39)    | Placebo<br>(N=44)    | CX-8998<br>(N=39)    | Placebo<br>(N=44)    |
| Baseline, N                                 | 39                   | 44                   | 39                   | 44                   |
| Mean (SD)                                   | 10.6 (4.33)          | 12.0 (5.35)          | 10.6 (4.33)          | 12.0 (5.35)          |
| Median (minimum, maximum)                   | 10.0 (4.3,<br>25.9)  | 11.0 (3.7,<br>25.0)  | 10.0 (4.3,<br>25.9)  | 11.0 (3.7,<br>25.0)  |
| Day 15 or Day 28, N                         | 38                   | 42                   | 37                   | 41                   |
| Mean (SD)                                   | 9.1 (4.46)           | 10.8 (5.21)          | 9.3 (4.28)           | 10.4 (4.84)          |
| Median (minimum, maximum)                   | 7.9 (2.6,<br>27.3)   | 10.1 (2.8,<br>25.9)  | 7.8 (3.8,<br>26.0)   | 10.3 (3.3,<br>24.2)  |
| Change from baseline to Day 15 or Day 28, N | 38                   | 42                   | 37                   | 41                   |
| Mean (SD)                                   | -1.5 (3.06)          | -1.4 (2.97)          | -1.4 (3.35)          | -1.8 (3.00)          |
| Median (minimum, maximum)                   | -1.1 (-12.2,<br>4.9) | -0.8 (-13.9,<br>2.3) | -0.7 (-11.7,<br>5.4) | -1.3 (-13.7,<br>3.6) |
| Analysis Results <sup>2,3</sup>             |                      |                      |                      |                      |
| LS mean (SE)                                | -2.0 (0.52)          | -1.6 (0.51)          | -1.7 (0.52)          | -1.6 (0.50)          |
| LS mean difference from placebo (95% CI)    | -0.4 (-1.7, 0.9)     |                      | 0.0 (-1.4, 1.3)      |                      |
| p-value <sup>5</sup>                        | 0.350                |                      | 0.421                |                      |

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares.

<sup>1</sup> Kinesia ONE scores are presented as the sum of the scores of the left and right hands. Values for each test range from 0 (no tremor) to 4 (severe tremor). The total overall score is the sum of all individual items.

<sup>2</sup> LS means, standard errors, difference from placebo, 95% CIs, and p-values were estimated using an ANCOVA model, with effects for treatment, anti-tremor medication use, site type, and baseline value of the accelerometry total score.

<sup>3</sup> The analysis was performed on ranked data; LS means, standard errors, the difference from placebo, and 95% CIs were estimated using unranked data, and the p-value was calculated using ranked data.

The LS mean ( $\pm$  SE) CGI-I score was significantly greater (improved) at Day 28 (exploratory endpoint) by CX-8998 ( $1.0 \pm 0.13$ ) compared to placebo ( $0.4 \pm 0.13$ ),  $p = 0.001$  (Figure 50A and Table 29). At Day 28, 23% of patients treated with CX-8998 were rated as much/very much improved compared to 7% on placebo (Figure 50B). The mean PGIC score was significantly greater (improved) at Day 15 (exploratory endpoint) ( $p = 0.003$ ) and trended toward significant improvement at Day 28 (exploratory endpoint) ( $p = 0.089$ ). (Table 30) The mean GAS score was significantly greater (improved) at Day 28 (exploratory endpoint) for CX-8998 patients ( $44.8 \pm 1.72$ ) compared to placebo ( $40.0 \pm$

1.67),  $p = 0.034$ . Detailed results on the GAS including a post-hoc analysis of the proportion of patients who achieved 1 or more or 2 or more goals is presented in Table 31.

5 Table 29. CGI-I

| CGI-I Category <sup>1</sup>                 | Day 15 (Exploratory Endpoint) |                   | Day 28 (Exploratory Endpoint) |                   |
|---|-------------------------------|-------------------|-------------------------------|-------------------|
|   | CX-8998<br>(N=39)             | Placebo<br>(N=44) | CX-8998<br>(N=39)             | Placebo<br>(N=44) |
| -3 Very much worse                          | 0                             | 0                 | 0                             | 0                 |
| -2 Much worse                               | 0                             | 1 (2%)            | 0                             | 0                 |
| -1 Minimally worse                          | 0                             | 2 (5%)            | 0                             | 2 (5%)            |
| 0 No change                                 | 14 (36%)                      | 21 (48%)          | 13 (33%)                      | 30 (68%)          |
| 1 Minimally improved                        | 19 (49%)                      | 14 (32%)          | 15 (38%)                      | 7 (16%)           |
| 2 Much improved                             | 6 (15%)                       | 5 (11%)           | 9 (23%)                       | 2 (5%)            |
| 3 Very much improved                        | 0                             | 1 (2%)            | 0                             | 1 (2%)            |
| <hr/>                                       |                               |                   |                               |                   |
| N   | 39                            | 44                | 37                            | 42                |
| Mean (SD)                                   | 1 (0.7)                       | 1 (0.9)           | 1 (0.8)                       | 0 (0.7)           |
| Median (minimum, maximum)                   | 1 (0, 2)                      | 0 (-2, 3)         | 1 (0, 2)                      | 0 (-1, 3)         |
| <hr/>                                       |                               |                   |                               |                   |
| Analysis Results <sup>2</sup>               |                               |                   |                               |                   |
| LS mean (SE)                                | 0.9 (0.14)                    | 0.6 (0.14)        | 1.0 (0.13)                    | 0.4 (0.13)        |
| LS mean difference from placebo<br>(95% CI) | 0.3 (-1.0, 0.6)               |                   | 0.6 (0.3, 0.9)                |                   |
| p-value                                     | 0.152                         |                   | <b>0.001</b>                  |                   |

<sup>1</sup> The CGI-I was rescaled to allow a more intuitive interpretation of the results.

<sup>2</sup> Least squares (LS) means, standard errors, difference from placebo, 95% confidence intervals (CIs), and p-values were estimated using an analysis of covariance (ANCOVA) model, with effects for treatment, anti-tremor medication use, and site type.

10

Table 30. GIC

| PGIC Category <sup>1</sup> | Day 15 (Exploratory Endpoint) |                   | Day 28 (Exploratory Endpoint) |                   |
|----------------------------|-------------------------------|-------------------|-------------------------------|-------------------|
|                            | CX-8998<br>(N=39)             | Placebo<br>(N=44) | CX-8998<br>(N=39)             | Placebo<br>(N=44) |
| -3 Very much worse         | 0                             | 0                 | 1 (3%)                        | 0                 |
| -2 Much worse              | 1 (3%)                        | 4 (9%)            | 1 (3%)                        | 1 (2%)            |
| -1 Minimally worse         | 1 (3%)                        | 1 (2%)            | 1 (3%)                        | 2 (5%)            |
| 0 No change                | 11 (28%)                      | 27 (61%)          | 14 (36%)                      | 29 (66%)          |
| 1 Minimally improved       | 17 (44%)                      | 8 (18%)           | 10 (26%)                      | 6 (14%)           |

|   |  |            |                |            |                 |
|---|--|------------|----------------|------------|-----------------|
| 2 | Much improved                            | 8 (21%)    | 3 (7%)         | 7 (18%)    | 2 (5%)          |
| 3 | Very much improved                       | 1 (3%)     | 1 (2%)         | 3 (8%)     | 2 (5%)          |
|   |  |            |                |            |                 |
|   | N  | 39         | 44             | 37         | 42              |
|   | Mean (SD)                                | 1 (1.0)    | 1 (1.0)        | 1 (1.3)    | 0 (0.9)         |
|   | Median (minimum, maximum)                | 1 (-2, 3)  | 0 (-2, 3)      | 1 (-3, 3)  | 0 (-2, 3)       |
|   | Analysis Results <sup>2</sup>            |            |                |            |                 |
|   | LS mean (SE)                             | 0.9 (0.17) | 0.3 (0.16)     | 0.8 (0.19) | 0.4 (0.18)      |
|   | LS mean difference from placebo (95% CI) |            | 0.7 (0.2, 1.1) |            | 0.4 (-0.1, 0.9) |
|   | p-value                                  |            | <b>0.003</b>   |            | 0.089           |

<sup>1</sup> The PGIC was rescaled to allow a more intuitive interpretation of the results.

<sup>2</sup> Least squares (LS) means, standard errors, difference from placebo, 95% confidence intervals (CIs), and p-values were estimated using an analysis of covariance (ANCOVA) model, with effects for treatment, anti-tremor medication use, and site type.

5

Table 31. GAS

| Statistic for Overall GAS Score <sup>1</sup> | Day 15 (Exploratory Endpoint) |                   | Day 28 (Exploratory Endpoint) |                   |
|--|-------------------------------|-------------------|-------------------------------|-------------------|
|  | CX-8998 (N=39)                | Placebo (N=44)    | CX-8998 (N=39)                | Placebo (N=44)    |
| N  | 39                            | 43                | 37                            | 41                |
| Mean (SD)                                    | 42.1 (8.55)                   | 39.1 (7.65)       | 44.4 (11.08)                  | 39.5 (8.41)       |
| Median (minimum, maximum)                    | 36.9 (26.2, 63.7)             | 36.8 (22.6, 63.7) | 41.2 (26.7, 69.7)             | 36.8 (27.2, 77.4) |
| Analysis Results <sup>2</sup>                |                               |                   |                               |                   |
| LS mean (SE)                                 | 43.2 (1.36)                   | 40.3 (1.33)       | 44.8 (1.72)                   | 40.0 (1.67)       |
| LS mean difference from placebo (95% CI)     |                               | 2.9 (-0.6, 6.4)   |                               | 4.8 (0.4, 9.3)    |
| p-value                                      |                               | 0.103             |                               | <b>0.034</b>      |

<sup>1</sup> The overall GAS score =  $50 + (10 * \text{sum of weights})/\text{square root} (0.7 * \text{sum of weights}^{**2}) + [0.3 * (\text{sum of weights})^{**2}]$ . Weights were specified at baseline and were assigned as 1 = fairly important, 2 = very important, 3 = extremely important.

<sup>2</sup> Least squares (LS) means, standard errors, difference from placebo, 95% confidence intervals (CIs), and p-values were estimated using an analysis of covariance (ANCOVA) model, with effects for treatment, anti-tremor medication use, and site type.

The QUEST questionnaire revealed that a higher percentage of CX-8998 patients compared to placebo experienced side effects from their treatment at Day 15 (36% versus 9%) and Day 28 (18% versus 9%) and a higher percentage of CX-8998 patients expressed satisfaction with symptom control at Day 15 (38% versus 11%) and Day 28

(38% versus 14%) (Table 32). No significant differences between CX-8998 and placebo groups were reported in the dimension scores at Days 15 or 28 (data not shown).

5 Table 32. Quality of Life in Essential Tremor Questionnaire (QUEST) General Questions Related to Anti-Tremor Medication

| Question   | CX-8998<br>(n = 39) | Placebo<br>(n = 44) |
|--|---------------------|---------------------|
| <b>Side effect from tremor medication in past month?</b>   |                     |                     |
| Baseline   | No                  | 35 (90%)            |
|  | Yes                 | 4 (10%)             |
| Day 15   | No                  | 25 (64%)            |
|  | Yes                 | 14 (36%)            |
| Day 28   | No                  | 30 (77%)            |
|  | Yes                 | 7 (18%)             |
| <b>Satisfied with control by medication in past month?</b> |                     |                     |
| Baseline   | No                  | 38 (97%)            |
|  | Yes                 | 1 (3%)              |
| Day 15   | No                  | 24 (62%)            |
|  | Yes                 | 15 (38%)            |
| Day 28   | No                  | 22 (56%)            |
|  | Yes                 | 15 (38%)            |

10 At least 1 TEAE was present in 58% of patients in the CX-8998 group compared to 49% of placebo. As expected, TEAEs in the CX-8998 group were primarily neurologic and psychiatric. TEAEs were predominantly mild or moderate in both groups. TEAEs in the CX-8998 group were mostly reported during the first week of study whereas TEAEs in the placebo group were reported throughout the study (Table 33). The most commonly reported drug-related TEAEs in the CX-8998 group were dizziness, headache, euphoria, disturbance in attention, paresthesia, hallucination (illusions, visual mostly when eyes were closed), insomnia, and dry mouth. Dizziness, nausea, somnolence, and vomiting were the most common drug-related TEAEs with placebo (Table 33).

15

Table 33. Summary of Treatment-Emergent Adverse Events Reported in Two or More Subjects in Either Treatment Group by (Safety Analysis Set)

| MedDRA System Organ Class/<br>Preferred Term <sup>1</sup> ,                  | CX-8998<br>(n = 48) | Placebo<br>(n = 47) |
|--|---------------------|---------------------|
| <b>Subjects with at least 1 treatment-emergent adverse event<sup>2</sup></b> | <b>28 (58%)</b>     | <b>23 (49%)</b>     |
| <b>Nervous System Disorders</b>  | <b>20 (42%)</b>     | <b>10 (21%)</b>     |
| Dizziness  | 10 (21%)            | 3 (6%)              |
| Headache   | 4 (8%)              | 2 (4%)              |
| Disturbance in attention   | 2 (4%)              | 1 (2%)              |
| Dysgeusia  | 2 (4%)              | 0                   |
| Paraesthesia   | 2 (4%)              | 1 (2%)              |
| Somnolence   | 1 (2%)              | 2 (4%)              |
| Hypesthesia  | 0                   | 2 (4%)              |
| <b>Psychiatric Disorders</b>   | <b>12 (52%)</b>     | <b>1 (2%)</b>       |
| Euphoric mood  | 3 (6%)              | 0                   |
| Insomnia   | 3 (6%)              | 0                   |
| Abnormal dreams  | 2 (4%)              | 1 (2%)              |
| Hallucination  | 2 (4%)              | 0                   |
| <b>Gastrointestinal Disorders</b>  | <b>9 (19%)</b>      | <b>7 (15%)</b>      |
| Dry mouth  | 2 (4%)              | 1 (2%)              |
| Nausea   | 1 (2%)              | 3 (6%)              |
| Vomiting   | 0                   | 2 (4%)              |
| <b>Infections and Infestations</b>   | <b>4 (8%)</b>       | <b>3 (6%)</b>       |
| Urinary Tract Infection  | 2 (4%)              | 1 (2%)              |
| <b>Ear and Labyrinth Disorders</b>   | <b>2 (4%)</b>       | <b>0</b>            |
| Tinnitus   | 2 (4%)              | 0                   |

5      1      Adverse event mapping was based on MedDRA (Medical Dictionary for Regulatory Activities), version 20.1 thesaurus. Subjects who experienced the same event more than once were counted once for the preferred term. Subjects who experienced more than 1 event within a system organ class were counted only once in the system organ class.

2 The number and percentage of subjects in the system organ class represents all subjects who had at least 1 adverse event (preferred term) in the system organ class. Only adverse events that were reported in 2 or more subjects in either treatment group in the nervous system, psychiatric system, and gastrointestinal system are displayed.

5

Serious adverse events (SAEs) of alcohol withdrawal syndrome, major depression, and suicidal ideation were reported in one patient on CX-8998. This patient had a history of chronic alcohol dependence and depression with suicide attempt that he did not disclose during screening. These SAEs were deemed to be unrelated to study 10 drug. No SAEs occurred with placebo. Discontinuation of study treatment due to TEAEs occurred in 8 (17%) of CX-8998 patients compared to 2 (4%) in the placebo group. Dosage reduction due to TEAEs was conducted in 6% of CX-8998 patients and 2% of placebo patients and generally occurred during the first 2 weeks of treatment (Table 34).

15 Table 34. Discontinuations and Dosage Reductions

| Discontinuation <sup>1</sup>                              |                | CX-8998 (N=48)      |           | Placebo (N=47) |  |                        |                   |
|---|----------------|---------------------|-----------|----------------|--|------------------------|-------------------|
| Subjects with at least 1 event leading to discontinuation |                | 8 (17%)             |           | 2 (4%)         |  |                        |                   |
| Nervous System Disorders                                  |                | 4 (8%)              |           | 1 (2%)         |  |                        |                   |
| Psychiatric Disorders                                     |                | 4 (8%)              |           | 0              |  |                        |                   |
|   |                |                     |           |                |  |                        |                   |
| Dosage Reduction <sup>2</sup>                             |                | CX-8998 (N=48)      |           | Placebo (N=47) |  |                        |                   |
| Dosage reduced during study                               |                | 4 (8%)              |           | 1 (2%)         |  |                        |                   |
| Due to adverse event                                      |                | 3 (6%)              |           | 1 (2%)         |  |                        |                   |
| Due to other reasons                                      |                | 1 (2%) <sup>3</sup> |           | 0              |  |                        |                   |
| Dosage Reductions Due to Adverse Events                   |                |                     |           |                |  |                        |                   |
| Treatment Group   | Subject Number | Dosage Reduction    |           |                | Adverse Event (MedDRA Preferred Term) <sup>4</sup> | Study Day of Last Dose | Study Disposition |
|   |                | Study Day           | From      | To             |  |                        |                   |
| CX-8998   | 26-001         | 25                  | 10 mg BID | 8 mg BID       | Anxiety  | 33                     | Completed study   |

|         |        |    |                |                |                                   |    |   |
|---------|--------|----|----------------|----------------|-----------------------------------|----|---|
|         | 31-023 | 8  | 8 mg BID       | 4 mg BID       | Electrocardiogram T-wave abnormal | 8  | Withdrawn (Day 8) Investigator decision |
|         | 33-004 | 8  | 4 mg BID       | 2 mg BID       | Headache                          | 15 | Withdrawn (Day 45) Lost to follow-up    |
| Placebo | 38-018 | 15 | 4 capsules BID | 2 capsules BID | Headache                          | 28 | Completed study                         |

BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities.

1 Adverse event mapping was based on MedDRA (Medical Dictionary for Regulatory Activities), version 20.0 thesaurus. Subjects who experienced the same event more than once were counted once for the preferred term. Subjects who experienced more than 1 event within a system organ class were counted only once in the system organ class.

5

2 Rescalation of the dosage after dosage reduction was not allowed.

3 Subject had inadequate drug supply at Visit 4.

4 Events in all subjects were considered related to the study drug.

10 An analysis examined whether the observed differences in TETRAS performance subscore were due to differential scoring by item, and the extent to which such items can shed light into the factors underlying the discordant ratings (Figure 51). The upper panel of Figure 51 shows the difference scores (independent video rated [CR] minus investigator rated [PR]) by item, where negative scores indicate lower scoring by the independent video rater (CR) than the investigator (PR). As Figure 51 indicates, first, all the items were scored comparatively lower by the independent video rater than the investigator. Secondly and more importantly, some items showed particularly large difference scores. These items were related to leg tremor, standing, face and protrusion of the tongue (Tp2: face tremor; Tp3: voice tremor; Tp5Al: left lower limb extended; Tp5Ar: right lower limb extended; Tp9: standing). Consistent with these observations, ANOVAs comparing independent video rated and investigator rated groups on individual items showed statistically significant differences for 14 out of the 19 items (p-values <0.05). All items pertaining to leg tremor, standing and subtle tremor reached significance. Interestingly, the discrepancies appear to be systematic in that the magnitude of differential scoring of particular items remained consistent across visits. For example, item 5Al and 5Ar showed large difference scores consistently across all visits (Figure 51, lower panel).

15

20

25

No clinically meaningful differences were detected in clinical laboratory parameters of CX-8998 and placebo groups. No clinically significant abnormalities occurred in vital signs, ECG, or neurological and physical examinations.

**Example 26. CX-8998 HCl salt and free base formulations**

5 A CX-8998 IR formulation releases as much CX-8998 as quickly as possible. An exemplary CX-8998 IR formulation was made using extrusion/spheronization to generate beads containing either CX-8998 - HCl salt or CX-8998 free base.

In one experiment, formulations containing either CX-8998 - HCl salt or CX-8998 free base are as shown in Table 35.

10

Table 35. Bead formulations with HCl salt and free base CX-8998 (wt %)

| Component                  | CX-8998 - HCl salt formulation | CX-8998 free base formulation |
|----------------------------|--------------------------------|-------------------------------|
| CX-8998 HCl salt           | 3.5%                           |                               |
| CX8998 free base           |                                | 3.2%                          |
| Microcrystalline cellulose | 88.75%                         | 88.95%                        |
| Sodium starch glycolate    | 3.5%                           | 3.5%                          |
| Croscarmellose sodium      | 3.5%                           | 3.5%                          |
| Magnesium stearate         | 0.5%                           | 0.5%                          |
| Stearic acid               | 0.50%                          | 0.50%                         |
| Methionine                 | 0.05%                          | 0.05%                         |

Release profiles are shown in Figure 54A.

Formulations containing microcrystalline cellulose, which is typically used in IR formulations of other active ingredients, released about 80% CX-8998, and took an hour to achieve this level of release.

In one experiment, formulations containing CX-8998 free base are as shown in  
5 Table 36.

Table 36. Bead formulations with HCl salt and free base CX-8998 (wt %)

| Component                  | CX-8998 formulation |
|----------------------------|---------------------|
| CX8998 free base           | 3.2                 |
| Microcrystalline cellulose | 8.0                 |
| Lactose monohydrate        | 80.6                |
| Sodium starch glycolate    | 3.5                 |
| Croscarmellose sodium      | 3.5                 |
| Magnesium stearate         | 0.50                |
| Steric acid                | 0.50                |
| Polysorbate 80             | 0.2                 |

Release profiles are shown in Figure 54B.

Formulations containing lactose monohydrate (e.g., and not containing  
10 microcrystalline cellulose released greater than 80% of CX-8998 within 20 minutes.

**Example 27. CX-8998 bead formulation with no microcrystalline cellulose**

Microcrystalline cellulose is typically a key ingredient in drug beads formed by extrusion spheroidization. A formulation containing no microcrystalline cellulose and providing fast release of CX-8998 is provided in Table 37. Dissolution results for this  
15 formulation are provided in Figure 55.

Table 37. CX-8998 drug bead formulation containing no microcrystalline cellulose

| Component                      | Composition ((wt % of core bead wt)) |
|--------------------------------|--------------------------------------|
| CX-8998 (HCl salt)             | 5.0                                  |
| Lactose monohydrate            | 57.7                                 |
| Crospovidone                   | 25.0                                 |
| Citric Acid Anhydrous          | 8.0                                  |
| Sodium Lauryl Sulfate (SLS)    | 2.0                                  |
| Hydroxypropyl Cellulose (HPC)  | 2.0                                  |
| Butylated Hydroxyanisole (BHA) | 0.3                                  |
| Butylated Hydroxytoluene (BHT) | 0.1                                  |

5 BHA and BHT were dissolved in ethanol in one beaker while citric acid, SLS, and HPC were dissolved in water in a second beaker. The two solutions were combined and sprayed on the remaining ingredients, which were blended in a V-blender, to form a paste. The paste was then extruded through an extruder, and the extrudate was immediately transferred to a spheronizer. The resulting wet drug beads were dried in a fluid bed dryer.

10 **Example 28. CX-8998 delayed-release (DR) bead formulation**

15 A CX-8998 DR formulation can be any composition from which release of CX-8998 is largely delayed following administration. Release of CX-8998 from the composition of this example can be controlled by application of a pH-sensitive coating that is targeted to dissolve at a pH in the range of 6.0 – 6.5. The composition is provided in Table 38.

Table 38. CX-8998 drug bead formulation containing no microcrystalline cellulose

| Component           | Composition (wt % of core bead wt) |
|---------------------|------------------------------------|
| Core Beads          |                                    |
| CX-8998 (HCl salt)  | 5.0%                               |
| Lactose monohydrate | 57.7%                              |

|                                |       |
|--------------------------------|-------|
| Crospovidone                   | 25.0% |
| Citric Acid Anhydrous          | 8.0%  |
| Sodium Lauryl Sulfate (SLS)    | 2.0%  |
| Hydroxypropyl Cellulose (HPC)  | 2.0%  |
| Butylated Hydroxyanisole (BHA) | 0.3%  |
| Butylated Hydroxytoluene (BHT) | 0.1%  |
| Coating                        |       |
| Methacrylic Acid Copolymer L   | 6.25% |
| Methacrylic Acid Copolymer S   | 6.25% |
| Triethyl citrate               | 1.25% |
| Talc, USP                      | 6.25% |

Core beads were prepared as described in Example 27. The dried beads were loaded into a fluid bed dryer with Würster inserts and spray coated with the coating ingredients listed above suspended in 95% isopropanol. Spray coating was continued until the mass of the coating was about 20% of the mass of the uncoated beads. The beads were dried in the fluid bed until residual solvent content was negligible.

**Example 29. CX-8998 delayed release bead formulation (later release)**

Another delayed release bead formulation is targeted to release later in the intestinal tract. The composition of this formulation is provided in Table 39.

Table 39. CX-8998 drug bead formulation containing no microcrystalline cellulose

| Component           | Composition (wt % of core bead wt) |
|---------------------|------------------------------------|
| Core Beads          |                                    |
| CX-8998 (HCl salt)  | 5.0%                               |
| Lactose monohydrate | 57.7%                              |
| Crospovidone        | 25.0%                              |

|                                |        |
|--------------------------------|--------|
| Citric Acid Anhydrous          | 8.0%   |
| Sodium Lauryl Sulfate (SLS)    | 2.0%   |
| Hydroxypropyl Cellulose (HPC)  | 2.0%   |
| Butylated Hydroxyanisole (BHA) | 0.3%   |
| Butylated Hydroxytoluene (BHT) | 0.1%   |
| Coating                        |        |
| Eudragit FS 30 D               | 17.4%* |
| Plasacryl T20                  | 2.6%*  |

Core beads were prepared as described in Example 27. The dried beads were loaded into a fluid bed dryer with Würster inserts and spray coated with the coating ingredients listed above suspended in purified water. Spray coating was continued until 5 the mass of the coating was about 20% of the mass of the uncoated beads. The beads were dried in the fluid bead.

**Example 30. 8-mg CX-8998 controlled release capsules for twice daily dosing**

A controlled release drug product was generated by combining the immediate release beads of Example 27 with the delayed release beads of **Error! Reference source not found.** Size 0 hard gelatin capsules were manually filled with about 128 mg of the immediate release beads and about 104 mg of the delayed release beads per capsule. Each capsule thus filled contained the equivalent of 8 mg of CX-8998 free base.

**Example 31. 8-mg CX-8998 controlled release capsules for once daily dosing**

A controlled release drug product was generated by combining the immediate release beads of Example 27 with the delayed release beads of Example 29. Size 0 hard gelatin capsules were manually filled with about 85 mg of the immediate release beads and about 158 mg of the delayed release beads per capsule. Each capsule thus filled contained the equivalent of 8 mg of CX-8998 free base.

**Example 32. 20-mg CX-8998 controlled release capsules for twice daily dosing**

A controlled release drug product was generated by combining the immediate release beads of Example 27 with the delayed release beads of Example 28. Size 00 hard gelatin capsules were manually filled with about 320 mg of the immediate release beads and about 260 mg of the delayed release beads per capsule. Each capsule thus filled contained the equivalent of 20 mg of CX-8998 free base.

**Example 33. 20-mg CX-8998 controlled release capsules for once daily dosing**

A controlled release drug product was generated by combining the immediate release beads of Example 27 with the delayed release beads of Example 29. Size 0 hard gelatin capsules were manually filled with about 212 mg of the immediate release beads and about 395 mg of the delayed release beads per capsule. Each capsule thus filled contained the equivalent of 20 mg of CX-8998 free base.

**Example 34. Dissolution of MR1 20 mg capsules**

The capsules described in Example 32 were tested in a USP type 2 dissolution apparatus for two hours in a medium containing 3% Tergitol in 0.1N hydrochloric acid and subsequently for 12 hours in a medium containing 3% Tergitol in pH 6.8 phosphate buffer. Mean data are provided in Table 40.

Table 40. Mean dissolution data for 20-mg “MR1” capsules

| hours | % of label claim dissolved |
|-------|----------------------------|
| 1     | 50                         |
| 2     | 60                         |
| 2.5   | 68                         |
| 3     | 86                         |
| 4     | 97                         |

|    |     |
|----|-----|
| 6  | 102 |
| 10 | 102 |
| 14 | 102 |

### Example 35. Dissolution of MR2 20 mg capsules

The capsules described in Example 33 were tested in a USP type 2 dissolution apparatus for two hours in a medium containing 3% Tergitol in 0.1N hydrochloric acid and subsequently for 12 hours in a medium containing 3% Tergitol in pH 6.8 phosphate buffer. Mean data are provided in Table 41.

Table 41. Mean dissolution data for 20-mg “MR2” capsules

| hours | % of label claim dissolved |
|-------|----------------------------|
| 1     | 48                         |
| 2     | 49                         |
| 2.5   | 51                         |
| 3     | 54                         |
| 4     | 61                         |
| 6     | 72                         |
| 10    | 84                         |
| 14    | 91                         |

### 10 Example 36. CX-8998 formulation pharmokinetics

Bead formulations of Examples 27 - 29 were evaluated for dissolution. Dissolution rates of IR, MR1, and MR2 are shown in Figure 56. Dissolution rates of IR, MR1, and MR2 after 10 days of storage at 40°C / 75% RH or 10 days of storage at 5°C are shown in Figure 57.

5 Bead formulation dissolution rates were subjected to PK modeling. In vitro release profiles for IR, MR1, and MR2 beads were plugged into a PK model developed based on IR data. PK modeling for bead ratio and total dose was performed as separate 2-compartment models for elderly and non-elderly (“young”) subjects. PK from different ratios of IR and MR1 and of IR and MR2 can be predicted. Total dose can be optimized based on a target for  $C_{max}$ ,  $C_{min}$ , or  $C_{ave}$ .

Dissolution rates of IR and MR1 combinations in the elderly over a 7 day time course and at steady state are shown in Figure 58. 60% IR / 40% MR1 demonstrated quick uptake (low  $t_{max}$ ) and blunted  $C_{max}$ .

10 Dissolution rates of IR and MR2/CR7 combinations in the elderly over a 7 day time course and at steady state are shown in Figure 59. 60% IR / 40% MR2/CR7 demonstrated quick uptake (low  $t_{max}$ ), blunted  $C_{max}$ , and extended duration.

15 Dissolution rates of IR and MR1 combinations in the non-elderly over a 7 day time course and at steady state are shown in Figure 60. 60% IR / 40% MR1 demonstrated blunted  $C_{max}$ , but no improvement in duration of action over IR.

Dissolution rates of IR and MR2/CR7 combinations in the non-elderly over a 7 day time course and at steady state are shown in Figure 61. 60% IR / 40% MR2/CR7 demonstrated good ratios for non-elderly subjects.

### Example 37. CX-8998 Combined Prototypes Formulation

20 A relative bioavailability study is used to confirm profiles between BID and QD (sustained release) are similar and achieve therapeutic minimums, and that BID and QD avoid maximum tolerated concentrations in target concentrations in ideal range for waking hours only.

25 Simulations were performed using formulations having 40% IR, 25% MR1 (pH 6), and 35% MR2/CR7 (pH 7) at dosages of 25 mg, 15, mg, and 8 mg. Simulated dissolution rates of various dosage forms are shown in Figure 62.

Table 42.  $C_{max}$  of 25 mg QD Dosage Form

| dosage form | $C_{max}$ (ng/mL) |     |
|-------------|-------------------|-----|
|             | Day 1             | SS  |
| <b>IR</b>   | 614               | 719 |
| <b>CR</b>   | 282               | 385 |

Table 43.  $C_{max}$  of 15 mg QD Dosage Form

| dosage form | $C_{max}$ (ng/mL) |     |
|-------------|-------------------|-----|
|             | Day 1             | SS  |
| <b>IR</b>   | 453               | 550 |
| <b>CR</b>   | 263               | 360 |

## 5 Example 38. Clinical pharmacokinetics of CX-8998 formulations

A bioavailability study was performed to evaluate the pharmacokinetics of various CX-8998 formulations in human subjects.

### Methods

This is an open-label, single-dose, randomized, 3-way crossover, single-center study of the safety, tolerability, and PK of 2 CR test formulations, as compared with the original IR capsule formulation, in a maximum of 15 subjects. Subjects will be screened for study eligibility within 28 days before administration of the first dose of study drug. Subjects who meet the study eligibility criteria will be admitted to the clinical research unit in the afternoon of the day before administration of the first dose of study drug (Period 1/Day -1). Subjects who continue to meet the study eligibility criteria will be randomized to a treatment sequence and will receive single, 8 mg doses of each of the following CX-8998 treatments in randomized order, with each treatment separated from the previous one by a minimum 7-day washout period:

- Original IR capsule (4 capsules, each containing 2 mg CX-8998 under fasted conditions (Treatment A),

- CR test formulation #1 (multi-particulate capsule formulation containing 8 mg of CX-8998 in the form of IR and modified-release type 1 [MR1] beads) under fasted conditions (Treatment B), and
- CR test formulation #2 (multi-particulate capsule formulation containing 8 mg of CX-8998 in the form of IR and modified-release type 2 [MR2] beads) under fasted conditions (Treatment C).
- CR test formulation #2 (multi-particulate capsule formulation containing 8 mg of CX-8998 in the form of IR and modified-release type 2 [MR2] beads) under fed conditions (Treatment D).

5

10

Treatments A, B, and C will be separated by a minimum 7-day washout period. Subjects who receive Treatments A, B, and C may also receive an optional additional treatment consisting of CR test formulation #2 under fed conditions (Treatment D). Administration of Treatment D may be separated from administration of Treatments A, 15 B, and C by approximately 4 weeks to allow for analysis of the bioanalytical samples from the first 3 treatments.

## 1 Treatments

The following is a list of the study treatment abbreviations and ordering that will 20 be used in the TFLs.

| Study Treatment Name   | Short name                  | Abbreviation | Treatment Order on TFLs |
|--|-----------------------------|--------------|-------------------------|
| Original IR capsule, single 8 mg dose, fasted conditions                   | 8mg CX-8998 IR (Fasted)     | A            | 1                       |
| CR test formulation #1 (IR-MR1 beads), single 8 mg dose, fasted conditions | 8mg CX-8998 IR-MR1 (Fasted) | B            | 2                       |

|  |                             |   |   |
|--|-----------------------------|---|---|
| CR test formulation #2 (IR-MR2 beads), single 8 mg dose, fasted conditions | 8mg CX-8998 IR-MR2 (Fasted) | C | 3 |
| CR test formulation #2 (IR-MR2 beads), single 8 mg dose, fed conditions    | 8mg CX-8998 IR-MR2 (Fed)    | D | 4 |

Abbreviations: CR = controlled release; IR = immediate release; MR1 = modified-release type 1; MR2 = modified-release type 2.

## 2 SAMPLE SIZE JUSTIFICATION

In 2 previous single-dose PK studies, the average intersubject coefficient of variation (CV%) following a 12 mg single dose of CX-8998 ranged from 21% to 35% for maximum observed plasma concentration ( $C_{max}$ ) and from 22% to 26% for area under the curve (AUC) (Studies PN001/Part 1 and PN002/Part 2). Assuming that the intrasubject variability would be 18% (i.e., approximately 50% of the maximum CV% of 35%), a total of 13 subjects would be adequate to estimate the bioavailability of CX-8998 with >80% power, 5% probability, and  $\mu=1.0$ . A maximum of 15 subjects will be enrolled in the study.

Subjects who prematurely withdraw from the study for reasons other than treatment-related adverse events (TEAEs) may be replaced, at the sponsor's discretion, to ensure that at least 13 subjects complete the study.

## Results

A single dose, crossover clinical trial was conducted in 15 subjects ranging in age from 35-75 years. Demographic characteristics at baseline are shown in Table 44.

Table 44. Study Subject Demographics at Baseline

| Parameter | All Subjects<br>N=15 | Tremor POC<br>N=95 |
|-----------|----------------------|--------------------|
| Sex       |                      |                    |

|                        |                      |                      |
|------------------------|----------------------|----------------------|
| Male                   | 6 (40%)              | 50 (53%)             |
| Female                 | 9 (60%)              | 45 (47%)             |
| Age                    |                      |                      |
| Mean (SD)              | 53 (11.5)            | 63 (10.2)            |
| Median (min, max)      | 51 (37, 70)          | 66 (21, 75)          |
| Race                   |                      |                      |
| Race 5                 | 11 (73.3%)           | 91 (96%) (white)     |
| Race 3                 | 3 (20%)              | 4 (4%) (black)       |
| Race 1                 | 1 (6.7%)             |                      |
| Ethnicity              |                      |                      |
| Not Hispanic or Latino | 10 (66.7%)           | 93 (98%)             |
| Hispanic or Latino     | 5 (33.3%)            | 1 (1%)               |
| Not Reported           | 0                    | 1 (1%)               |
| Weight (kg)            |                      |                      |
| Mean (SD)              | 75.5 (11.1)          | 86.8 (20.0)          |
| Median (min, max)      | 74.1 (55, 91.6)      | 84.6 (49.3, 131.5)   |
| Height (cm)            |                      |                      |
| Mean (SD)              | 166.7 (8.4)          | 171.8 (10.4)         |
| Median (min, max)      | 167.5 (153.2, 180.8) | 172.7 (149.9, 193.0) |

Each subject received, in randomized order, an 8-mg dose of CX-8998, M01, or M02 immediate release capsules and each of the capsules of Example 30 (MR1 capsules) and Example 31 (MR2 capsules), with a 7 day washout period between doses.

5 Compared to the immediate release dose, the CR capsules yielded lower  $C_{max}$  values with similar AUC. Values for the pharmacokinetic parameters obtained from the study are provided in Tables 45-48 and in Figure 63.

Table 45. PK parameters for CX-8998

| Subject No. | IR Formulation |           |                   | MR1 Formulation |           |                   | MR2 Formulation |           |                   |
|-------------|----------------|-----------|-------------------|-----------------|-----------|-------------------|-----------------|-----------|-------------------|
|             | Cmax (ng/L)    | Tmax (hr) | AUC0-24 (ng·hr/L) | Cmax (ng/L)     | Tmax (hr) | AUC0-24 (ng·hr/L) | Cmax (ng/L)     | Tmax (hr) | AUC0-24 (ng·hr/L) |
| 101         | 221            | 0.5       | 3185              | 423             | 1.0       | 3823              | 397             | 1.0       | 3085              |
| 102         | 875            | 1.0       | 8628              | 439             | 1.0       | 8959              | 316             | 1.5       | 10011             |
| 103         | 820            | 0.5       | 6910              | 471             | 1.0       | 7114              | 321             | 1.0       | 5947              |
| 104         | 538            | 1.5       | 9175              | 465             | 1.0       | 9384              | 387             | 4.0       | 11133             |
| 105         | 869            | 0.5       | 4786              | 350             | 1.0       | 4782              | 282             | 1.0       | 3862              |
| 106         | 1538           | 0.5       | 6911              | 563             | 1.0       | 7028              | 339             | 1.5       | 8964              |
| 107         | 1406           | 0.5       | 7288              | 488             | 0.5       | 7387              | 305             | 1.0       | 6813              |
| 108         | 626            | 1.0       | 4586              | 287             | 0.5       | 4163              | 305             | 0.5       | 4833              |
| 109         | 391            | 1.5       | 7940              | 355             | 1.0       | 8335              | 255             | 3.0       | 8189              |
| 110         | 712            | 1.5       | 13262             | 641             | 1.0       | 13295             | 342             | 1.5       | 10830             |
| 111         | 1238           | 0.5       | 7237              | 423             | 1.0       | 8177              | 287             | 1.0       | 6034              |
| 112         | 1243           | 0.5       | 7365              | 473             | 0.5       | 6271              | 371             | 1.0       | 6730              |
| 113         | 1338           | 1.0       | 9382              | 584             | 1.0       | 9353              | 371             | 1.0       | 10153             |
| 114         | 983            | 0.5       | 5463              | 460             | 0.5       | 5184              | 292             | 1.0       | 4873              |
| 115         | 688            | 1.5       | 6845              | 394             | 3.0       | 7886              | 281             | 1.5       | 6136              |
| N           | 15             | 1.5       | 15                | 15              | 1.5       | 15                | 15              | 1.5       | 15                |
| Mean        | 916            | 0.5       | 7435              | 440             | 1.0       | 7528              | 318             | 1.0       | 7119              |
| SD          | 328            |           | 2318              | 85              |           | 2381              | 40              |           | 2334              |
| CV%         | 35.8           |           | 31.3              | 18.3            |           | 30.3              | 12.4            |           | 35.6              |

Median value for Tmax

Table 46. PK parameters for M02

| Subject No. | IR Formulation |           |                   | MR1 Formulation |           |                   | MR2 Formulation |           |                   |
|-------------|----------------|-----------|-------------------|-----------------|-----------|-------------------|-----------------|-----------|-------------------|
|             | Cmax (ng/L)    | Tmax (hr) | AUC0-24 (ng·hr/L) | Cmax (ng/L)     | Tmax (hr) | AUC0-24 (ng·hr/L) | Cmax (ng/L)     | Tmax (hr) | AUC0-24 (ng·hr/L) |
| 101         | 129            | 12.0      | 3981              | 111             | 12.0      | 6546              | 98              | 12.0      | 3983              |
| 102         | 105            | 48.0      | 6690              | 121             | 24.0      | 7647              | 128             | 48.0      | 7386              |
| 103         | 87             | 48.0      | 5835              | 96              | 24.0      | 6019              | 79              | 48.0      | 4781              |
| 104         | 118            | 38.0      | 7641              | 101             | 38.0      | 6084              | 149             | 48.0      | 8536              |
| 105         | 121            | 1.0       | 8907              | 86              | 34.0      | 4887              | 76              | 34.0      | 4118              |
| 106         | 117            | 0.5       | 6438              | 128             | 24.0      | 7294              | 126             | 48.0      | 7276              |
| 107         | 128            | 24.0      | 8751              | 132             | 24.0      | 7802              | 110             | 48.0      | 6086              |
| 108         | 131            | 12.0      | 6138              | 109             | 16.0      | 5695              | 112             | 24.0      | 5822              |
| 109         | 86             | 48.0      | 5100              | 99              | 34.0      | 6098              | 90              | 48.0      | 5847              |
| 110         | 148            | 48.0      | 8547              | 220             | 48.0      | 13173             | 126             | 72.0      | 10232             |
| 111         | 132            | 48.0      | 7706              | 123             | 24.0      | 7231              | 99              | 34.0      | 5752              |
| 112         | 145            | 24.0      | 7677              | 135             | 24.0      | 7521              | 117             | 24.0      | 6720              |
| 113         | 116            | 24.0      | 6789              | 158             | 38.0      | 7068              | 131             | 24.0      | 7569              |
| 114         | 102            | 8.0       | 6093              | 98              | 24.0      | 9349              | 83              | 24.0      | 9124              |
| 115         | 127            | 24.0      | 7034              | 127             | 24.0      | 7161              | 95              | 48.0      | 5705              |
| N           | 15             | 15        | 15                | 15              | 15        | 15                | 15              | 15        | 15                |
| Mean        | 122            | 24        | 6829              | 120             | 24        | 6897              | 111             | 48        | 6342              |
| SD          | 19             |           | 1049              | 31              |           | 1836              | 29              |           | 1688              |
| CV%         | 16.0           |           | 15.4              | 26.0            |           | 27.7              | 26.3            |           | 26.6              |

Median value for Tmax

Table 47. PK parameters for M01

| Subject No. | IR Formulation |          |                           | MR1 Formulation |          |                           | MR2 Formulation |          |                           |
|-------------|----------------|----------|---------------------------|-----------------|----------|---------------------------|-----------------|----------|---------------------------|
|             | Cmax (μM)      | Tmax (h) | AUC <sub>0-∞</sub> (μM·h) | Cmax (μM)       | Tmax (h) | AUC <sub>0-∞</sub> (μM·h) | Cmax (μM)       | Tmax (h) | AUC <sub>0-∞</sub> (μM·h) |
| 101         | 122            | 3.0      | 2381                      | 83              | 8.0      | 1987                      | 81              | 4.0      | 1182                      |
| 102         | 133            | 4.0      | 4438                      | 112             | 12.0     | 4789                      | 89              | 12.0     | 3825                      |
| 103         | 88             | 2.5      | 3360                      | 96              | 6.0      | 3463                      | 74              | 24.0     | 2684                      |
| 104         | 87             | 8.0      | 4872                      | 82              | 12.0     | 4278                      | 104             | 16.0     | 5831                      |
| 105         | 103            | 1.0      | 3926                      | 82              | 4.0      | 3187                      | 64              | 2.0      | 2343                      |
| 106         | 109            | 2.0      | 3882                      | 128             | 8.0      | 4688                      | 77              | 12.0     | 3337                      |
| 107         | 103            | 2.0      | 3778                      | 57              | 1.0      | 2961                      | 106             | 6.0      | 3173                      |
| 108         | 129            | 3.0      | 2226                      | 100             | 4.0      | 2661                      | 70              | 12.0     | 2762                      |
| 109         | 79             | 3.0      | 3831                      | 71              | 24.0     | 3845                      | 58              | 14.0     | 2897                      |
| 110         | 104            | 24.0     | 6212                      | 107             | 36.0     | 6557                      | 81              | 48.0     | 4886                      |
| 111         | 129            | 1.0      | 3674                      | 99              | 12.0     | 3628                      | 46              | 24.0     | 1901                      |
| 112         | 87             | 8.0      | 3289                      | 112             | 8.0      | 3347                      | 92              | 8.0      | 3628                      |
| 113         | 134            | 12.0     | 5553                      | 108             | 12.0     | 5229                      | 110             | 24.0     | 5126                      |
| 114         | 127            | 2.0      | 3408                      | 82              | 8.0      | 2362                      | 77              | 12.0     | 2687                      |
| 115         | 125            | 2.5      | 4126                      | 98              | 24.0     | 4474                      | 62              | 18.0     | 3998                      |
| N           | 15             | 15       | 15                        | 15              | 15       | 15                        | 15              | 15       | 15                        |
| Mean        | 123            | 3.0      | 3809                      | 94              | 8.0      | 3739                      | 73              | 13       | 3334                      |
| SD          | 39             |          | 1182                      | 18              |          | 1247                      | 20              |          | 1208                      |
| CV%         | 23.9           |          | 28.9                      | 19.1            |          | 33.5                      | 26.7            |          | 37.4                      |

Median value for Tmax

Table 48. Bioavailability parameters for CX-8998 from MR1 and MR2 capsules

| Subject No.          | MR1          |              | MR2          |              |
|----------------------|--------------|--------------|--------------|--------------|
|                      | Cmax Ratio   | AUC Ratio    | Cmax Ratio   | AUC Ratio    |
| 101                  | 0.813        | 1.09         | 0.57         | 0.60         |
| 102                  | 0.592        | 1.04         | 0.35         | 1.16         |
| 103                  | 0.374        | 1.03         | 0.39         | 0.86         |
| 104                  | 0.881        | 1.02         | 0.75         | 1.21         |
| 105                  | 0.407        | 0.99         | 0.34         | 0.81         |
| 106                  | 0.368        | 1.02         | 0.23         | 1.17         |
| 107                  | 0.333        | 1.01         | 0.22         | 0.93         |
| 108                  | 0.475        | 0.89         | 0.49         | 1.03         |
| 109                  | 0.600        | 1.05         | 0.43         | 1.03         |
| 110                  | 0.900        | 0.95         | 0.48         | 0.78         |
| 111                  | 0.343        | 1.33         | 0.23         | 0.84         |
| 112                  | 0.379        | 0.86         | 0.39         | 0.92         |
| 113                  | 0.337        | 1.00         | 0.33         | 1.08         |
| 114                  | 0.468        | 0.95         | 0.30         | 0.91         |
| 115                  | 0.593        | 1.17         | 0.42         | 0.90         |
| N                    | 15           | 15           | 15           | 15           |
| Geometric Mean Ratio | 0.50         | 1.01         | 0.37         | 0.93         |
| Estimated 90% CI     | [0.39, 0.61] | [0.97, 1.06] | [0.29, 0.43] | [0.84, 1.03] |

Adverse events following single-dose administration of CX-8998 were evaluated. Treatment emergent adverse events, related to study drug, and observed in two or more subjects following a single 8 mg dose of CX-8998 are provided in Table 49 and in Figure 5 64.

Table 49. Adverse Event observed in complete cohort (n = 15).

| Adverse Event<br>SOC<br>PT | Any<br>Treatment<br>N=15 | Original IR<br>N=15 | MR1*<br>N=15 | MR2**<br>N=15 |
|----------------------------|--------------------------|---------------------|--------------|---------------|
| Any                        | 11 (73%)                 | 8 (53%)             | 7 (47%)      | 4 (27%)       |
| Nervous System             | 10 (67%)                 | 6 (40%)             | 7 (47%)      | 4 (27%)       |
| Paresthesias               | 7 (47%)                  | 6 (40%)             | 4 (27%)      | 3 (20%)       |
| Dizziness                  | 5 (33%)                  | 3 (20%)             | 5 (33%)      | 3 (20%)       |
| Headache                   | 5 (33%)                  | 3 (20%)             | 2 (13%)      | 2 (13%)       |
| Feeling abnormal           | 4 (27%)                  | 3 (20%)             | 0            | 1 (7%)        |
| Psychiatric                | 5 (33%)                  | 4 (27%)             | 2 (13%)      | 1 (7%)        |
| Abnormal dreams            | 3 (20%)                  | 2 (13%)             | 1 (7%)       | 0             |
| Euphoric mood              | 2 (13%)                  | 2 (13%)             | 1 (7%)       | 1 (7%)        |

\*Modified release prototype formulation 1 (MR1 for BID): 60% IR beads, 40% CR (pH 6) beads, single capsule, designed to achieve 25% reduction of  $C_{max}$  relative to IR and 8 hours coverage above threshold

10 \*\*Modified release prototype formulation 2 (MR2 for QD): 40% IR beads, 60% CR (pH 7) beads, single capsule, designed to achieve 45% reduction in  $C_{max}$  and 12-16 hours coverage above threshold

15 Adverse events in view of the pharmacokinetics of CX-8998 are shown in Figures 66-68. For IR formulations, CNS adverse events and psychiatric adverse events generally occurred within 2-hours of dosing, and many CNS adverse events were associated with concentrations at or below the average concentration of CX-8998 (Figure 65). For MR1 formulations, CNS adverse events and psychiatric adverse events generally occurred within 2-hours of dosing at CX-8998 concentrations generally lower

than those observed with the IR formulation, suggesting that the threshold concentration for producing CNS adverse events and psychiatric adverse events is below 400 nM (Figure 66). For MR2 formulations, CNS adverse events and psychiatric adverse events generally occurred within 2-hours of dosing at CX-8998 peak concentrations below 400 nM (Figure 67).

Adverse events in view of the treatment period of CX-8998 are shown in Figure 68. There was no clear evidence of a period effect.

Plasma concentrations of CX-8998, metabolite M01, and metabolite M02 following administration of a single dose (1 x 8 mg) IR CX-8998, MR1 CX-8998, or 10 MR2 CX-8998 were evaluated. Data are shown in Tables 50-52 and Figure 72. No impact of formulation was seen on the AUC Ratio.  $C_{max}$  effects were consistent with reduced parent.

15 Table 50. Metabolite M01 and M02 Concentrations Following a Single 8 mg Dose of IR CX-8998

| IR                    | CX-8998 | M01   |       | M02   |       |
|-----------------------|---------|-------|-------|-------|-------|
|                       |         | Value | Ratio | Value | Ratio |
| T <sub>max</sub> (hr) | 1.0     | 29    | -     | 5     | -     |
| C <sub>max</sub> (nM) | 913     | 124   | 0.14  | 122   | 0.13  |
| AUC <sub>72hr</sub>   | 7486    | 6876  | 0.92  | 3671  | 0.49  |

Table 51. Metabolite M01 and M02 Concentrations Following a Single 8 mg Dose of MR1 CX-8998

| MR1                   | CX-8998 | M01   |       | M02   |       |
|-----------------------|---------|-------|-------|-------|-------|
|                       |         | Value | Ratio | Value | Ratio |
| T <sub>max</sub> (hr) | 1.0     | 26    | -     | 11    | -     |
| C <sub>max</sub> (nM) | 447     | 121   | 0.27  | 94    | 0.21  |
| AUC <sub>72hr</sub>   | 7530    | 7118  | 0.95  | 3343  | 0.44  |

Table 52. Metabolite M01 and M02 Concentrations Following a Single 8 mg Dose of MR2 CX-8998

| MR2                   | CX-8998 | M01   |       | M02   |       |
|-----------------------|---------|-------|-------|-------|-------|
|                       |         | Value | Ratio | Value | Ratio |
| T <sub>max</sub> (hr) | 1.5     | 39    | -     | 16    | -     |
| C <sub>max</sub> (nM) | 319     | 113   | 0.35  | 73    | 0.23  |
| AUC <sub>72hr</sub>   | 7125    | 6395  | 0.90  | 3142  | 0.44  |

5

**Example 39. Clinical pharmacokinetics of CX-8998 formulations in fed versus fasted human subjects**

A bioavailability study was performed to evaluate the pharmacokinetics of CX-8998 formulations in human subjects that were in a fed state compared to the pharmacokinetics of CX-8998 formulations in human subjects that were in a fasted state.

**Methods**

The methods were performed as described in Example 38, Treatment D.

**Results**

Plasma concentrations of CX-8998 following administration of a single dose (1 x 8 mg) of MR2 CX-8998 were evaluated. Data are shown in Table 53 and Figures 74 and 75. The p-values listed in Table 53 are for a 2-tailed t-test.

Table 53. Pharmacokinetics of CX-8998 formulations

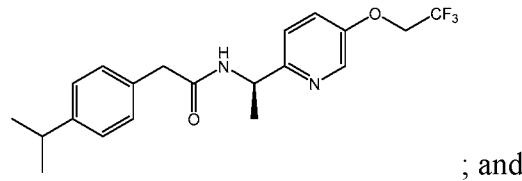
|         | AUC  | C <sub>max</sub> | t <sub>max</sub> |
|---------|------|------------------|------------------|
| fasted  | 6786 | 315              | 1.3              |
| fed     | 7570 | 254              | 8.9              |
| p-value | 0.61 | 0.12             | 0.00000005       |

Whether the patient is administered the CX-8998 in a fed state or a fasted state impacts early absorption of the CX-8998, but does not appear to significantly impact late absorption. The fed state of the patient when taking CX-8998 does not appear to 5 significantly impact overall exposure of CX-8998 as measured by AUC.

**Example 40. Exemplary Embodiments**

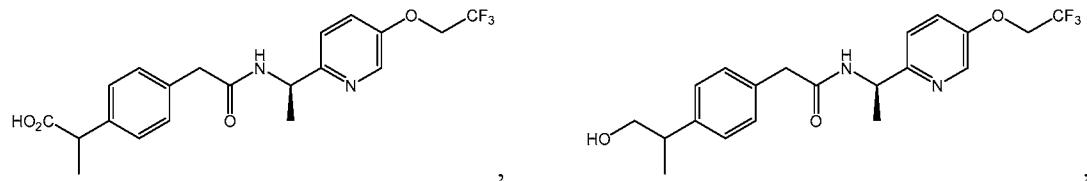
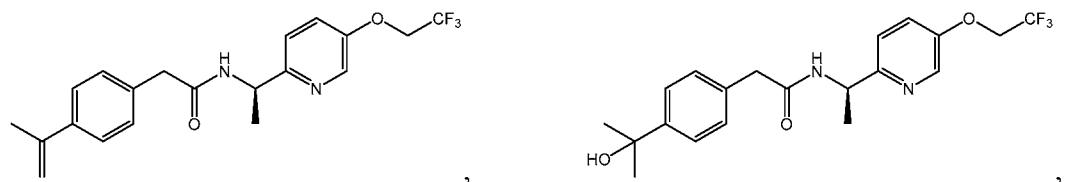
Embodiment 1. An oral dosage form comprising:

an immediate release component comprising from about 2 mg to about 20 mg of a 10 compound having the structure



a delayed release component comprising from about 2 mg to about 20 mg of said compound or a metabolite thereof.

15 Embodiment 2. The oral dosage form of claim 1, said oral dosage form further comprising one or more metabolites of said compound, wherein said metabolites are selected from the group consisting of



and combinations thereof.

Embodiment3. The oral dosage form of Embodiment 1 of Embodiment 2, wherein said oral dosage form comprises a capsule, and wherein said immediate release component and said delayed release component are contained within said capsule.

5

Embodiment 4. The oral dosage form of Embodiment 3, wherein said capsule is a gelatin capsule.

10 Embodiment 5. The oral dosage form of Embodiment 4, wherein said gelatin capsule is a hard gelatin capsule.

Embodiment 6. The oral dosage form of any one of Embodiment 3 to Embodiment 5, wherein said capsule is a size 4 capsule.

15 Embodiment 7. The oral dosage form of any one of Embodiment 1 to Embodiment 6, wherein said immediate release component is in the form of a plurality of beads.

Embodiment 8. The oral dosage form of Embodiment 7, wherein said beads further comprise lactose monohydrate, crospovidone, citric acid, and sodium lauryl sulfate.

20

Embodiment 9. The oral dosage form of Embodiment 8, wherein said beads comprise, by weight, about 5% of said compound, about 60% lactose monohydrate, about 25% crospovidone, about 8% citric acid, and about 2% sodium lauryl sulfate.

25 Embodiment 10. The oral dosage form of any one of Embodiment 7 to Embodiment 9, wherein said beads are formed by extrusion and spheroidization.

30 Embodiment 11. The oral dosage form of any one of Embodiment 1 to Embodiment 10, wherein said delayed release component is in the form of a plurality of beads coated with an enteric polymer having a pH of pH 5.5.

Embodiment 12. The oral dosage form of Embodiment 11, wherein said beads further comprise lactose monohydrate, crospovidone, citric acid, and sodium lauryl sulfate.

5

Embodiment 13. The oral dosage form of Embodiment 12, wherein said beads comprise, by weight, about 5% of said compound, about 60% lactose monohydrate, about 25% crospovidone, about 8% citric acid, and about 2% sodium lauryl sulfate.

10 Embodiment 14. The oral dosage form of any one of Embodiment 11 to Embodiment 13, wherein said beads are formed by extrusion and spheronization and film coated using a fluidized bed spray coating process.

15 Embodiment 15. The oral dosage form of any one of Embodiment 1 to Embodiment 14, wherein said immediate release component comprises about 10 mg of said compound, and wherein said delayed release component comprises about 10 mg of said compound.

20 Embodiment 16. The oral dosage form of any one of Embodiment 1 to Embodiment 14, wherein said immediate release component comprises about 7 mg of said compound, and wherein said delayed release component comprises about 13 mg of said compound.

25 Embodiment 17. The oral dosage form of any one of Embodiment 1 to Embodiment 16, wherein said immediate release component is formulated to release, when delivered to a human, at least 80% of said compound present in the immediate release component within 45 minutes.

30 Embodiment 18. The oral dosage form of any one of Embodiment 1 to Embodiment 17, wherein said delayed release component is formulated to provide, when delivered to a human, a minimum plasma level of from about 100 nM to about 300 nM of said compound.

Embodiment 19. The oral dosage form of Embodiment 18, wherein said minimum plasma level of said compound is maintained for about 12 hours.

5 Embodiment 20. The oral dosage form of Embodiment 18, wherein said minimum plasma level of said compound is maintained for about 24 hours.

Embodiment 21. The oral dosage form of any one of Embodiment 18 to Embodiment 20, wherein said minimum plasma level of said compound is about 200 nM.

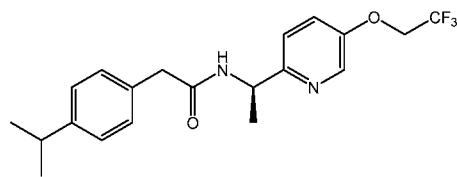
10 Embodiment 22. The oral dosage form of any one of Embodiment 1 to Embodiment 21, wherein said delayed release component is formulated to provide, when delivered to a human, a maximum plasma level of from about 900 nM to about 1800 nM of said compound.

15 Embodiment 23. The oral dosage form of Embodiment 21, wherein said maximum plasma level of said compound is about 900 nM.

20 Embodiment 24. The oral dosage form of Embodiment 21, wherein said maximum plasma level of said compound is about 1000 nM.

Embodiment 25. A method of treating a human having a movement disorder, said method comprising:

25 administering to said human an oral dosage form, said oral dosage form comprising:  
an immediate release component comprising from about 2 mg to about 16 mg of a compound having the structure



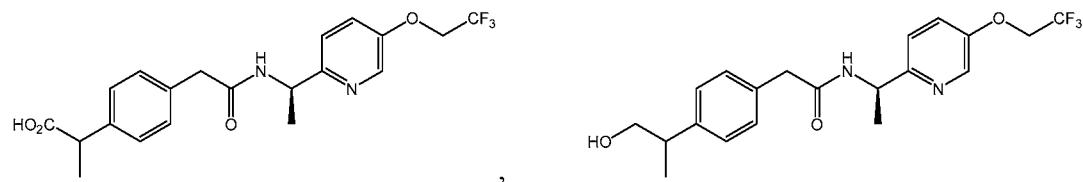
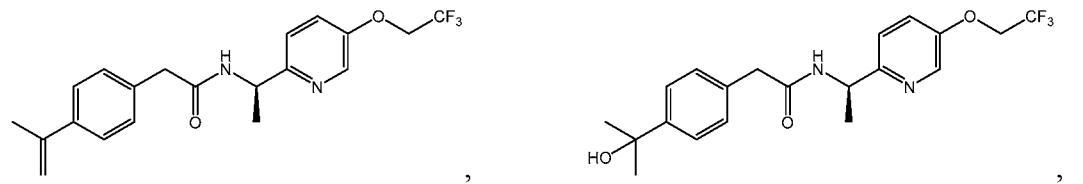
; and

a delayed release component comprising from about 2 mg to about 16 mg of said compound;

wherein said oral dosage form is administered once daily.

5

Embodiment 26. The method of Embodiment 25, said oral dosage form further comprising one or more metabolites of said compound, wherein said metabolites are selected from the group consisting of



and combinations thereof.

10

Embodiment 27. The method of Embodiment 25 or Embodiment 26, wherein said human is an adult.

15 Embodiment 28. The method of Embodiment 27, wherein said adult is 60 years of age or older.

Embodiment 29. The method of any one of Embodiment 25 to Embodiment 28, wherein said movement disorder is essential tremor.

5 Embodiment 30. The method of any one of Embodiment 25 to Embodiment 28, wherein said movement disorder is Parkinson's disease.

Embodiment 31. The method of any one of Embodiment 25 to Embodiment 30, wherein said oral dosage form is administered in the morning.

10 Embodiment 32. The method of any one of Embodiment 25 to Embodiment 31, wherein said oral dosage form is administered within 4 hours of waking.

15 Embodiment 33. The method of any one of Embodiment 25 to Embodiment 32, wherein said delayed release component of said oral dosage form is formulated to release said compound within said delayed release component at an intestinal pH.

Embodiment 34. The method of any one of Embodiment 25 to Embodiment 33, wherein said human has fasted for at least 4 hours prior to administering said oral dosage form.

20

Embodiment 35. The method of any one of Embodiment 25 to Embodiment 34, wherein said compound is effective to reduce or eliminate one or more symptoms of the movement disorder.

25

## OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended

claims. Other aspects, advantages, and modifications are within the scope of the following claims.

---

## 4 NONCLINICAL STUDIES

### 4.1 Nonclinical Test Material

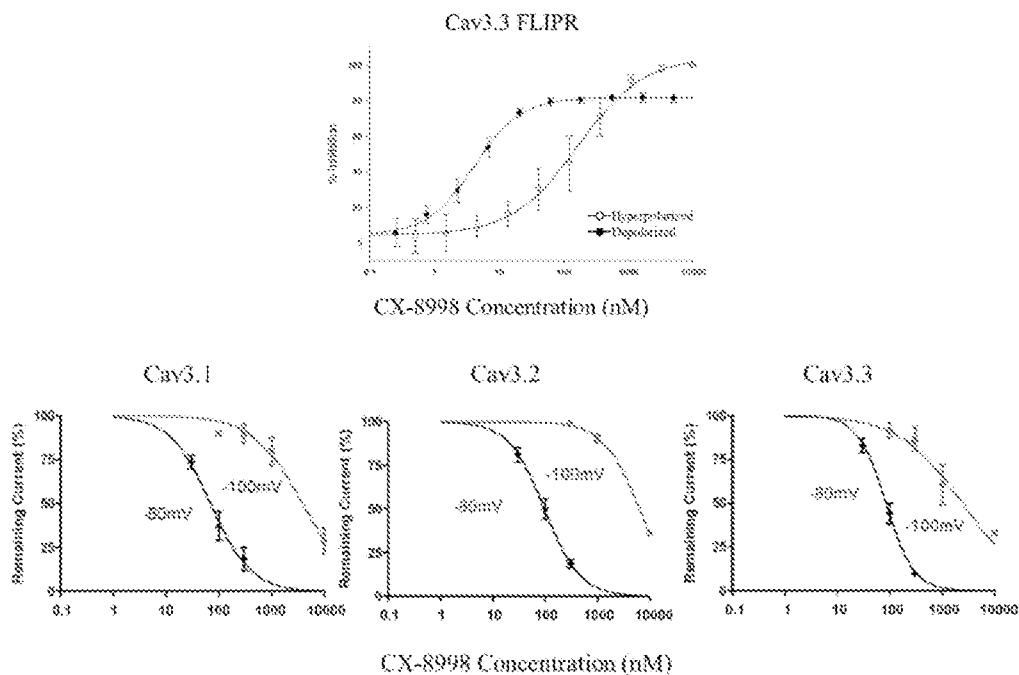
Multiple different batches of drug substance (CX-8998) were synthesized by Merck and used in all nonclinical studies except for the 90-day toxicology studies in rats and dogs, which used a new lot that was synthesized by Cavyon. The drug substance was a powder that was typically mixed with the control article/vehicle used in the study. For in vitro studies, stock solutions in 100% dimethylsulfoxide (DMSO) were produced and serially diluted for test article administration into appropriate buffer/medium to a final DMSO concentration of 0.1% to 0.5%. Some in vitro and in vivo metabolism and excretion studies used <sup>14</sup>C-labeled CX-8998 from a stock solution of 158.4 µCi/mg in methanol diluted with unlabeled material to an assay-appropriate specific activity in relevant vehicle. In vivo studies used multiple different vehicle formulations including 0.5 or 1% methylcellulose, 90% polyethylene glycol (PEG) 400, 80% PEG-200, 10% Tween-80, and 30% cyclodextrin. The pivotal toxicology studies used 0.5% methylcellulose/10% polysorbate-80 as the vehicle for oral administration.

### 4.2 Nonclinical Pharmacology

#### 4.2.1 Primary Pharmacodynamics

##### 4.2.1.1 In Vitro Studies

The in vitro activity on functional inhibition of Cav3.3 was assessed in a Fluorometric Imaging Plate Reader (FLIPR) assay, which measures the inhibition of calcium influx through channels heterologously expressed in human embryonic kidney (HEK)293 cells. Under depolarizing conditions (enriching the proportion of channels in the inactivated state), CX-8998 demonstrated an IC<sub>50</sub> (concentration that produced half-maximal inhibition) of 3.6 nM in the FLIPR assay (Figure 1, top panel). However, under hyperpolarizing conditions (enriching the closed or resting channel state), the IC<sub>50</sub> in this assay shifted 45-fold to 161 nM, suggesting that CX-8998 is a state-dependent antagonist of Cav3.3. This was confirmed with standard whole-cell voltage-clamp assays, which showed an IC<sub>50</sub> of CX-8998 of 84 nM for Cav3.3, using a holding potential (V<sub>h</sub>) of -80 mV, and a 29-fold shift to an IC<sub>50</sub> of 2.4 µM when V<sub>h</sub> = -100 mV (Figure 1, bottom panel). Similar electrophysiology experiments using cells expressing Cav3.1 (V<sub>h</sub> = -80 mV, IC<sub>50</sub> = 69 nM) and Cav3.2 (V<sub>h</sub> = -80 mV, IC<sub>50</sub> = 96 nM) showed that the compound potently inhibited all Cav3 family members in a state-dependent manner. These results demonstrate that CX-8998 is a potent, selective antagonist of all 3 Cav3 isoforms.

**Figure 1: CX-8998 Inhibition of  $\text{Ca}_v3$  Activity In Vitro**

FLIPR = Fluorometric Imaging Plate Reader.

Source: Merck Nonclinical Report PD001.

CX-8998 is metabolized in vivo by the cytochrome P450 (CYP) enzymes CYP3A4 and CYP2C9 to 4 distinct products (designated as M01, M02, M03, and M04) (see Section 4.3.5). Metabolism is primarily via hydroxylation on the isopropyl moiety, resulting in the tertiary and primary alcohols, M02 and M04, and the aliphatic dehydrogenation of the isopropyl moiety to form M01. Further oxidation of the tertiary alcohol M04 results in formation of a carboxylic acid derivative M03.

The 4 metabolites of CX-8998 were individually synthesized and evaluated in the FLIPR assay for inhibition of  $\text{Ca}_v3.3$  activity. These studies show a similar level of potency and state dependence for M01 and CX-8998 (Table 1). M02 and M04 are approximately 5-fold less potent than CX-8998 but retain a high level of state dependence, whereas M03 is significantly less potent and state dependent than either CX-8998 or the other metabolites.

**Table 1: Potency of CX-8998 and Metabolites in the Ca<sub>v</sub>3.3 FLIPR Assay**

| Parameter                         | Analyte |      |      |      |      |
|-----------------------------------|---------|------|------|------|------|
|                                   | CX-8998 | M01  | M02  | M03  | M04  |
| Depolarized FLIPR potency (nM)    | 3.6     | 2.3  | 17   | 948  | 19   |
| Hyperpolarized FLIPR potency (nM) | 161     | 86   | 2839 | 3319 | 1809 |
| State dependence (fold)           | 45      | 37   | 166  | 3.5  | 95   |
| Human-free fraction (%)           | 0.4     | <0.1 | 14   | 21   | 13   |
| Brain-to-plasma ratio             | 0.51    | 0.27 | 0.32 | 0.01 | ND   |

FLIPR = Fluorometric Imaging Plate Reader; ND = not done.

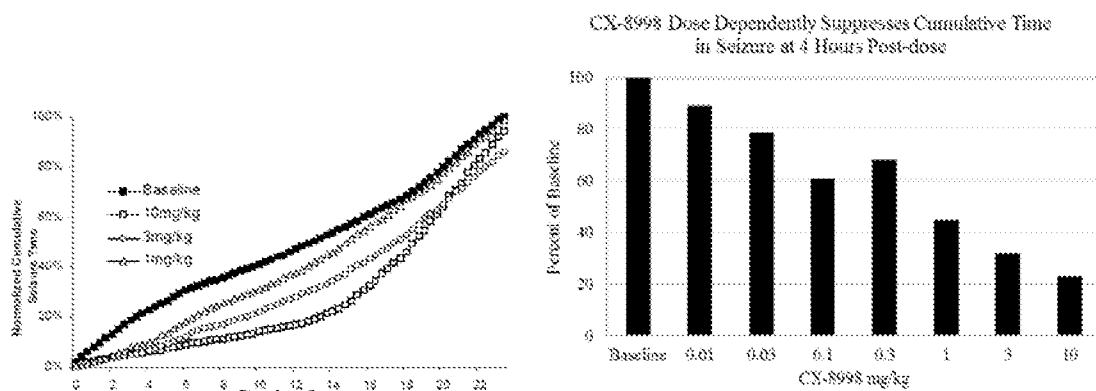
Sources: Merck Nonclinical Reports PD001, PK001 Addendum, and PK003; Cavyon Nonclinical Report 427-PDSFEB-2018-Perkin-III-R009.

#### 4.2.1.2 In Vivo Studies

CX-8998 has shown activity in multiple in vivo rodent models that are predictive of therapeutic effects in tremor, epilepsy, pain, and psychomotor activity. CX-8998 has also shown effects in rodent and nonhuman primate in vivo models of sleep architecture.

##### 4.2.1.2.1 Wistar Albino Glaxo/Rijswijk Rat Model of Absence Epilepsy

CX-8998 was evaluated in the Wistar Albino Glaxo/Rijswijk (WAG/Rij) rat model of absence epilepsy in which rats display spontaneous seizures characterized by high-amplitude, low-frequency spike-and-wave discharges in electrocorticogram recordings. CX-8998 dose-dependently suppressed accumulated time in seizure, whereas vehicle treatment had no effect (Figure 2). At a dose of 1 mg/kg, CX-8998 treatment resulted in a 55% reduction in the cumulative time spent in seizure at 4 hours after dosing. At a dose of 10 mg/kg, CX-8998 suppressed accumulated time in seizure by 77% and 54% at 4 and 15 hours after dosing, respectively. Seizure frequency was also dose dependently suppressed by up to 50% at the 10 mg/kg dose. Other T-type antagonists from structurally diverse series have shown similar efficacy in this model (Broicher, 2007; Blumenfeld, 2008; Broicher, 2008; Shipe, 2008; Yang, 2008; Uebele, 2009; Russo, 2010; Russo, 2011).

**Figure 2: Effect of CX-8998 on Seizure Time in Male WAG/Rij Rats**

Male Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats implanted with telemetric monitors to simultaneously record electrocorticograms received oral vehicle or CX-8998 (0.1-10 mg/kg); 24-hour postdose recordings were collected and compared to 24-hour predose baseline recordings. Data were scored with automated seizure analysis software, averaged, and normalized to enable treatment comparisons.

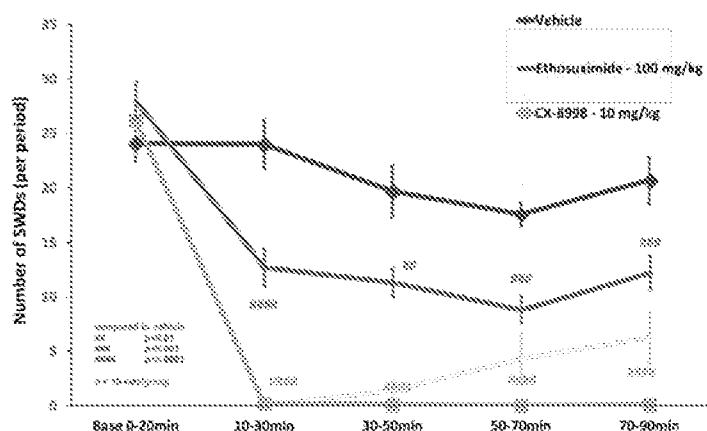
Source: Merck Nonclinical Report PD002.

The metabolites of CX-8998 (M01, M02, M03, and M04) were administered orally at doses of up to 10 mg/kg to investigate the efficacy of the metabolites in the WAG/Rij model of absence epilepsy (Merck Nonclinical Report PD002). Percent of inhibition at a dose of 10 mg/kg was 77% for CX-8998 and 71%, 67%, 71%, and 60% for M01, M02, M03, and M04, respectively. M02, like CX-8998, demonstrated dose-dependent suppression of accumulated time in seizure. Metabolites M01, M03, and M04 suppressed seizure frequency and duration at 4 hours after dosing at a dose of 10 mg/kg.

#### 4.2.1.2.2 Genetic Absence Epilepsy Rat from Strasbourg Model

CX-8998 was evaluated in the Genetic Absence Epilepsy Rat from Strasbourg (GAERS) rat model of absence epilepsy in which rats display spontaneous recurrent generalized nonconvulsive seizures characterized by bilateral, synchronous spike-and-wave discharges in electrocorticogram recordings. CX-8998 at a dose of 10 mg/kg completely suppressed the number and frequency of seizures relative to vehicle treatment in the same animals (Figure 3). Ethosuximide, at a clinically relevant dose of 100 mg/kg, only partially suppressed the number and frequency of seizures in this cohort. The GAERS model is considered a gold standard model of clinically relevant, nonconvulsive seizures and is considered predictive of effects in humans and harbors a mutation in  $\text{Ca}_v3.2$  that results in elevated channel function (Proft, 2017). Other T-type antagonists from a structurally diverse series have shown efficacy in this model (Tringham, 2012).

**Figure 3: Effect of CX-8998 on Seizures in Male GAERS Rats**



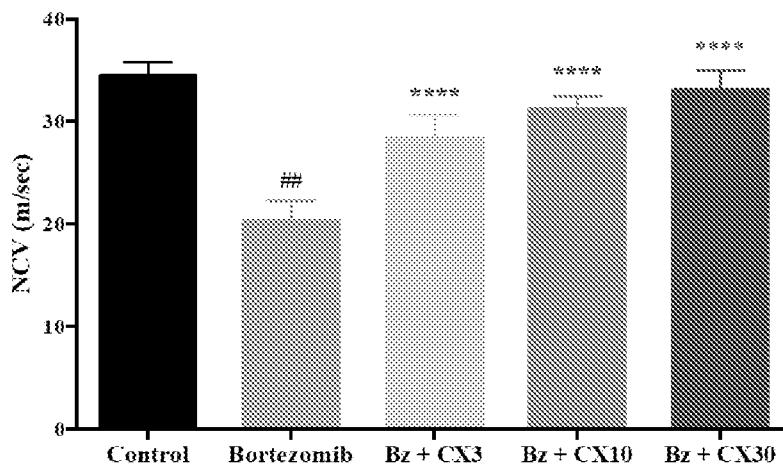
Male Genetic Absence Epilepsy Rats from Strasbourg (GAERS) rats implanted with telemetric monitors to simultaneously record electrocorticograms received oral vehicle, ethosuximide (100 mg/kg), or CX-8998 (10 mg/kg); 90 minutes of postdose recordings were collected and compared to 20 minutes of predose baseline recordings.

Source: Cavion Nonclinical Report USCAV18-1G.

#### 4.2.1.2.3 Rat Model of Bortezomib-Induced Peripheral Neuropathy

CX-8998 was evaluated in a model of bortezomib-induced peripheral neuropathy, including impacts on nerve conduction velocity (NCV), tactile sensitivity, and proteasome inhibition. Treatment with CX-8998 resulted in a statistically significant dose-dependent reduction in tactile sensitivity and improvement in caudal NCV without impairing bortezomib-induced proteasome inhibition (Figure 4).

**Figure 4: Effects of CX-8998 on Nerve Conduction Velocity in Rat Model of Bortezomib-Induced Chemotherapeutic Neuropathy**

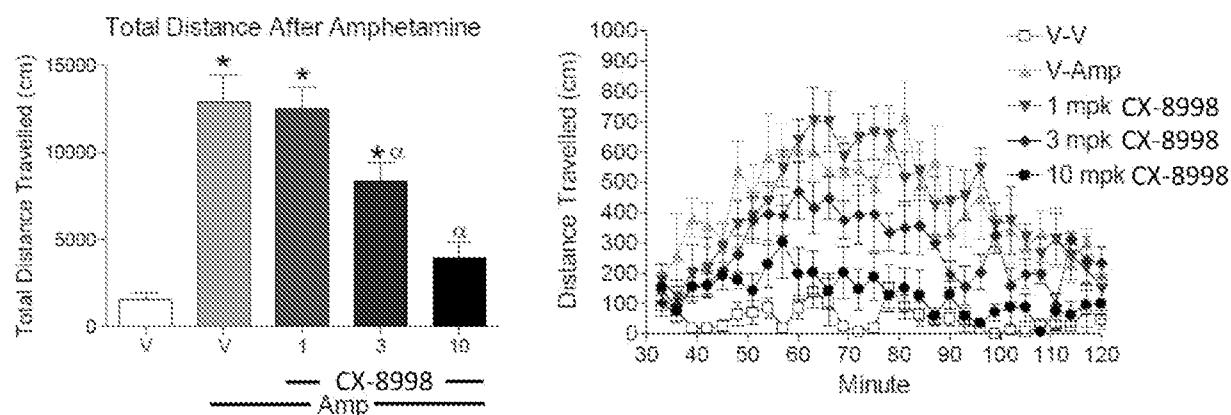


Bortezomib (Bz, 0.2 mg/kg) was administered intravenously via the tail vein 3 times/week for 8 weeks. CX-8998 was administered by oral gavage daily starting from Day 29 through Week 8 at doses of 3 (CX3), 10 (CX10), or 30 (CX30) mg/kg. Control animals received vehicle administrations. Nerve conduction velocity (NCV) along the caudal nerve was determined with an electromyography apparatus (Myto2 ABN Neuro, Firenze, Italy) on Day 58. ## p<0.0001 vs Control; \*\*\* p<0.0001 vs Bz. Source: Cavion Nonclinical Report 15.14.

#### 4.2.1.2.4 Attenuation of Psychomotor Effects of Amphetamine

CX-8998 was evaluated for its ability to attenuate the psychomotor activating effects of amphetamine. The assay is sensitive to compounds with antipsychotic potential, as classic and atypical antipsychotics, but not sedatives, suppress the response to amphetamine. CX-8998 significantly suppressed the hyperactivity induced by amphetamine in a dose-dependent manner in this model (Figure 5).

**Figure 5: Effects of CX-8998 on Amphetamine-Induced Psychomotor Activity in a Rat Predictive Model of Antipsychotic Efficacy**



Amp = amphetamine; mpk = mg/kg; V = vehicle.

Amphetamine (Amp, 1.5 mg/kg) was administered subcutaneously 60 minutes after CX-8998 administration by oral gavage at doses of 1, 3, or 10 mg/kg. Locomotor activity was monitored from 30 minutes after CX-8998 administration to 90 minutes after amphetamine administration in a 43.2- x 43.2-cm Med-Associates apparatus. Distance traveled was monitored over time (right panel) and total distance traveled over the 90- minute post-amphetamine period was summed (left panel). \* indicates significantly different from vehicle-vehicle treatment, whereas α indicates significantly different from vehicle-amphetamine treatment.

Source: Merck TTA Package Description.

#### 4.2.1.2.5 Effects on Sleep Architecture

The in vivo activity of CX-8998 was investigated in studies of rodent and nonhuman primate sleep architecture (Merck Nonclinical Report PD002).  $\text{Ca}_v3$  channels are abundantly expressed in corticothalamic loop neurons that underlie the well-characterized oscillatory activity leading to changes in the electroencephalogram (EEG) that define vigilance states. The resting membrane potential and the state of the  $\text{Cav}3$  channel determine 1 of 2 distinct network activities: tonic activity, which is associated with depolarization and the wake state, or bursting activity, which is associated with hyperpolarization and slow wave sleep.

In rat sleep studies, CX-8998 showed dose-dependent increases in slow wave sleep and decreases in rapid eye movement (REM) sleep early in the sleep period and increases in REM sleep late in the sleep period. In Rhesus monkey sleep studies, CX-8998 showed a significant decrease in active wake, with an increase in slow wave sleep (delta sleep) early in the sleep period and a sustained increase in REM sleep late in the sleep period. Thus, both studies showed CX-8998 impacted wake, slow wave sleep, and REM sleep.

#### 4.2.1.2.6 Comparison of $\text{Ca}_v3$ Antagonist Pharmacologic Properties of CX-8998 With Other $\text{Ca}_v3$ Antagonists

Several other  $\text{Ca}_v3$  antagonists have been reported to have activity in nonclinical models of tremor, epilepsy, pain, weight gain, and sleep architecture. A comparison of the pharmacologic properties of CX-8998 in rats with those of other  $\text{Ca}_v3$  antagonists is presented in Table 2.

**Table 2: Summary of Ca<sub>v</sub>3 Antagonist Pharmacological Properties in Rodents**

| Parameter                      | Compound      |                     |                     |                     |
|--------------------------------|---------------|---------------------|---------------------|---------------------|
|                                | CX-8998       | TTA-A2 <sup>a</sup> | TTA-P2 <sup>b</sup> | TTA-Q6 <sup>c</sup> |
| TTA class                      | Pyridyl amide | Pyridyl amide       | Piperidine          | Quinazolinone       |
| Ca <sub>v</sub> 3 potency (nM) | 70-100        | 89-98               | 84-196              | 221                 |
| State dependency (fold)        | 45            | ≥40                 | 1                   | 4.5                 |
| T <sub>max</sub> (hr)          | 0.5           | 0.3                 | 0.7                 | NR                  |
| C <sub>max</sub> (nM)          | 3500          | 7500                | 480                 | 3000                |
| AUC <sub>last</sub> (nM•hr)    | 6300          | 30000               | 1940                | NR                  |
| t <sub>1/2</sub> (hr)          | 0.8           | 1.5                 | 1.8                 | 5.9                 |
| Plasma-free fraction (%)       | 0.4           | 0.6                 | 5.7                 | 1.3                 |
| Brain/plasma ratio             | 0.5           | 0.27                | 6.0                 | 1.1                 |

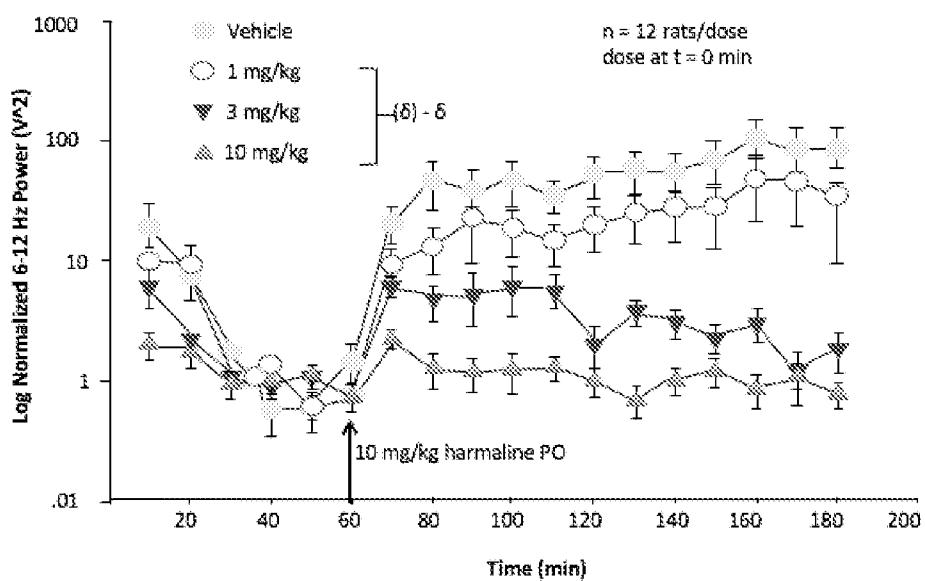
AUC<sub>last</sub> = area under the plasma concentration-time curve from time zero to the last measurable concentration; C<sub>max</sub> = maximum plasma drug concentration; NR = not reported; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time of maximum plasma drug concentration; TTA = T-type calcium channel antagonist.

<sup>a</sup> From Uebel, 2009; Kraus, 2010; Reger, 2011; Francois, 2013.

<sup>b</sup> From Shipe, 2008.

<sup>c</sup> From Barrow, 2010.

The Ca<sub>v</sub>3 antagonists, TTA-P2 and TTA-Q6, were evaluated in the harmaline-induced tremor model in rats at dose levels up to 10 mg/kg. TTA-P2, normalized both physiologic tremor prior to harmaline administration and harmaline-induced tremor in a dose-dependent fashion (Figure 6).

**Figure 6: TTA-P2 Normalization of Harmaline Tremor in Rats**

Rats that were assigned to vehicle or 1 of 3 ascending doses of TTA-P2 demonstrated a dose-dependent response to harmaline-induced tremor following per os administration. Rats also demonstrated dose-dependent response to a reduction in physiologic tremor before administration of harmaline (Shipe, 2008).

---

TTA-Q6 also demonstrated efficacy in controlling harmaline-induced tremor (Shipe, 2008).

#### 4.2.2 Secondary Pharmacodynamics

The in vitro receptor activity profile of CX-8998 was determined in a panel of over 170 enzyme and receptor binding sites, ion channels, and transporters (Merck Nonclinical Report PD001 Addendum). No off-target effects of CX-8998 were observed at a concentration of 10  $\mu$ M except for the cannabinoid 2 receptor (CB2), which showed 53% inhibition of binding at 10  $\mu$ M and a calculated IC<sub>50</sub> of 5.34  $\mu$ M.

Two metabolites of CX-8998 were evaluated in a similar screen consisting of 87 enzyme and receptor binding sites. The potential for human peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) binding (54% inhibition) and 79% inhibition of guinea pig adenosine transporter were identified at a concentration of 10  $\mu$ M of M01. The IC<sub>50</sub> value for functional inhibition of the adenosine transporter by M01 was determined to be 2.92  $\mu$ M (AB75238-1207060). No significant results (ie,  $\geq$ 50% inhibition or stimulation) were observed at a concentration of 10  $\mu$ M of M02 in the 87 targets tested (AB75238-1207061).

#### 4.2.3 Safety Pharmacology

##### 4.2.3.1 Effects on Cardiovascular System

###### 4.2.3.1.1 In Vitro hERG Channel Assay in Human Embryonic Kidney Cells

CX-8998 was tested for its effects on hERG (human ether-à-go-go-related gene) channels heterologously expressed in Chinese hamster ovary (CHO)-K1 cells using standard whole-cell voltage-clamp techniques (Study 06-4794). Treatment with CX-8998 resulted in relatively weak inhibition of hERG current (IC<sub>50</sub> = 21  $\mu$ M and IC<sub>20</sub> = 4  $\mu$ M) that was largely reversible after a brief washout. Assessment of the effects of CX-8998 on hERG at doses up to 30  $\mu$ M using the same cells in a PatchXpress higher-throughput assay provided similar results (IC<sub>50</sub> = 28  $\mu$ M and IC<sub>20</sub> = 8.7  $\mu$ M) (Study 06-4720).

###### 4.2.3.1.2 In Vitro Na<sub>v</sub>1.5 Assay in Human Embryonic Kidney Cells

In an assay using human cardiac voltage-dependent calcium channel (Na<sub>v</sub>1.5)-stably expressed in HEK cells, CX-8998 at concentrations up to 30  $\mu$ M showed only a slight inhibitory effect on Na<sub>v</sub>1.5 current (22%-26%) (Study 06-4736).

###### 4.2.3.1.3 In Vivo Studies in Dogs

The effects of CX-8998 on cardiovascular function, including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, electrocardiographic parameters (PR, QRS, and QT intervals), and core body temperature, were evaluated with telemetry measurements in conscious dogs after administration of single, oral doses of 2, 20, and 300 mg/kg of CX-8998 in a Latin Square design study, with a 7-day washout period between doses (Study 06-5634). The effects of CX-8998 on cardiovascular function (blood pressure, heart rate, blood flow, and electrocardiogram [ECG] intervals) were also evaluated in anesthetized vagotomized dogs after cumulative intravenous (IV) doses of 1, 3, and 10 mg/kg of CX-8998 (Study 06-5065).

No treatment-related effects were observed on any parameter after oral administration of 2 mg/kg of CX-8998 (plasma concentration at 2 hours after dosing:  $\sim$ 3.4  $\mu$ M). Dose-dependent increases in heart rate and corresponding decreases in QT interval were observed at the 20 and

---

300 mg/kg dose levels (maximum plasma drug concentration [ $C_{max}$ ]: ~30  $\mu$ M and 60  $\mu$ M, respectively). Peak increases in heart rate (+47 beats/min, 48%) and decreases in QT interval (-14 msec, 7%) were observed at the 300 mg/kg dose level at approximately 2 hours after dosing, coincident with the anticipated time of maximum plasma drug concentration ( $T_{max}$ ), and gradually returned to baseline over 24 to 36 hours. Peak changes in heart rate (+28 beats/min, 30%) and QT interval (-27 msec, 12%) were transiently observed up to 2 hours after administration of the 20 mg/kg dose level. No treatment-related effects were observed on blood pressure; PR, QRS, or QTc interval; or core body temperature at any dose of CX-8998. Based on the transient nature of the cardiovascular changes at the 20 mg/kg dose level and the treatment-related changes at the 300 mg/kg dose level, 20 mg/kg was considered the no-observed-adverse-effect level (NOAEL). The no-observed-effect level (NOEL) was determined to be 2 mg/kg.

No treatment-related effects of CX-8998 were noted on cardiovascular parameters after IV administration of 1 or 3 mg/kg of CX-8998 ( $C_{max}$ : 9.0  $\mu$ M and 22  $\mu$ M, respectively). A 15% decrease was observed in mean arterial pressure and a 7% increase was observed in PR interval after IV administration of 10 mg/kg of CX-8998 ( $C_{max}$ : 60  $\mu$ M); no changes in heart rate, blood flow, or QRS or QTc interval were observed.

#### 4.2.3.2 Effects on Central and Peripheral Nervous System Effects

The acute neurobehavioral effects of CX-8998 were evaluated in conscious female rats after administration of single oral doses of 5, 15, and 30 mg/kg of CX-8998 using a functional observational battery (FOB) of tests (Study 06-5644). CX-8998 had no effect on neurobehavioral function at a dose of 5 mg/kg. Abnormal posture and gait, increased foot splay width, decreased body temperature, and prolongation of the hot plate latency time were observed at the 30 mg/kg dose level at 2 hours after dosing but were not evident at 24 hours after dosing. Only increased foot splay width was observed at the 15-mg/kg dose level. The NOEL was determined to be 5 mg/kg, which demonstrated a plasma concentration of 1.1  $\mu$ M at 2 hours after dosing.

Neurobehavioral function was also evaluated in female rats after administration of single, oral doses of 30, 300, and 2000 mg/kg of CX-8998 on Day 1 of a 4-week GLP (Good Laboratory Practice) toxicology study (Study 06-1088; see also Section 4.4.3.1.2). Treatment-related findings were observed at all doses and included increased number of urine pools and foot splay, decreased body temperature and number of rears, and abnormal gait at doses  $\geq$ 30 mg/kg/day and increased hot plate latency, hypotonia, abnormal approach response and posture, abnormal breath sounds, and lack of pinna response at the 300 and 2000 mg/kg/day dose levels. The low-observed-effect level (LOEL) for the FOB (including increases in the number of urine pools and foot splay, decreases in body temperature and the number of rears, and abnormal gait) was 30 mg/kg/day based on the low incidence, minimal severity, and type of responses at this dose (plasma area under the plasma concentration-time curve from the time of dosing to 24 hours after dosing [ $AUC_{24}$ ]/ $C_{max}$  for female rats, 43  $\mu$ M•hr/21  $\mu$ M).

Overall, treatment-related findings in these FOB studies at doses relevant to human exposures were small in magnitude, reversible, and consistent with sedation.

#### 4.2.3.3 Effects on the Respiratory System

The effects of CX-8998 on respiratory function were evaluated in conscious female rats after administration of single oral doses of 30, 300, and 2000 mg/kg of CX-8998 using whole body plethysmography (Study 06-5634). CX-8998 produced small decreases in tidal volume and minute ventilation after administration of doses  $\geq$ 30 mg/kg. Increases (144%-212%) in PenH (an index of airway resistance), which are indicative of potential increases in airway resistance in either the upper or lower respiratory tract, were observed at doses of 300 and 2000 mg/kg (estimated  $C_{max}$ , approximately 28 and 34  $\mu$ M, respectively). The NOEL for CX-8998 for respiratory function was <30 mg/kg in conscious female rats; however, given the minimal magnitude of the observed changes and that no treatment-related effect was observed on PenH at the 30 mg/kg dose level, the 30 mg/kg dose was considered the NOAEL for this study.

The effect of CX-8998 on airway resistance was also evaluated in isoflurane-anesthetized male rats after IV administration of 6 mg/kg over 30 minutes (Study 06-5001). No change in airway resistance was observed during the 30-minute IV infusion or during the entire 125-minute observation period. The  $C_{max}$  of CX-8998 was 24  $\mu$ M after administration of a 6-mg/kg IV dose of CX-8998.

### 4.3 Pharmacokinetics and Product Metabolism in Animals

#### 4.3.1 Analytical Methods and Validation

Plasma concentrations of CX-8998, M01, and M02 were quantitated using validated bioanalytical methods that were developed by Merck, as described in the relevant US Food and Drug Administration (FDA) guidance document (FDA Guidance for Industry, 2001). The validity and reproducibility of the assays were determined, and the precision and accuracy for calibration standards and quality control samples were examined.

Recovery was shown to be adequate and consistent across the quantitation range. No interferences were observed in the different lots of blank plasma that were tested. The analytes were stable in plasma under the storage and assay conditions. The 2 alcohol metabolites (M02 and M04) coeluted under these conditions, but a normal phase method revealed that M02 was present in large excess over M04 in all species. These methods were used in the nonclinical and clinical studies that were conducted by Merck.

Cavion has developed and validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) bioanalytical methods for the simultaneous quantitation of CX-8998 and metabolites (M01, M02, M03, and M04) in rat, dog, and human plasma as per recent FDA guidance (FDA Guidance for Industry, 2018). Assay performances were satisfactory and met acceptance criteria for system performance suitability, quantitation range, calibration linearity, assay accuracy and precision, and assay recovery. These “5-in-1” bioanalytical methods were used to quantitate CX-8998 and its 4 metabolites in samples that were collected in the GLP 90-day toxicology studies in rats and dogs and in ongoing Cavion-sponsored Phase 2 clinical studies.

#### 4.3.2 Absorption and Pharmacokinetics

The pharmacokinetic profile and absorption, distribution, metabolism, and excretion (ADME) of CX-8998 and its metabolites were investigated in studies in rats, dogs, and rhesus monkeys as part of exploratory and pivotal toxicology studies (see Section 4.4).

CX-8998 showed acceptable oral bioavailability after single-dose administration in rats and dogs (42% and 76%, respectively) but low (<3%) oral bioavailability in rhesus monkey due to significant hepatic first-pass metabolism (hepatic extraction of ~95%) (Table 3). This was reflected by higher exposure after oral administration in rats and dogs than in monkeys as measured by  $C_{max}$  and the area under the plasma concentration-time curve (AUC) in the 3 species. CX-8998 was rapidly absorbed in rats and dogs, with mean  $T_{max}$  values of 0.5 hours and 1.4 hours, respectively. Absorption was slower in monkeys, with  $C_{max}$  reached in a mean of 8.3 hours.

**Table 3: Summary of Pharmacokinetic Parameters of CX-8998 in Rats, Dogs, and Rhesus Monkeys After Intravenous and Oral Doses of CX-8998**

| Species | CX-8998 Dose (mg/kg) |      | IV Administration <sup>a,b</sup> |                       | Oral Administration <sup>c,d</sup> |                       |             |           |
|---------|----------------------|------|----------------------------------|-----------------------|------------------------------------|-----------------------|-------------|-----------|
|         | IV                   | Oral | CL (mL/min/kg)                   | t <sub>1/2</sub> (hr) | C <sub>max</sub> (μM)              | T <sub>max</sub> (hr) | AUC (μM·hr) | F (%)     |
| Rat     | 2                    | 10   | 29                               | 0.8                   | 3.5 (1.6)                          | 0.5 (0.0)             | 6.3 (1.9)   | 42 (13)   |
| Dog     | 0.25                 | 0.5  | 1.5 (0.4)                        | 7.3 (3.1)             | 0.75 (0.20)                        | 1.4 (1.0)             | 11.3 (7.0)  | 76 (47)   |
| Monkey  | 2                    | 20   | 15.9 (2.5)                       | 1.3 (0.3)             | 0.13 (0.03)                        | 8.3 (14)              | 1.5 (0.5)   | 2.8 (10.) |

AUC = area under the plasma concentration-time curve;  $C_{max}$  = maximum plasma drug concentration; CL = clearance; F = bioavailability; IV = intravenous; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> CX-8998 was administered in dimethylsulfoxide over 30 minutes.

<sup>b</sup> Results are expressed as mean values from 2 animals (rats) or as mean (SD) from 3 animals (dog and monkey).

<sup>c</sup> CX-8998 was administered via oral gavage in 0.5% or 1% methylcellulose.

<sup>d</sup> Results are expressed as mean (SD).

Source: Study PK001.

Exposure of metabolites M01 and M02 was significant in all species after oral administration of CX-8998 (Table 4). The mean AUC<sub>24</sub> value for M01 was approximately 20% to 70% of the mean AUC<sub>24</sub> value for CX-8998, with the greatest exposure observed in rats. The greatest exposure of M02 relative to CX-8998 was observed in monkeys, with a metabolite-to-parent ratio for AUC<sub>24</sub> of 17 for the 25-mg/kg oral dose of CX-8998 and 44 for the 75-mg/kg oral dose of CX-8998. Mean AUC<sub>24</sub> values of M02 in rats and dogs were approximately 1- to 2-fold greater than the mean AUC<sub>24</sub> value of CX-8998.

**Table 4: Summary of Exposure to CX-8998 and Metabolites (M01 and M02) in Rats, Dogs, and Rhesus Monkeys After Single Oral Doses of CX-8998**

| Species | Sex    | Dose <sup>a</sup><br>(mg/kg) | AUC <sub>24</sub> (μM·hr) <sup>b</sup> |     |      | Ratio of AUC <sub>24</sub> |             |
|---------|--------|------------------------------|--|-----|------|----------------------------|-------------|
|         |        |                              | CX-8998                                | M01 | M02  | M01/CX-8998                | M02/CX-8998 |
| Rat     | Male   | 10                           | 5.9                                    | 3.7 | 10   | 0.63                       | 1.7         |
|         | Female | 10                           | 13                                     | 8.7 | 31   | 0.52                       | 2.4         |
| Dog     | Male   | 0.5                          | 6.7                                    | 1.4 | 7.8  | 0.21                       | 1.2         |
| Monkey  | Male   | 2                            | 2.1                                    | 0.5 | 36.6 | 0.24                       | 2.7         |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing.

<sup>a</sup> CX-8998 was administered via oral gavage in 0.5% or 1% methylcellulose.

<sup>b</sup> Results are expressed as mean values from 2 animals.

Source: Study PK001.

### 4.3.3 Toxicokinetics

#### 4.3.3.1 Rat

##### 4.3.3.1.1 Dose-Range-Finding Study in Female Rats

Female rats were administered 10, 100, or 500 mg/kg/day via oral gavage in an exploratory, 7-day, dose-range-finding toxicology study (Study 06-2515; Section 4.4.3.1.1). Exposure to CX-8998 was not dose proportional over the range of 10 to 500 mg/kg/day in female rats (Table 5).

**Table 5: Key Toxicokinetic Parameters of CX-8998 in Female Rats in a 7-Day, Oral, Dose Range-Finding Toxicology Study**

| Parameter <sup>a</sup>    | CX-8998 Dose <sup>b</sup> |               |               |
|---------------------------|---------------------------|---------------|---------------|
|                           | 10 mg/kg/day              | 100 mg/kg/day | 500 mg/kg/day |
| AUC <sub>24</sub> (μM·hr) | 20.7 (7.2)                | 94.6 (27.3)   | 219 (98)      |
| C <sub>max</sub> (μM)     | 5.20 (1.95)               | 14.7 (8.0)    | 24.0 (9.7)    |
| T <sub>max</sub> (hr)     | 3.4 (1.3)                 | 3.6 (0.9)     | 4.8 (1.8)     |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> Values are expressed as mean (SD).

<sup>b</sup> CX-8998 was administered via oral gavage for 7 days

Source: Study 06-2515.

##### 4.3.3.1.2 4-Week Oral Toxicity Study in Male and Female Rats

Male and female rats were administered 30, 300, or 2000 mg/kg/day of CX-8998 via oral gavage in a 4-week toxicology study (Study 06-1088; Section 4.4.3.1.2). Exposure was greater in female rats than in male rats (Table 6). Dose proportionality was not observed over the dose range of 30 to 2000 mg/kg/day of CX-8998 in either male or female rats.

**Table 6: Key Toxicokinetic Parameters of CX-8998 in Male and Female Rats in a 4-Week Oral Toxicology Study**

| Parameter <sup>a</sup>    | Sex    | CX-8998 Dose <sup>b</sup> |               |                |
|---------------------------|--------|---------------------------|---------------|----------------|
|                           |        | 30 mg/kg/day              | 300 mg/kg/day | 2000 mg/kg/day |
| AUC <sub>24</sub> (μM·hr) | Male   | 35.1 (1.69)               | 333 (39.1)    | 467 (65.1)     |
|                           | Female | 43.6 (2.82)               | 438 (5.83)    | 610 (70.9)     |
| C <sub>max</sub> (μM)     | Male   | 13.2 (1.55)               | 26.1 (2.50)   | 28.9 (2.21)    |
|                           | Female | 21.6 (3.71)               | 28.3 (5.16)   | 33.5 (1.79)    |
| T <sub>max</sub> (hr)     | Male   | 0.5                       | 2.0           | 2.0            |
|                           | Female | 0.5                       | 8.0           | 8.0            |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> Values are expressed as mean (SD) or as the median (T<sub>max</sub>); values represent Day 28 data.

<sup>b</sup> CX-8998 was administered via oral gavage for 28 days.

Source: Study 06-1088.

#### 4.3.3.1.3 90-Day Oral Toxicity Study in Male and Female Rats

Male and female rats were administered 5, 15, 100, or 300 mg/kg/day of CX-8998 via oral gavage in a 90-day toxicology study (Study 20131957; Section 4.4.3.1.4). Exposure was greater in female rats than in male rats (Table 7).

**Table 7: Key Toxicokinetic Parameters of CX-8998 in Male and Female Rats in a 90-Day Oral Toxicology Study**

| Parameter <sup>a</sup>    | Sex    | CX-8998 Dose <sup>b</sup> |              |               |               |
|---------------------------|--------|---------------------------|--------------|---------------|---------------|
|                           |        | 5 mg/kg/day               | 15 mg/kg/day | 100 mg/kg/day | 300 mg/kg/day |
| AUC <sub>24</sub> (μM·hr) | Male   | 3.85                      | 12.1         | 170           | 261           |
|                           | Female | 5.41                      | 26.6         | 554           | 566           |
| C <sub>max</sub> (μM)     | Male   | 1.41                      | 5.41         | 29.1          | 22.5          |
|                           | Female | 2.90                      | 6.40         | 41.0          | 52.9          |
| T <sub>max</sub> (hr)     | Male   | 1                         | 1            | 2             | 1             |
|                           | Female | 1                         | 1            | 2             | 1             |
| t <sub>1/2</sub> (hr)     | Male   | NC                        | 2.87         | 3.72          | 5.68          |
|                           | Female | 1.60                      | NC           | 9.25          | 5.28          |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; NC = not calculated; T<sub>max</sub> = time of maximum plasma drug concentration; t<sub>1/2</sub> = terminal half-life.

<sup>a</sup> Values are expressed as the mean or as the median (T<sub>max</sub>); values represent Day 90 data.

<sup>b</sup> CX-8998 was administered via oral gavage for 90 days.

Source: Study 20131957.

Mean AUC values for CX-8998 and its metabolites were consistently higher in male rats on Day 1 than the respective values on Day 45 or 90 across all dose levels. Conversely, levels of CX-8998 and metabolites were highest in female rats on Day 90 at all dose levels except the highest dose of 300 mg/kg/day.

M01, M02, M03 and M04 are all significant CX-8998 metabolites in rats, with plasma exposure observed at or greater than 10% relative to that of CX-8898 (Table 8). Plasma AUC values on

Day 90 for both sexes are, from highest to lowest, CX-8998, followed by M02, followed by M01, followed by M03, followed by M04.

**Table 8: Summary of Exposure to CX-8998 Metabolites M01, M02, M03, and M04 in Male and Female Rats in a 90-Day Oral Toxicology Study**

| Dose (mg/kg) | Sex    | AUC <sub>24</sub> (μM·hr) <sup>a</sup> |      |      |      | Ratio <sup>b</sup> of AUC <sub>24</sub> |             |             |             |
|--------------|--------|--|------|------|------|---|-------------|-------------|-------------|
|              |        | M01                                    | M02  | M03  | M04  | M01/CX-8998                             | M02/CX-8998 | M03/CX-8998 | M04/CX-8998 |
| 5            | Male   | 4.33                                   | 12.0 | 23.9 | 1.32 | 1.1                                     | 3.1         | 6.2         | 0.34        |
|              | Female | 5.02                                   | 16.7 | 9.85 | 3.19 | 0.93                                    | 3.1         | 1.8         | 0.59        |
| 15           | Male   | 11.3                                   | 26.1 | 34.9 | 2.47 | 0.93                                    | 2.3         | 2.9         | 0.20        |
|              | Female | 20.3                                   | 54.8 | 19.7 | 8.04 | 0.76                                    | 2.1         | 0.74        | 0.30        |
| 100          | Male   | 85.9                                   | 186  | 181  | 15.5 | 0.51                                    | 1.1         | 1.1         | 0.09        |
|              | Female | 231                                    | 567  | 159  | 61.9 | 0.42                                    | 1.0         | 0.29        | 0.11        |
| 300          | Male   | 125                                    | 258  | 213  | 19.4 | 0.48                                    | 0.99        | 0.82        | 0.07        |
|              | Female | 234                                    | 511  | 169  | 55.3 | 0.41                                    | 0.90        | 0.30        | 0.10        |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing.

<sup>a</sup> Values are expressed as the mean and represent Day 90 data.

<sup>b</sup> Ratio calculated from CX-8998 AUC<sub>24</sub> values for each sex in Table 7.

Source: Study 20131957.

#### 4.3.3.2 Dogs

##### 4.3.3.2.1 Dose-Range-Finding Study in Beagle Dogs

One male and 1 female Beagle dog were administered escalating oral doses of 3, 30, and 300 mg/kg of CX-8998 in a 10-day, exploratory, dose-range-finding toxicology study (Study 06-1055; Section 4.4.3.2.1). Each dose was administered for 3 days, with no washout period between doses. Exposure was generally greater in the female dog than in the male dog (Table 9). Exposure was not dose proportional over the range of 3 to 300 mg/kg/day in either the male or female dog.

**Table 9: Key Toxicokinetic Parameters of CX-8998 in Male and Female Dogs in 10-Day Oral Toxicology Study**

| Parameter                 | Sex <sup>a</sup> | CX-8998 Dose <sup>b</sup> |                         |                          |
|---------------------------|------------------|---------------------------|-------------------------|--------------------------|
|                           |                  | 3 mg/kg/day<br>(Day 3)    | 30 mg/kg/day<br>(Day 6) | 300 mg/kg/day<br>(Day 9) |
| AUC <sub>24</sub> (μM·hr) | Male             | 62.5                      | 707.7                   | 1808                     |
|                           | Female           | 52.3                      | 932.7                   | 2078                     |
| C <sub>max</sub> (μM)     | Male             | 8.4                       | 73.5                    | 253                      |
|                           | Female           | 5.9                       | 58.5                    | 158                      |
| T <sub>max</sub> (hr)     | Male             | 1.0                       | 2.0                     | 4.0                      |
|                           | Female           | 1.0                       | 4.0                     | 4.0                      |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> N = 1 for each sex.

<sup>b</sup> Escalating oral doses of 3, 30, and 300 mg/kg of CX-8998 were each administered via oral gavage for 3 days. The reported values are those on the last day of administration of each dose level (ie, Days 3, 6, and 9 for the 3, 30, and 300 mg/kg doses, respectively).

Source: Study 06-1055.

#### 4.3.3.2.2 4-Week Oral Toxicology Study in Beagle Dogs

Male and female Beagle dogs were administered 2, 20, or 800 mg/kg/day of CX-8998 via oral gavage in a 4-week toxicology study (Study 06-1087; Section 4.4.3.2.2). Dose proportionality was not observed over the dose range of 2 to 800 mg/kg/day of CX-8998 on Day 1 or Day 28 in either the male or female dogs.

**Table 10: Key Toxicokinetic Parameters of CX-8998 in Male and Female Dogs in 4-Week Oral Toxicology Study**

| Parameter <sup>a</sup>    | Sex    | CX-8998 Dose <sup>b</sup> |              |              |             |               |             |
|---------------------------|--------|---------------------------|--------------|--------------|-------------|---------------|-------------|
|                           |        | 2 mg/kg/day               |              | 20 mg/kg/day |             | 800 mg/kg/day |             |
|                           |        | Day 1                     | Day 28       | Day 1        | Day 28      | Day 1         | Day 28      |
| AUC <sub>24</sub> (μM·hr) | Male   | 48.2 (16.7)               | 50.4 (4.22)  | 425 (41.8)   | 350 (31.7)  | 1910 (208)    | 747 (236)   |
|                           | Female | 40.8 (8.81)               | 42.7 (7.06)  | 510 (62.5)   | 372 (66.5)  | 1650 (373)    | 890 (ID)    |
| C <sub>max</sub> (μM)     | Male   | 13.4 (8.09)               | 7.12 (0.94)  | 49.4 (11.0)  | 38.0 (3.99) | 91.6 (10.1)   | 43.6 (8.52) |
|                           | Female | 5.98 (0.429)              | 6.42 (0.913) | 49.7 (1.00)  | 39.8 (2.25) | 105 (19.3)    | 59.1 (ID)   |
| T <sub>max</sub> (hr)     | Male   | 1.0 (0.5)                 | 0.67 (0.17)  | 1.0 (0.0)    | 1.2 (0.44)  | 6.7 (1.3)     | 2.8 (1.2)   |
|                           | Female | 0.5 (0.0)                 | 0.83 (0.17)  | 1.3 (0.33)   | 1.3 (0.33)  | 12 (6.1)      | 2.6 (ID)    |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; ID = insufficient data; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> Values are expressed as mean (SEM).

<sup>b</sup> CX-8998 was administered via oral gavage for 28 days.

Source: Study 06-1087.

#### 4.3.3.2.3 90-Day Oral Toxicology Study in Beagle Dogs

Male and female dogs were administered 10, 30, or 300/100 mg/kg/day of CX-8998 via oral gavage in a 90-day toxicology study (Study 20131958; Section 4.4.3.2.3). Mean values for C<sub>max</sub> and AUC on Day 90 generally increased with increasing dose, with greater exposures observed in male dogs than in female dogs at the highest dose level (Table 11).

**Table 11: Key Toxicokinetic Parameters of CX-8998 in Male and Female Dogs in a 90-Day Oral Toxicology Study**

| Parameter <sup>a</sup>    | Sex    | CX-8998 Dose <sup>b</sup> |              |                   |
|---------------------------|--------|---------------------------|--------------|-------------------|
|                           |        | 10 mg/kg/day              | 30 mg/kg/day | 100/300 mg/kg/day |
| AUC <sub>24</sub> (μM·hr) | Male   | 191                       | 335          | 1570              |
|                           | Female | 163                       | 363          | 520               |
| C <sub>max</sub> (μM)     | Male   | 24.8                      | 39.4         | 206               |
|                           | Female | 23.6                      | 43.4         | 59.5              |
| T <sub>max</sub> (hr)     | Male   | 1.50                      | 1.17         | 5.33              |
|                           | Female | 1.50                      | 1.67         | 1.33              |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> Values are expressed as the mean or as the median (T<sub>max</sub>); values represent Day 90 data.

<sup>b</sup> CX-8998 was administered via oral gavage for 90 days.

Source: Study 20131958.

AUC<sub>24</sub> values of CX-8998 and metabolites (M01, M02, M03, and M04) were consistently comparable between male and female Beagle dogs across study days at 10 and 30 mg/kg/day (Table 12). However, the AUC<sub>24</sub> values of CX-8998 and metabolites (M01, M02, M03, and M04) on Day 90 were 3- to 5-fold higher in male than in female Beagle dogs at 100 mg/kg/day dose level.

**Table 12: Key Toxicokinetic Parameters of CX-8998 Metabolites M01, M02, M03 and M04 in Male and Female Dogs in a 90-Day Oral Toxicology Study**

| Dose (mg/kg) | Sex    | AUC <sub>24</sub> (μM·hr) <sup>a</sup> |      |      |      | Ratio <sup>b</sup> of AUC <sub>24</sub> |             |             |             |
|--------------|--------|--|------|------|------|---|-------------|-------------|-------------|
|              |        | M01                                    | M02  | M03  | M04  | M01/CX-8998                             | M02/CX-8998 | M03/CX-8998 | M04/CX-8998 |
| 10           | Male   | 54.9                                   | 149  | 10.5 | 3.37 | 0.29                                    | 0.78        | 0.055       | 0.018       |
|              | Female | 38.6                                   | 103  | 8.4  | 2.19 | 0.24                                    | 0.63        | 0.051       | 0.013       |
| 30           | Male   | 121                                    | 213  | 12.3 | 2.25 | 0.36                                    | 0.64        | 0.037       | 0.007       |
|              | Female | 103                                    | 209  | 15.4 | 3.75 | 0.28                                    | 0.58        | 0.042       | 0.010       |
| 300/100      | Male   | 1770                                   | 1800 | 79.6 | 33.9 | 1.13                                    | 1.15        | 0.051       | 0.022       |
|              | Female | 431                                    | 339  | 17.2 | 8.10 | 0.83                                    | 0.65        | 0.033       | 0.016       |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing.

<sup>a</sup> Values are expressed as the mean and represent Day 90 data.

<sup>b</sup> Ratio calculated from CX-8998 AUC<sub>24</sub> values for each sex in Table 11.

Source: Study 20131958.

#### 4.3.4 Distribution

The mean volume of distribution at steady state (V<sub>dss</sub>) was similar in rats (1.3 L/kg), dogs (0.8 L/kg), and monkeys (0.9 L/kg) (Study PK001).

CX-8998 showed in vitro plasma protein binding of approximately 99.2%, 99.7%, 98.8%, and 99.6% in rat, dog, monkey, and human plasma, respectively, and blood-to-plasma partition ratio of 0.6 to 0.7 respectively (Study PK003). The M01 metabolite showed in vitro plasma protein binding of 99.6%, 99.7%, 99.6%, and >99.9% in rat, dog, monkey and human plasma, respectively. The M02 metabolite was much less protein bound, showing values of 71%, 82%, 83%, and 86% in rat, dog, monkey and human plasma, respectively. The higher plasma protein

binding of CX-8998 (including both metabolites M01 and M02) in human plasma than in rat plasma is notable. CX-8998 showed little to no irreversible protein binding in vitro (rat and human) and in vivo (rat).

CX-8998 distributes readily to the brain in rats and to brain and cerebral spinal fluid (CSF) in dogs. An exploratory study was conducted in male rats to determine the brain penetration of CX-8998 and its metabolites at 2 hours after oral administration of a 25 mg/kg of CX-8998 in 1% methylcellulose and in 90% PEG 400 (Study PK001). Exposure of CX-8998 in brain was approximately 50% of that in plasma (Table 13). Peak plasma concentrations of the M01 metabolite were comparable to those of the parent, whereas peak plasma concentrations of the M02/M04 metabolite were lower and peak plasma concentrations of the M03 metabolite were higher than those of the parent. Brain-to-plasma ratios of the M01 and M02/04 metabolites were slightly less than for CX-8998, whereas the brain-to-plasma ratios of the M03 metabolite were approximately 50-fold lower than for CX-8998.

**Table 13: Plasma and Brain Concentrations of CX-8998 and Metabolites in Male Rats at Two Hours After Oral Administration of 25 mg/kg of CX-8998**

| Compound             | Vehicle            | Concentration ( $\mu\text{M}$ ) <sup>a</sup> |       | Brain:Plasma Ratio |
|----------------------|--------------------|--|-------|--------------------|
|                      |                    | Plasma                                       | Brain |                    |
| CX-8998              | 1% Methylcellulose | 6.3  | 3.1   | 0.49               |
|                      | 90% PEG 400        | 3.3  | 1.8   | 0.54               |
| M01                  | 1% Methylcellulose | 6.9  | 1.9   | 0.27               |
|                      | 90% PEG 400        | 5.5  | 1.5   | 0.27               |
| M02/M04 <sup>b</sup> | 1% Methylcellulose | 2.1  | 0.6   | 0.29               |
|                      | 90% PEG 400        | 1.1  | 0.4   | 0.36               |
| M03                  | 1% Methylcellulose | 10.1   | 0.1   | 0.01               |
|                      | 90% PEG 400        | 12.2   | 0.1   | 0.01               |

PEG = polyethylene glycol.

<sup>a</sup> N = 2 rats per group; values represent the mean of measurements.

<sup>b</sup> M02 and M04 were chromatographically quantified together.

Source: Study PK001 Addendum.

One male and 1 female Beagle dog were administered escalating oral doses of 3, 30, and 300 mg/kg of CX-8998 in an exploratory dose-range-finding toxicity study (Study 06-1055). Each dose was administered for 3 days, with no washout period between doses. The animals were terminated on Day 10, approximately 24 hours after administration of the last 300 mg/kg dose, samples of brain and CSF were collected, and concentrations of CX-8998, M01, and M02/M04 were determined. Central nervous system (CNS) exposure to CX-8998, M01, and M02/M04 was generally greater in the female dog than in the male dog (Table 14). The brain-to-plasma ratios for CX-8998 were comparable between the male and female dogs; however, differences in the ratios were observed for the metabolites, with higher ratios observed in the female dog than in the male dog. The CSF-to-plasma ratios for CX-8998 and M01 were generally consistent with their low free fraction (0.3%) in dog plasma. The CSF-to-plasma ratios for M02 were more variable between the 2 dogs but, overall, were greater than for CX-8998 or M01 and in line with the greater free fraction of this metabolite in dog plasma (18%).

**Table 14: Brain and Cerebrospinal Fluid Concentrations (Plasma Ratios) of CX-8998 and Its Metabolites in Male and Female Beagle Dogs at 24 Hours After Oral Administration of 300 mg/kg of CX-8998**

| Tissue Concentration ( $\mu\text{M}$ ) | CX-8998 <sup>a</sup> |               | M01 <sup>a</sup> |               | M02/M04 <sup>a,b</sup> |              |
|--|----------------------|---------------|------------------|---------------|------------------------|--------------|
|  | Male (N=1)           | Female (N=1)  | Male (N=1)       | Female (N=1)  | Male (N=1)             | Female (N=1) |
| Brain-frontal cortex                   | 0.337 (0.039)        | 3.20 (0.056)  | 0.190 (0.012)    | 0.696 (0.059) | 0.36 (0.015)           | 2.26 (0.086) |
| Brain - thalamus                       | 0.29 (0.034)         | 3.37 (0.059)  | 0.208 (0.013)    | 0.772 (0.066) | 0.402 (0.016)          | 2.52 (0.096) |
| CSF                                    | 0.144 (0.017)        | 0.602 (0.011) | 0.149 (0.009)    | 0.112 (0.010) | 1.055 (0.043)          | 5.47 (0.208) |

CSF = cerebrospinal fluid.

<sup>a</sup> The values in parenthesis are the concentration ratios of brain or CSF to plasma.

<sup>b</sup> M02 and M04 were chromatographically quantified together.

Source: Study PK001 Addendum.

#### 4.3.5 Metabolism

The metabolism of CX-8998 has been evaluated in vitro in pooled liver microsome preparations and in freshly isolated or cryopreserved hepatocytes from rat, dog, monkey, and human tissues and with recombinant CYP enzymes, including CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 (Study PK003). Metabolism of CX-8998 is mediated largely by the CYP3A and CYP2C enzyme families to form 4 main products (M01, M02, M03, and M04). Metabolism is primarily via hydroxylation on the isopropyl moiety, resulting in a tertiary alcohol (M02), a primary alcohol (M04), and an aliphatic dehydrogenation of the isopropyl moiety (M01). Further oxidation of the 2 alcohols (M02 and M04) leads to the formation of their respective dioxygenated metabolites and to a carboxylic acid derivative of M04 (designated as M03). Formation of M02 and M04 is extensive in rat liver microsomes (M02 > M04); however, formation of M04 (and subsequently M03) is not significant in preparations from dog, monkey, or human tissue. Glucuronide conjugates of the oxygenated metabolites are detected in human, monkey, and dog hepatocyte preparations.

CX-8998 is extensively metabolized in vivo in rat and dog, and all 4 metabolites are measurable at significant levels using a validated 5-in-1 bioanalytical assay. Both M01 and M02 have been measured at significant levels in humans in Phase 1 clinical studies. Preliminary unaudited data from pharmacokinetic samples that were collected from patients with essential tremor in study CX-8998-CLN2-001 (T-CALM; Section 5.4.2.1) confirm these findings and demonstrate that levels of M03 and M04 are not significant in humans. All 4 metabolites of CX-8998 are covered by wide exposure margins in nonclinical toxicology species as compared with their respective intended human clinical free exposure.

Of the recombinant CYPs tested, CYP3A4, CYP3A5, CYP2C9, CYP2C19, and CYP2D6 efficiently catalyze the formation of both M01 and M02. However, the abundance of CYP3A5, CYP2C19, and CYP2D6 in human liver microsomes is low (2%-5%) relative to the primary contributors, CYP3A4 (~30%) and CYP2C9 (~20%). Both M01 and M02 show lower  $K_M^*$  values for CYP2C9 reactions (~3  $\mu\text{M}$ ), suggesting that the contribution of CYP2C9 is more significant than CYP3A4 at low substrate concentrations; this observation is more pronounced for M01 than for M02 (Study PK003). The contribution of the CYP3A family was further

\*  $K_M$  (Michaelis constant) is the substrate concentration at which the reaction rate is half of the maximum.

---

confirmed by the significant inhibition (>80% at 1  $\mu$ M CX-8998) of both M01 and M02 reactions by antihuman CYP3A antibody. Combination of antihuman CYP3A and CYP2C antibodies inhibited metabolism almost completely (>90% at 10  $\mu$ M CX-8998). Thus, CYP3A4 and CYP2C9 are the primary enzymes that are responsible for the oxidative metabolism of CX-8998 in humans.

CX-8998 and M01 did not demonstrate any activity as a substrate or inhibitor in bidirectional transport assays with human, monkey, and rat P-glycoprotein, whereas M02 showed increased efflux in the rat and monkey assays (Study PK003). CX-8998 was not a substrate in breast cancer resistance protein (BCRP) assays, but both CX-8998 and M01 inhibited transport by 57% at high concentrations (30  $\mu$ M). M02 did not inhibit BCRP-mediated transport up to a concentration of 30  $\mu$ M. Although this study did not exclude M01 and M02 as substrates of BCRP, transport of these metabolites in this system is most likely limited (Study 2266N-1703).

#### 4.3.6 Excretion

Plasma clearance of CX-8998 was relatively high in the rat and rhesus monkey (29 mL/min/kg and 16 mL/min/kg, respectively; Table 3) but lower in the dog (1.5 mL/min/kg), with a correspondingly short half-life in the rat and monkey (0.8 hours and 1.3 hours respectively) relative to the dog (7.3 hours).

After oral administration of  $^{14}\text{C}$ -labeled CX-8998 (20 mg/kg) to rats, most of the radioactivity was recovered in rat urine and bile samples (43% and 46%, respectively), with approximately 5% of the radioactivity remaining in the feces (Study PK003). Less than 1% of the total dose was excreted in feces as unchanged drug, suggesting extensive metabolism. Recovery of label was nearly complete after 72 hours (~96%), suggesting good oral absorption. The decline of radioactivity in all excreta was rapid, with the majority (>85% of total recovered radioactivity) of the dose excreted in the first day. Major circulating components of rat plasma after oral administration included M01, M02, M03, and M04, with further metabolic products of these metabolites representing minor components. The dioxygenated metabolites of M02 were primarily cleared through urinary excretion, whereas M03 and its corresponding glucuronide were excreted as major components in both bile and urine.

#### 4.3.7 Pharmacokinetic Drug Interactions

CX-8998 is metabolized primarily by CYP enzymes CYP3A4 and CYP2C in human liver microsomes to form 4 main products M01, M02, M03, and M04. CX-8998, M01, and M02 were not potent inhibitors of CYP1A2, CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 in human liver microsomes ( $\text{IC}_{50} > 20 \mu\text{M}$ ) (Merck Nonclinical Reports PK003 and 2266N-1702). Time-dependent inhibition of CYP3A4 or CYP2B6 by CX-8998, M01, and M02 was insignificant. CX-8998 and metabolites M01 and M02 showed low potential to induce CYP3A4 mRNA or activity, with  $\leq 10\%$  of control effect at 10  $\mu\text{M}$  in primary human hepatocytes. Consistently, activation of human pregnane X receptor (PXR) by CX-8998, M01, and M02 was modest, with  $\leq 34\%$  of control effect at 10  $\mu\text{M}$ , respectively. Furthermore, CX-8998, M01, and M02 did not significantly activate rat and monkey PXR (~4%-6% and 6%-22% of control at 10  $\mu\text{M}$ , respectively). Thus, CX-8998 showed a low potential to induce human CYP3A4. Production of CYP2B6 mRNA was induced by CX-8998 in human hepatocytes at 30  $\mu\text{M}$  (3.8- to 8.6-fold in 3 donors); M01 and M02 were also mild to moderate inducers (Study 2266N-1701).

---

## 4.4 Toxicology

### 4.4.1 Toxicology Studies Conducted With CX-8998

The toxicology of CX-8998 has been characterized in a series of nonclinical studies, including pivotal repeat-dose toxicology studies of up to 90 days in duration in rats and dogs and in vitro and in vivo genetic toxicology studies. Information on reproductive and developmental toxicology was obtained in a 28-day pivotal female fertility study in rats and in preliminary embryo-fetal development studies in rats and rabbits. The repeat-dose toxicology studies of CX-8998 are summarized in Table 15.

**Table 15: Nonclinical Repeat-Dose Studies of CX-8998**

| Species             | Study Type  | Compliance | Design   | Findings  | Source                           |
|---------------------|---|------------|--|---|----------------------------------|
| Sprague-Dawley Rat  | 7-Day exploratory toxicity                        | Non-GLP    | 0, 10, 100, or 500 mg/kg/day by oral gavage for 7 days                                   | NOEL, 500 mg/kg/day. No findings indicative of dose-limiting toxicity were observed.  | 06-2515                          |
|                     | 4-Week toxicity with FOB                          | GLP        | 0, 30, 300, or 2000 mg/kg/day by oral gavage for 4 weeks                                 | NOAEL, 30 mg/kg. Reversible changes, indicating extended diestrus, were observed in female reproductive organs; non-adverse FOB changes were also observed.                                 | 06-1088                          |
|                     | 4-Week investigative female histology             | GLP        | 0, 10, or 1000 mg/kg/day QD for 4 weeks by oral gavage with 8-week recovery              | NOEL, 10 mg/kg/day for female reproductive organ changes. Changes were reversible at 1000 mg/kg/day,  | 07-0034                          |
|                     | 90-Day toxicity with 4-week recovery              | GLP        | 0, 5, 15, 100, or 300 mg/kg/day by oral gavage   | NOAEL, 300 mg/kg/day in both sexes.   | 20131957 (audited draft results) |
|                     | Female fertility study                            | GLP        | 0, 10, 30, 100, or 1000 mg/kg/day by oral gavage   | NOEL, $\geq$ 1000 mg/kg/day for female rat fertility parameters.<br>NOEL, 100 mg/kg/day for general toxicity parameters.  | 08-7370                          |
|                     | Exploratory oral developmental toxicology         | Non-GLP    | 0, 10, 30, 100, 300, or 1000 mg/kg/day by oral gavage on GD 6 through GD 20              | Maternal toxicity was observed at $\geq$ 30 mg/kg/day and was excessive at 1000 mg/kg/day. Developmental toxicity was observed at $\geq$ 100 mg/kg/day.                                     | 07-7175                          |
|                     | Micronuclei induction in bone marrow              | GLP        | 0, 30, 300, or 2000 mg/kg/day by oral gavage for 4 weeks                                 | Negative at up to 2000 mg/kg/day in bone marrow collected in Study 06-1088.   | 06-8923                          |
| Beagle Dog          | 10-Day, exploratory dose-range-finding toxicology | Non-GLP    | 0, 3, 30, and 300 mg/kg/day by oral gavage; escalating doses for 3 days, with no washout | No treatment-related findings were observed at any dose.  | 06-1055                          |
|                     | 4-Week toxicity                                   | GLP        | 0, 20, or 800 mg/kg/day by oral gavage for 4 weeks                                       | NOEL. 20 mg/kg/day. Dose-limiting toxicity (mortality, physical signs) was observed at 800 mg/kg/day  | 06-1087                          |
|                     | 90-Day toxicity with 4-week recovery              | GLP        | 0, 10, 30, or 300/100 mg/kg/day by oral gavage for 90 days                               | NOAEL, 30 mg/kg/day in both sexes. Excessive weight loss and poor condition was observed at 300 mg/kg/day; the dose was reduced to 100 mg/kg/day on Day 43 and was followed by improvement. | 20131958 (audited draft results) |
| Dutch Belted Rabbit | Exploratory maternal and developmental toxicity   | Non-GLP    | 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage on GD 7 through GD 20.                 | Maternal toxicity was observed at doses $\geq$ 30 mg/kg/day and was excessive at 1000 mg/kg/day. No evidence of developmental toxicity was observed at 30, 100, or 300 mg/kg/day.           | 07-7185                          |

FOB = functional observational battery; GD = gestation day; GLP = Good Laboratory Practices; NOAEL = no-observed-adverse-effect level; NOEL = no-observed-effect level; QD = once daily.

---

#### 4.4.2 Single-Dose Studies

##### 4.4.2.1 Dog

A single-dose (800 mg/kg by oral gavage) exploratory toxicokinetic study (Study 06-1092) in 1 male and 1 female dog showed no mortality or treatment-related signs; however, the male dog experienced emesis within 1 hour after dosing. Exposure (AUC<sub>24</sub>) to CX-8998 was higher in the female dog than in the male dog (3341  $\mu\text{M}\cdot\text{hr}$  vs 1325  $\mu\text{M}\cdot\text{hr}$ ). T<sub>max</sub> of CX-8998 occurred later in the male dog than in female dog (24 hours vs 8 hours), but this was perhaps influenced by the episode of emesis shortly after dosing. T<sub>max</sub> was 8 hours for M01 and M02 for both dogs; T<sub>max</sub> for M03 was 8 hours in the female dog and 24 hours in the male dog.

##### 4.4.2.2 Rabbit

An exploratory single-dose toxicokinetic study was performed in nonpregnant Dutch Belted rabbits (Study 08-7027). Ten female rabbits were assigned to 3 groups of 3 animals each and were administered a single dose of 3, 30, 100, 300, or 1000 mg/kg of CX-8998 in a dose-escalating regimen. All rabbits survived until study termination without clinical signs. Mean CX-8998 exposure (AUC<sub>24</sub>) was 0.75, 6.65, 13.4, 74.0, and 119  $\mu\text{M}\cdot\text{h}$  for the 3, 30, 100, 300, and 1000 mg/kg doses, respectively. Mean C<sub>max</sub> values were 0.18, 1.0, 1.45, 3.87, and 6.47  $\mu\text{M}$ , respectively.

#### 4.4.3 Repeat-Dose Studies

##### 4.4.3.1 Rat

###### 4.4.3.1.1 Dose-Range-Finding Study in Female Rats

Female rats were administered 10, 100, or 500 mg/kg/day via oral gavage in an exploratory, 7-day, dose-range-finding study (Study 06-2515). No treatment-related findings were observed on mortality, physical signs, food consumption, body weight, serum biochemistry (on Day 8), organ weights, or gross or histomorphologic examination. No treatment-related findings indicative of dose-limiting toxicity were observed at doses up to 500 mg/kg/day.

###### 4.4.3.1.2 4-Week Oral Toxicology Study in Male and Female Rats

Male and female rats were administered 0 (vehicle), 30, 300, or 2000 mg/kg/day of CX-8998 via oral gavage in a 4-week toxicology study (Study 06-1088). Neurobehavioral function was also evaluated in the female rats, using an FOB of tests, on Day 1.

Treatment-related findings were observed at all doses and included increased number of urine pools and foot splay, decreased body temperature and number of rears, and abnormal gait at doses  $\geq 30$  mg/kg/day and increased hot plate latency, hypotonia, abnormal approach response and posture, abnormal breath sounds, and lack of pinna response at the 300 and 2000 mg/kg/day dose levels. The LOEL for the FOB (including increases in the number of urine pools and foot splay, decreases in body temperature and the number of rears, and abnormal gait) was 30 mg/kg/day based on the low incidence, minimal severity, and type of responses at this dose (plasma AUC<sub>24</sub>/C<sub>max</sub> values for female rats, 43  $\mu\text{M}\cdot\text{hr}/21 \mu\text{M}$ ).

All other ante-mortem findings during the study were seen only at the high dose (2000 mg/kg/day) and included mortality, physical signs (primarily audible respiratory sounds

but also labored breathing, distended abdomen, decreased activity, and cool to touch), body weight loss (intermittent)/decreased mean body weight gain (males), decreased food consumption, and abnormal hematological, serum biochemical, and urinalysis findings. Gross postmortem findings (increased liver size and decreased prostate and seminal vesicle sizes) were only observed at the high dose. Changes in organ weight were seen at all doses in females and at the middle and high doses in males and constituted decreased ovary (all doses), prostate (300 and 2000 mg/kg/day), and pituitary (both sexes, 300 and 2000 mg/kg/day) weights and increased liver (both sexes at 2000 mg/kg/day) and thyroid (males at 2000 mg/kg/day) weights.

Histological findings were observed at all doses in females and at the middle and high doses in males; these included renal tubular epithelial degeneration (both sexes at 2000 mg/kg/day), liver and thyroid hypertrophy (males at 300 mg/kg/day and both sexes at 2000 mg/kg/day), nose and nasopharyngeal inflammation (both sexes at 2000 mg/kg/day), stomach cellular infiltration and ulcer (male or female at 2000 mg/kg/day), prostate lower secretion (300 and 2000 mg/kg/day), seminal vesicle lower secretion (2000 mg/kg/day), and uterus smaller size, vagina epithelial thinning, and ovary fewer corpora lutea (all doses in females). Pituitary glands from female rats in the control and 2000 mg/kg/day dose groups were stained (immunohistochemistry) for prolactin hormone, with decreased staining seen in females in the 2000 mg/kg/day group.

The cause of death of animals in the high-dose group was due to nasopharyngeal inflammation (due to the pH of the dosing formulation and to reflux during dosing). There was clear evidence of dose-limiting toxicity at the 2000 mg/kg/day dose level (plasma AUC<sub>24</sub>/C<sub>max</sub> values for female rats for sexes combined, 546  $\mu\text{M}\cdot\text{hr}/30.2 \mu\text{M}$ ), as evidenced by the mortality, marked physical signs, and histological changes of pronounced inflammation in the nasopharynx, as well as epithelial tubular degeneration in the kidney.

Findings in male rats at plasma exposures at the lowest dose tested (30 mg/kg/day; plasma AUC<sub>24</sub>/C<sub>max</sub> values for males, 35  $\mu\text{M}\cdot\text{hr}/13 \mu\text{M}$ ) were limited to FOB effects that are reversible and could be monitored in the clinic; no gross pathology, organ weight, or histological findings were observed in males at this exposure. The NOAEL was 30 mg/kg/day in males and <30 mg/kg/day in females (based on decreased ovarian weight and corpora lutea, shown to be reversible in a subsequent study). The NOEL was <30 mg/kg/day in both sexes.

#### **4.4.3.1.3 4-Week Oral Toxicology Study in Female Rats With an 8-Week Recovery Period**

A 4-week oral toxicology study, with an 8-week recovery period, was performed in female rats to determine if there was a NOEL for female reproductive organ toxicities at 10 mg/kg/day; the potential reversibility of the female reproductive organ toxicity at 1000 mg/kg/day; and the toxicokinetic profile of CX-8998 and 2 of its metabolites (M01 and M02) (Study 07-0034). Rats were administered 0 (vehicle), 10, or 1000 mg/kg/day of CX-8998 via oral gavage for 4 weeks.

All rats survived to scheduled termination. Treatment-related ante-mortem findings were only seen at the 1000 mg/kg/day dose and included physical signs (primarily audible respiratory sounds and salivation but also labored breathing, gasping, urine staining, decreased activity, decreased skin turgor, coolness to the touch, and unkempt appearance), decreases in body weight gain (approximately 10% decrease relative to the concurrent control), and food consumption. All treatment-related ante-mortem findings resolved during the recovery phase, indicating reversibility.

Postmortem findings were limited to the 1000 mg/kg/day dose group. At interim necropsy, there were gross findings of lower ovarian and uterine size in 6 and 9 rats, respectively; lower organ weights (ovarian weight relative to brain weight decreased 38% versus concurrent control; pituitary weight relative to brain weight decreased 40% versus concurrent control); and histomorphological findings (both fewer, and sometimes smaller, corpora lutea in the ovary and smaller uterine size in 8 rats; and decreased mucosal thickness of the vagina characterized by thinning of the mucosal epithelial thickness, sometimes with mucinification, in 7 rats) at the 100 mg/kg/day dose level. At final (recovery) necropsy, there were no gross or histomorphological findings in the reproductive organs at this dose level, demonstrating recovery in these tissues, and there was a trend toward recovery in the pituitary weight (pituitary weight only decreased 14% relative to brain weight versus concurrent control at final necropsy).

The NOEL for postmortem changes attributable to CX-8998 and for female reproductive tissue changes (ovary, uterus, and vagina) was 10 mg/kg/day. Reversibility of the female reproductive tissue changes at the 1000 mg/kg/day dose level was demonstrated during an 8-week recovery period. Mean AUC<sub>24</sub> values at the NOEL (10 mg/kg/day) were 13.1, 8.11, and 31.7  $\mu\text{M}\cdot\text{h}$  for CX-8998, M01, and M02, respectively, and mean C<sub>max</sub> values at the NOEL were 5.91, 2.66, and 5.40  $\mu\text{M}$  for CX-8998, M01, and M02, respectively. At the NOEL for reproductive effects in the rat, there is a 2-fold or greater safety margin for CX-8998, M01, and M02 as compared with the estimated human steady-state exposures at a dose of 8 mg twice daily (BID) under fasted conditions. Under simulated “fed” dosing conditions (in which there is a 45% reduction in C<sub>max</sub>), there is still a 2-fold or greater safety margin for CX-8998 (parent drug) at a dose of 10 mg BID.

#### **4.4.3.1.4 90-Day Oral Toxicology Study in Male and Female Rats With a 30-Day Recovery Period**

A 90-day oral toxicology study, with a 30-day recovery period, was performed in male and female rats (n=10 each sex for main study; n=5 each sex for recovery period) to determine the toxicity and toxicokinetics (see Section 4.3.3.1.3) of CX-8998 and 4 metabolites (M01, M02, M03 and M04) (Study 20131957). Rats were administered 0 (vehicle), 5, 15, 100, or 300 mg/kg/day of CX-8998 via oral gavage for at least 90 days. The following were evaluated: clinical signs, body weight, body weight gain, food consumption, ophthalmology, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathologic examinations.

No test article-related mortality was observed in the study. Transient CX-8998-related decreased activity was noted from Days 1 to 9 in males and female animals at  $\geq 100$  mg/kg/day. CX-8998-related decreases in body weight gain were noted in males at 300 mg/kg/day and resulted in an absolute mean body weight that was 4% lower than controls on Day 90. Correlating decreases in food consumption of up to 19% were also noted. A CX-8998-related 46% decrease in serum triglyceride levels was noted in males in the 300 mg/kg/day dose group relative to controls at the end of the dosing period (Day 90); the lower serum triglyceride levels correlated with the observed decreases in food consumption. Recovery was noted in body weight gain, food consumption, and serum triglyceride levels by the end of the 30-day dose-free period. These changes were not considered adverse. There were no CX-8998-related changes in ophthalmic examinations, hematology parameters, coagulation parameters, or urinalysis data during this study. There were no CX-8998-related gross observations, changes in absolute or relative organ weights, or microscopic findings observed at main or recovery termination.

In summary, administration of CX-8998 by once-daily oral gavage for a minimum of 90 days was well tolerated by male and female rats at doses up to 300 mg/kg/day. No CX-8998-related mortality or evidence of any systemic toxicity was observed, and no target organs were identified. Transiently decreased activity was evident in animals at 100 and 300 mg/kg/day during study Days 1 to 9 but not after Day 9. Non-adverse decreases in body weight gain (4%) and food consumption (19%), which were accompanied by decreases in serum triglyceride levels (46%), were observed in males in the 300 mg/kg/day dose group at the end of the dosing phase, but reversal of these effects was noted after the 30-day recovery period. These effects were not accompanied by gross pathology or histological changes and were not considered adverse. Based on these results, NOAEL was determined to be 300 mg/kg/day in male and female rats. At 300 mg/kg/day, mean CX-8998  $C_{max}$  was 22500 nM and 52900 nM in male and female rats, respectively, on Day 90, and mean CX-8998  $AUC_{24}$  was 261000 nM•hr and 566000 nM•hr in male and female rats, respectively, on Day 90.

#### 4.4.3.2 Dog

##### 4.4.3.2.1 Dose-Range-Finding Study in Beagle Dogs

One male and 1 female Beagle dog were administered escalating oral doses of 3, 30, and 300 mg/kg of CX-8998 in a 10-day, exploratory dose-range-finding toxicology study (Study 06-1055). Each dose was administered for 3 days, with no washout period between doses. The animals were terminated on Day 10, approximately 24 hours after administration of the last 300 mg/kg dose, and concentrations of CX-8998, M01, and M02/M04 in plasma, brain (frontal cortex and thalamus) and CSF were determined. No treatment-related findings were observed at any dose. Concentrations of CX-8998 and M02/M04 (which coeluted in the bioanalytical assay) were greater in plasma than in the frontal cortex, thalamus, or CSF (shown in Table 14).

##### 4.4.3.2.2 4-Week Oral Toxicology Study in Beagle Dogs

Male and female Beagle dogs were administered 0 (vehicle), 2, 20, or 800 mg/kg/day of CX-8998 via oral gavage in a 4-week toxicology study (Study 06-1087).

Treatment-related findings were observed only at the 800 mg/kg/day dose level and included mortality of 1 female (sacrificed early due to body weight loss/physical signs) and physical signs (eg, emesis, unsteady gait, trembling, decreased activity, salivation, ears cool to the touch). Mean body weight loss was observed, as were minor changes in serum biochemical and hematological parameters that were considered secondary to physical signs, stress, and/or the body weight loss. Organ weight differences (higher liver weight and lower testes and prostate weight) and histological findings (eosinophilic cytoplasmic bodies in hepatocytes in the liver, seminiferous tubular epithelial degeneration and less spermatogenesis in the testes, and prostate immaturity) were also observed. Transmission electron microscopy revealed that the eosinophilic bodies in the hepatocytes were consistent with smooth endoplasmic reticulum (suggesting enzyme induction). The testicular/prostatic findings were consistent with delayed development caused by body weight loss in the males in the 800 mg/kg/day dose group.

Based on the mortality, physical signs consistent with neurologic effects, and emesis followed by body weight loss, there was clear dose-limiting toxicity at 800 mg/kg/day (mean  $AUC_{24}/C_{max}$  values for combined sexes, 804  $\mu\text{M}\cdot\text{hr}/49.8 \mu\text{M}$ ). The NOEL for the study was 20 mg/kg/day (mean  $AUC_{24}/C_{max}$  values for combined sexes, 361  $\mu\text{M}\cdot\text{hr}/38.9 \mu\text{M}$ ). Plasma exposures ( $AUC_{24}$ ) in the dog at the NOEL represented wider safety margins for CX-8998, M01, and M02

---

(approximately 30-, 6-, and 23-fold, respectively) over those expected clinically as compared with plasma exposures at the NOEL in the rat (ie, the rat was the more sensitive species). Toxicokinetic evaluation revealed an inductive effect on metabolism at the 800 mg/kg/day dose over the course of the study (decreased concentrations of CX-8998 and increased concentrations of M01), consistent with the hepatic microscopic findings.

#### **4.4.3.2.3 90-Day Oral Toxicology Study in Beagle Dogs With a 30-Day Recovery Period**

A 90-day oral toxicology study, with a 30-day recovery period, was performed in male and female Beagle dogs (n=4 each sex for main study; n=2 each sex for recovery period) to determine the toxicity and toxicokinetics (see Section 4.3.3.2.3) of CX-8998 and 4 metabolites (M01, M02, M03, and M04) (Study 20131958). Dogs were administered 0 (vehicle), 10, 30, or 300/100 mg/kg/day of CX-8998 via oral gavage for at least 90 days. The following parameters were evaluated: clinical signs, body weights, body weight gain, food consumption, ophthalmology, electrocardiography, clinical pathology parameters (hematology, coagulation, clinical chemistry, and urinalysis), toxicokinetic parameters, gross necropsy findings, organ weights, and histopathologic examinations.

No test article-related mortality was observed in the study; all animals survived until scheduled euthanasia. Test article-related clinical signs consisted of the following: tremors (i.e., shivering) in males at  $\geq 10$  mg/kg/day on Day 1, in females at  $\geq 30$  mg/kg/day on Day 1, and in females in at 300 mg/kg/day on Day 2; decreased activity in males and females at 30 mg/kg/day on Day 1 and in males and females at 300 mg/kg/day from Days 1 to 40; panting on Day 1 in males and females at 30 and 300 mg/kg/day; salivation in males at 10 mg/kg/day from Days 8 to 64, in females at 10 mg/kg/day from Days 8 to 15, and in both sexes at 30 and 300/100 mg/kg/day from Days 1 to 91; and thin appearance in males and females at 300 mg/kg/day beginning approximately Day 21.

Test article-related body weight loss and/or decreases in body weight gain occurred in males and females at 300 mg/kg/day from Days 1 to 29, resulting in absolute body weights that were up to 13% and 7% lower than in controls, respectively. The body weight changes correlated with significant decreases in mean food consumption (up to 23% lower than control) during the first week of the study and reduced appetite in individual animals and, subsequently, with thin appearance and loss in body condition, which necessitated feed supplementation in many animals in the 300 mg/kg/day dose group. The dose of CX-8998 was reduced from 300 mg/kg/day to 100 mg/kg/day beginning on Day 43 for the entire group. Recovery in body weight was noted after dose reduction during the remainder of the dosing phase and/or recovery phase in both males and females in the 300/100 mg/kg/day dose group.

Test article-related changes in hematology parameters on Day 91 consisted of red cell mass (erythrocytes, hemoglobin, and hematocrit) and red cell distribution width values that were 28% and 11% lower, respectively, in males in the 300/100 mg/kg/day dose group than in controls. In general, the values were outside normalized and actual historical control ranges and persisted after the 30-day recovery period. Test article-related changes in clinical chemistry parameters were considered non-adverse because they were generally of small magnitude and were within or near normalized historical control ranges. Full recovery was noted in all parameters except for serum triglycerides and albumin in males in the 300/100 mg/kg/day dose group and serum potassium in females in the 300/100 mg/kg/day dose group. There were no test article-related changes in coagulation parameters.

---

---

There were no test article-related changes in ophthalmic examinations, electrocardiography, urinalysis data, or gross pathology findings.

Test article-related higher mean absolute and relative liver weights were noted in both sexes at 300/100 mg/kg/day, which correlated microscopically with minimal hepatocellular hypertrophy. Liver changes were considered adaptive and non-adverse. Full recovery was noted after the 30-day drug-free period.

In summary, administration of CX-8998 by once-daily oral gavage for a minimum of 90 days was well tolerated in dogs at doses up to 30 mg/kg/day. No mortality was observed.

Administration of 300 mg/kg/day of CX-8998 resulted in body weight loss and/or decreases in body weight gain that were associated with decreased food consumption and thin appearance/loss in body condition, which necessitated feed supplementation in most of the animals. The dose level was subsequently reduced to 100 mg/kg/day beginning on Day 43, and body weight, food consumption, and body condition improved during the remainder of the study. Adaptive and non-adverse minimal hepatocellular hypertrophy was noted at 300/100 mg/kg/day and correlated with higher mean absolute and relative liver weights. Based on these results, the NOAEL of CX-8998 was 30 mg/kg/day in male and female dogs. At 30 mg/kg/day, mean CX-8998  $C_{max}$  was 39400 nM and 43400 nM in male and female dogs, respectively, on Day 90, and mean  $AUC_{24}$  was 335000 nM•hr and 363000 nM•hr in male and female dogs, respectively, on Day 90.

#### **4.4.4 Genotoxicity (Mutagenicity)**

CX-8998 was neither mutagenic (negative Ames assay at doses up to 6000  $\mu$ g/plate) nor genotoxic in assays that were conducted to detect mutagenicity, DNA strand breaks (negative alkaline elution assay at doses up to 20  $\mu$ M), chromosomal alterations (negative at doses up to 130  $\mu$ M), or micronuclei induction in bone marrow (negative at up to 2000 mg/kg orally) (Studies 06-8055, 06-8056, 06-8684 and 06-8923).

#### **4.4.5 Reproductive Toxicity**

Definitive embryotoxicity/teratology (Segment II) studies and prenatal/postnatal developmental (Segment III) studies have not been completed.

##### **4.4.5.1 Effects on Fertility**

The effects of CX-8998 on the fertility of paternal ( $F_0$ ) female rats were evaluated after once-daily oral administration of 0 (vehicle), 10, 30, 100, or 1000 mg/kg/day of CX-8998 (20 to 28 Crl:CD [Sprague-Dawley] rats per dose group) for 28 days before cohabitation, during cohabitation, and through gestation day (GD) 7 (Study 07-7370). The toxicokinetic profiles of CX-8998, M01, and M02 were evaluated in the 100 mg/kg/day group on Day 28. All surviving animals were euthanized on GD 15 to GD 17; the uterine contents were examined for embryonic/fetal viability, and the corpora lutea were counted.

Six females in the 1000 mg/kg/day group were euthanized early due to test article-related physical signs and body weight losses. Numerous test article-related physical signs were observed in the 1000 mg/kg/day dose group; a test article-related decrease in mean maternal body weight gain during premating and gestation and decreases in mean food consumption

---

during premating and gestation were also observed. There was no evidence of test article-related reproductive toxicity.

Based on these findings, the NOEL for rat female fertility parameters was  $\geq$ 1000 mg/kg/day. The NOEL for general toxicity parameters was 100 mg/kg/day

#### **4.4.5.2 Effects on Early Embryofetal Development**

##### **4.4.5.2.1 Rat**

An exploratory oral toxicology study was conducted in rats to assess the potential developmental toxicity of CX-8998 and to assist with dose selection in a definitive developmental toxicology study (Study 07-7175). Rats were administered 0 (vehicle), 10, 30, 100, 300, or 1000 mg/kg/day of CX-8998 (10 per dose group) via oral gavage on GD 6 through GD 20.

The 1000 mg/kg/day dose group was terminated on GD 13 to 16 due to excessive maternal toxicity. Treatment-related decreases in mean maternal body weight gain and mean food consumption were observed in the 30, 100, and 300 mg/kg/day dose groups. Treatment-related decreases in live fetal body weights were observed in the 100 and 300 mg/kg/day dose groups; no developmental toxicity was observed in the 10 or 30 mg/kg/day dose group.

Based on these findings, maternal toxicity was observed at doses  $\geq$ 30 mg/kg/day and the maternal toxicity was deemed excessive at the 1000 mg/kg/day dose (resulting in the early termination of this dose group). Developmental toxicity (decreased live fetal body weight) was observed at doses  $\geq$  100 mg/kg/day.

##### **4.4.5.2.2 Rabbit**

An exploratory oral toxicology study was conducted in rabbits to assess the maternal and developmental toxicity of CX-8998 and to assist with dose selection in a definitive developmental toxicity study (Study 07-7185). Rabbits were administered 0 (vehicle), 30, 100, 300, or 1000 mg/kg/day of CX-8998 (10 per dose group) via oral gavage on GD 7 through GD 20. All surviving animals were euthanized, and the uterine contents were examined.

One animal in the 1000 mg/kg/day dose group was found dead on GD 11, and the remaining animals in the 1000 mg/kg/day dose group were euthanized on GD 10 and GD 11 due to excessive body weight loss and maternal toxicity. Slight treatment-related decreases were observed in mean maternal body weights from GD 7 to GD 9 in the 30 and 100 mg/kg/day dose groups. There was no evidence of developmental toxicity at any dose level up to 300 mg/kg/day.

Based on these findings, maternal toxicity was observed at doses  $\geq$ 30 mg/kg/day and the maternal toxicity was deemed excessive at the 1000 mg/kg/day dose (resulting in the early termination of this dose group). No evidence of developmental toxicity was observed at a dose of 30, 100, or 300 mg/kg/day.

#### **4.4.6 Carcinogenicity**

Carcinogenicity studies have not been conducted.

## 4.5 Nonclinical Assessment of Safety

The response to CX-8998 in the toxicology studies can reasonably be divided into (1) overt toxicity, (2) behavioral effects, and (3) hormonal effects. The assessment for human risk should be considered separately for these 3 categories.

### 4.5.1 Overt Toxicity

CX-8998 showed a favorable safety profile in nonclinical toxicology studies in the rat and dog. Frank toxicity in the form of mortality/moribundity occurred at exposures that were >80-fold higher in nonclinical species than the intended free clinical exposure. Moribundity in the rat was attributed to nasopharyngeal inflammation related to the pH of the dosing formulation and to reflux during dosing, which would not be expected to occur in humans. Adverse kidney and stomach lesions also occurred in rats at lethal doses. Mortality in dogs was associated with adverse clinical signs. The NOAEL doses for these effects were at least 39 times (rat) and approximately 20 times (dog) the intended free clinical exposures.

### 4.5.2 Neurobehavioral Effects

Neurobehavioral changes (FOB effects and clinical signs) associated with CX-8998 treatment in animals are likely related to the intended pharmacology. This attribution is based on the fact that CX-8998 is a CNS-active compound and that these effects occur at pharmacologically active doses and do not occur at sub-pharmacologically active doses. These effects are monitorable and pose limited risk for clinical development.

### 4.5.3 Hormonal Effects

CX-8998-related effects on hormonally responsive organs were seen in rats in a 28-day study but were not seen in a 90-day study. In the 28-day study, changes to female reproductive organs that were indicative of a state of extended diestrus II were observed at all doses (30, 300, and 200 mg/kg/day). These changes were fully reversible after an 8-week off-drug period. Effects were of low incidence and severity and did not translate into effects on fertility or reproduction in rats at exposures >100 times the intended clinical free AUC. In contrast, there were no changes in hormonally responsive tissues in female rats in a subsequent 90-day study at doses of up to 300 mg/kg/day despite detailed, stage-aware histological analysis of reproductive organs.

The mechanism of hormonal disruption in the 28-day study is unknown, and it is also unclear why a difference in response was seen in the 2 studies. It is possible that animals acclimated to treatment with increasing duration of treatment (6-7 estrous cycles over 28-days vs 18-25 estrous cycles over 90 days). Alternatively, it was noted that the pH of the oral dosing formulation was very low in the 28-day study, leading to nasopharyngeal inflammation and stomach ulcers that were severe enough to cause mortality at the high dose. Therefore, it is possible that stress secondary to pain and distress occurred, which caused an indirect effect on hormonal regulation (Whirledge, 2010). The pH was raised to a more tolerable level in the 90-day study, and this could have prevented stress and a secondary hormonal response.

Changes to hormonally responsive tissues in rats were likely reflective of a changing hormonal state/hormonal disruption and are, therefore, not likely to represent a direct toxicity to these target organs. Additionally, there were no changes in mating, fertility, or litter parameters at doses of CX-8998 up to 1000 mg/kg/day in a female fertility study in which CX-8998 was

---

administered for 28 days before cohabitation, during cohabitation, and through GD 7. Additionally, adverse events related to hormonal disruption have not been reported in subjects who have been administered CX-8998 in clinical trials.

There were no findings in the oral exploratory developmental toxicity studies in rats and rabbits at the doses that could be used clinically in humans that would preclude women of childbearing potential from being enrolled in clinical trials. However, definitive embryotoxicity/ teratology (Segment II) studies and prenatal/postnatal developmental (Segment III) studies have not been completed, so appropriate precautions should be taken to avoid pregnancies during clinical trials.

#### 4.5.4 Safety Margins

Safety margins for CX-8998 and its metabolites M01 and M02 were calculated from exposures in the 90-day repeat-dose toxicology studies in rats and dogs at the NOAEL doses (300 mg/kg/day and 30 mg/kg/day, respectively) for free (unbound) CX-8998, M01, and M02, based on estimated human free plasma concentration ( $C_{ss}$ ) and  $AUC_{24}$  values at steady state for 10 mg BID dosing. In addition, safety margins for the potency normalized sum of the exposures of the active components (CX-8998, M01 and M02), the total active moiety (TAM), was also calculated.

CX-8998 and metabolites demonstrated comfortable safety margins in the 90-day toxicology studies. Calculated safety margins across analytes and species were generally >25-fold in rats and  $\geq$ 16-fold in dogs for  $AUC_{24}$  and generally >50-fold in rats and  $\geq$ 23-fold in dogs for  $C_{max}$ . Margins were generally lower in male rats than in female rats, whereas margins were similar between sexes in dogs.

The calculated safety margins for free  $AUC_{24}$  (female/male) are 81-/37-, >49-/>26-, and 129-/65-fold for CX-8998, M01, and M02, respectively, in rats and 19-/18-, >16-/>19, and 33-fold, respectively, in dogs (Table 16). The calculated safety margins for free  $C_{max}$  are 184-/78-, >81-/>51-, and 216-/117-fold for CX-8998, M01, and M02, respectively, in rats and 57-/51-, >23-/>29, and 59-fold, respectively, in dogs. The calculated safety margins for free  $AUC_{24}$  TAM are 114- and 57-fold in female and male rats, respectively, and 29-fold in both female and male dogs. The calculated safety margins for free  $C_{max}$  TAM are 193- and 101-fold in female and male rats, respectively, and 54- and 53-fold in female and male dogs, respectively.

Overall, the nonclinical toxicity noted with CX-8998 provides no contraindications to the conduct of clinical trials in accordance with the study protocol and local regulatory guidance.

**Table 16: Safety Margins in Humans Based on AUC<sub>24</sub> and C<sub>max</sub>**

| Analyte          | Day 90 Free <sup>c</sup> Plasma AUC <sub>24</sub> (nM•hr) at: |        |   |        | Human Plasma<br>Projected<br>Steady-State<br>AUC <sub>24</sub> (nM•hr) for<br>10 mg BID Dose                     | Day 90 Free <sup>c</sup> Margin for AUC <sub>24</sub> at: |      |   |      |  |
|------------------|---|--------|---|--------|--|---|------|---|------|--|
|                  | NOAEL <sup>a</sup> for Rat<br>90-Day Toxicology               |        | NOAEL <sup>b</sup> for Dog<br>90-Day Toxicology |        |  | NOAEL <sup>a</sup> for Rat<br>90-Day Toxicology           |      | NOAEL <sup>b</sup> for Dog<br>90-Day Toxicology |      |  |
|                  | Female  | Male   | Female  | Male   |  | Female  | Male | Female  | Male |  |
| CX-8998          | 4528  | 2088   | 1089  | 1005   | 56   | 81  | 37   | 19  | 18   |  |
| M01              | <936  | <500   | <309  | <363   | <19  | >49   | >26  | >16   | >19  |  |
| M02              | 148,190   | 74,820 | 37,620  | 38,340 | 1152   | 129   | 65   | 33  | 33   |  |
| TAM <sup>e</sup> | 37,117  | 18,585 | 9474  | 9626   | 327  | 114   | 57   | 29  | 29   |  |
| Analyte          | Day 90 Free <sup>c</sup> Plasma C <sub>max</sub> (nM) at:     |        |   |        | Human Free <sup>d</sup><br>Plasma Projected<br>Steady-State C <sub>max</sub><br>(nM) for 10 mg<br>BID Dose (Fed) | Day 90 Free <sup>c</sup> Margin for C <sub>max</sub> at:  |      |   |      |  |
|                  | NOAEL <sup>a</sup> for Rat<br>90-Day Toxicology               |        | NOAEL <sup>b</sup> for Dog<br>90-Day Toxicology |        |  | NOAEL <sup>a</sup> for Rat<br>90-Day Toxicology           |      | NOAEL <sup>b</sup> for Dog<br>90-Day Toxicology |      |  |
|                  | Female  | Male   | Female  | Male   |  | Female  | Male | Female  | Male |  |
| CX-8998          | 423   | 180    | 130   | 118    | 2.3  | 184   | 78   | 57  | 51   |  |
| M01              | <65   | <40    | <19   | <23    | <0.8   | >81   | >51  | >23   | >29  |  |
| M02              | 10,382  | 5597   | 2826  | 2808   | 48   | 216   | 117  | 59  | 59   |  |
| TAM <sup>e</sup> | 2,705   | 1,419  | 753   | 744    | 14   | 193   | 101  | 54  | 53   |  |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; BID = twice daily;

C<sub>max</sub> = maximum plasma drug concentration; NOAEL = no-observed-adverse-effect level; TAM = total active moiety.

<sup>a</sup> NOAEL for 90-day repeat-dose toxicology study in rats = 300 mg/kg/day.

<sup>b</sup> NOAEL for 90-day repeat-dose toxicology study in dogs = 30 mg/kg/day.

<sup>c</sup> In rats, the free fraction is 0.8%, 0.4%, and 29% for CX-8998, M01, and M02, respectively; in dogs, the free fraction is 0.3%, 0.3%, and 18% for CX-8998, M01, and M02, respectively.

<sup>d</sup> In humans, the free fraction is 0.4%, <0.1%, and 14% for CX-8998, M01, and M02, respectively.

<sup>e</sup> TAM calculated from the sum of potency normalized free exposures for CX-8998, M01 and M02

Source: Calculated Safety Margins, 90-day Toxicology Memo, 26 June 2018.

## 5 EFFECTS IN HUMANS

### 5.1 Listing of Clinical Studies Conducted With CX-8998

CX-8998 (previously known as MK-8998, Merck and Company, Inc) has been studied in 4 Phase 1 studies in healthy male and female subjects and in 1 Phase 2A study in acutely psychotic patients with schizophrenia. These trials were randomized, double-blind, placebo-controlled studies that explored single doses of 1 to 24 mg of CX-8998 (normal healthy subjects), multiple doses of 2 to 18 mg once daily for 7 days (normal healthy subjects), and 8 mg BID for 28 days (patients with schizophrenia). A 4-week, randomized, double-blind, placebo-controlled, dose-titration study of CX-8998 in adults with essential tremor has been completed in the clinic, and a 4-week, multicenter, open-label, dose-titration study of CX-8998 in adolescents and young adults with generalized epileptic syndrome with absence seizures is ongoing. An open-label digital substudy in patients with PDT (to assess the utility of digital assessment tools in the objective measurement of PDT) and a 4-week, multicenter, randomized, double-blind, placebo-controlled, dose-titration study of CX-8998 in patients with PDT are planned. The design features of the clinical studies are presented in Table 17.

**Table 17: Clinical Studies of CX-8998**

| Study Number             | Phase and Population  | Design (Endpoints)  | Dose of CX-8998 and Control  |
|--------------------------|---|---|--|
| <b>Completed Studies</b> |   |   |  |
| PN001                    |   |   |  |
| Part I                   | Phase 1<br>24 healthy male<br>subjects aged<br>20-40 years  | Randomized, double-blind,<br>placebo-controlled, 5-period,<br>single-, rising-dose<br>(safety and PK) | <u>Panel A:</u> 1 mg (fasted; all doses administered fasted unless specified fed), 1 mg (fed), 8 mg, 12 mg, and 12 mg (evening <sup>a</sup> ) of CX-8998 (N=6); placebo (N=2)<br><u>Panel B:</u> 3 mg, 4 mg (evening <sup>a</sup> ), 8 mg (evening <sup>a</sup> ), 12 mg, and 16 mg (evening <sup>a</sup> ) of CX-8998 (N=6); placebo (N=2)<br><u>Panel C:</u> 16 mg (evening <sup>a</sup> ), 20 mg (evening <sup>a</sup> ), and 24 mg (evening <sup>a</sup> ) of CX-8998 (N=6); placebo (N=2) |
| Part II                  | Phase 1<br>12 healthy male<br>subjects aged<br>22-39 years  | Randomized, double-blind,<br>placebo-controlled, 3-period<br>crossover<br>(safety and EEG)            | 5 and 18 mg of CX-8998 and placebo   |
| PN002                    |   |   |  |
| Part I                   | Phase 1<br>9 healthy middle-aged<br>and elderly male<br>subjects aged<br>55-75 years <sup>b</sup> | Randomized, double-blind,<br>placebo-controlled, 5-period,<br>single-, rising-dose<br>(safety and PK) | 2, 4, 8, 12, and 18 mg of CX-8998 (N=7) or placebo (N=2)   |
| Part II                  | Phase 1<br>40 healthy male<br>subjects aged<br>18-45 years  | Randomized, double-blind,<br>placebo-controlled,<br>multiple-, rising-dose<br>(safety, PK, and PD)    | Panel A: 2 mg/d CX-8998 (N=6) or placebo (N=2) x 7 d<br>Panel B: 4 mg/d CX-8998 (N=6) or placebo (N=2) x 7 d<br>Panel C: 8 mg/d CX-8998 (N=6) or placebo (N=2) x 7 d<br>Panel D: 12 mg/d CX-8998 (N=6) or placebo (N=2) x 7 d  |

**Table 17: Clinical Studies of CX-8998**

| Study Number                                     | Phase and Population   | Design (Endpoints)  | Dose of CX-8998 and Control   |
|--|--|---|---|
|  |  |   | Panel E: 18 mg/d CX-8998 (N=6) or placebo (N=2) x 7 d   |
| PN003  | Phase 1<br>28 healthy male subjects aged 40-66 years   | Multicenter, 2-part, adaptive-design, randomized, double-blind, placebo-controlled, single-dose, crossover (PK and polysomnography)                     | Part I Period 1: 12 mg CX-8998<br>Part I Period 2: 12 mg CX-8998 or placebo<br>Part I Period 3: placebo or 12 mg CX-8998<br>Part II: 4 mg, 8 mg CX-8998 or placebo                        |
| PN005  | Phase 1<br>9 healthy middle-aged and elderly female subjects aged 57-75 years  | Randomized, double-blind, placebo-controlled, single-dose (safety and PK)   | 8 mg CX-8998 (N=7) or placebo (N=2)   |
| PN004  | Phase 2A<br>216 adults aged 20-55 years with acute psychosis   | 4-Week, multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group (safety and PANSS)  | CX-8998 6 mg BID on Days 1-7 then 8 mg BID on Days 8-28 (N=86)<br>Olanzapine 5 mg BID on Days 1-7 then 5 mg in the morning and 10 mg in the evening on Days 8-28 (N=47)<br>Placebo (N=83) |
| <b>Ongoing Studies</b>                           |  |   |   |
| CX-8998-CLN2-001 (T-CALM)                        | Phase 2<br>up to 106 (planned) adults aged 18-75 years with essential tremor   | Multicenter, randomized, double-blind, placebo-control, dose-titration (safety, efficacy [TETRAS], and PK)  | CX-8998 4 mg BID in Week 1, 8 mg BID in Week 2, and 10 mg BID in Weeks 3 and 4 or placebo   |
| CX-8998-CLN2-002 (T-WAVE)                        | Phase 2A<br>up to 15 (planned) adolescents and young adults aged 16-55 years with generalized epileptic syndrome with absence seizures | Multicenter, open-label, dose-titration (safety, ambulatory EEG parameters, SERDAS, and PK) <sup>c</sup>  | CX-8998 2 mg BID on Days 1 and 2, 4 mg BID on Days 3-8, 6 mg BID on Days 9-14, 8 mg BID on Days 15-20, 10 mg BID on Days 21-26, and then 10 mg in the morning on Day 27                   |
| <b>Planned Studies</b>                           |  |   |   |
| CX-8998-CLN2-001, Open-label Digital Substudy #2 | Phase 2<br>up to 12 (planned) adults with PDT  | Open-label study to assess the utility of 3 digital assessment tools: MDS-UPRDS, iMotor application, and a continuous wearable tremor-monitoring device | CX-8998 4 mg BID in Week 1, 8 mg BID in Week 2, and 10 mg BID in Weeks 3 and 4  |
| CX-8998-CLN2-003 (T-CALM-PDT)                    | Phase 2<br>up to 60 (planned) adults aged 18-75 years with PDT   | Multicenter, randomized, double-blind, placebo-control, dose-titration (safety, efficacy [MDS-UPRDS], and PK)   | CX-8998 4 mg BID in Week 1, 8 mg BID in Week 2, and 10 mg BID in Weeks 3 and 4 or placebo   |

BID = twice daily; EEG = electroencephalogram; MDS-UPRDS = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; PANSS = Positive and Negative Syndrome Scale; PD = pharmacodynamic; PDT = Parkinson's disease tremor; PK = pharmacokinetic; SERDAS = Seizure-Related Disability Assessment Scale; TETRAS = The Essential Tremor Rating Assessment Scale.

<sup>a</sup> The dose was taken 4 hours after the evening meal.

<sup>b</sup> The study was planned to include 8 subjects; a ninth subject was randomized to replace a subject who discontinued from the study after Period 1.

## 5.2 Pharmacokinetics and Drug Metabolism

### 5.2.1 Single-Dose Pharmacokinetics

#### 5.2.1.1 Key Single-Dose Pharmacokinetic Parameters of CX-8998

The single-dose pharmacokinetics of CX-8998 were evaluated in 4 Phase 1 studies (PN001, PN002/Part I, PN003, and PN005). Mean (SD) pharmacokinetic parameters of CX-8998 are summarized by study in Table 18.

**Table 18: Mean (SD) Single-Dose Pharmacokinetic Parameters of CX-8998 (Studies PN001, PN002, PN003, and PN005)**

| Study No.     | Study Population (No. of Subjects)             | CX-8998 Dose (mg) <sup>a</sup> | C <sub>max</sub> (nM) | T <sub>max</sub> (hr) <sup>b</sup> | AUC <sub>inf</sub> (μM·hr) | t <sub>1/2</sub> (hr) <sup>c</sup> |
|---------------|--|--------------------------------|-----------------------|------------------------------------|----------------------------|------------------------------------|
| PN001/Part I  | Healthy male subjects aged 20-40 years (N=24)  | 1                              | 104 (19)              | 0.8                                | 765 (120)                  | 11.4 (5.8)                         |
|               |  | 1 (fed)                        | 56 (5)                | 4.0                                | 725 (104)                  | 10.2 (3.3)                         |
|               |  | 3                              | 316 (98)              | 1.0                                | 2734 (2645)                | 11.5 (5.0)                         |
|               |  | 8                              | 580 (122)             | 1.0                                | 4829 (867)                 | 9.7 (3.5)                          |
|               |  | 12                             | 687 (242)             | 1.0                                | 6861 (1780)                | 10.1 (3.6)                         |
|               |  | 4 (evening)                    | 295 (152)             | 1.0                                | 3543 (1896)                | 13.2 (4.0)                         |
|               |  | 8 (evening)                    | 522 (129)             | 1.0                                | 6370 (3598)                | 11.6 (5.5)                         |
|               |  | 12 (evening)                   | 577 (180)             | 2.0                                | 7030 (2235)                | 10.5 (4.0)                         |
|               |  | 16 (evening)                   | 873 (294)             | 1.0                                | 11655 (1529)               | 12.8 (5.7)                         |
|               |  | 20 (evening)                   | 966 (214)             | 2.0                                | 14088 (3519)               | 13.0 (3.2)                         |
|               |  | 24 (evening)                   | 1370 (257)            | 1.0                                | 14662 (2841)               | 11.7 (1.1)                         |
| PN001/Part II | Healthy male subjects aged 22-39 years (N=12)  | 5                              | 429 (69)              | 1.0                                | 4070 (581)                 | 13.5 (4.6)                         |
|               |  | 18                             | 1180 (352)            | 1.0                                | 14700 (3190)               | 13.3 (4.9)                         |
| PN002/Part I  | Healthy male subjects aged 55-75 years (N=9)   | 2                              | 198 (46)              | 0.5                                | 2017 (755)                 | 20.8 (10.4)                        |
|               |  | 4                              | 374 (58)              | 0.5                                | 4227 (1604)                | 20.6 (7.8)                         |
|               |  | 8                              | 708 (189)             | 0.5                                | 8388 (3169)                | 21.8 (6.1)                         |
|               |  | 12                             | 877 (66)              | 1.0                                | 10709 (4730)               | 18.8 (8.0)                         |
|               |  | 18                             | 1334 (325)            | 0.5                                | 18479 (6619)               | 22.6 (12.9)                        |
| PN003         | Healthy male subjects aged 40-66 years (N=28)  | 12 (evening)                   | 527 (173)             | 2.0                                | 9750 (3529)                | 14.4 (3.7)                         |
| PN005         | Healthy female subjects aged 57-70 years (N=7) | 8                              | 582 (170)             | 0.5                                | 9420 (2080)                | 30.3 (10.5)                        |

AUC<sub>inf</sub> = area under the plasma concentration-time curve from time zero to infinity; C<sub>max</sub> = maximum plasma drug concentration; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> Unless otherwise indicated, doses were administered in the morning after an overnight fast.

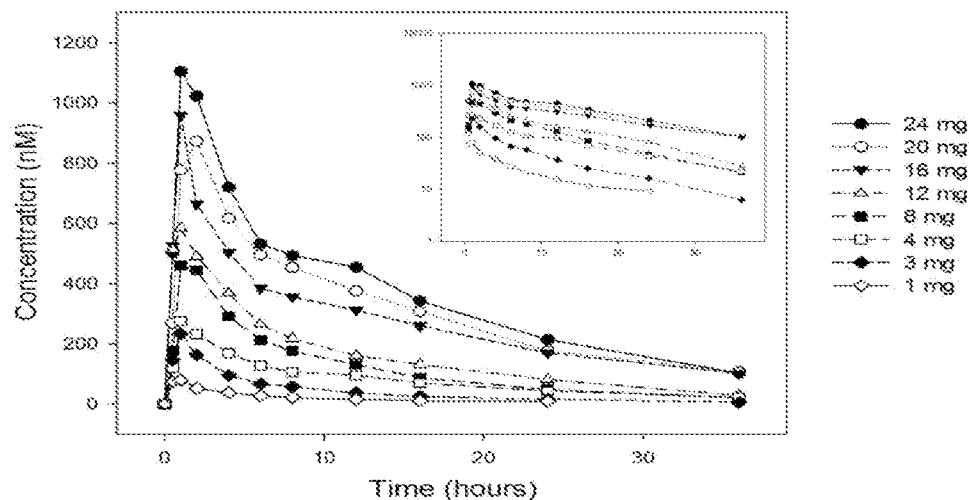
<sup>b</sup> Median value.

<sup>c</sup> Harmonic mean value and pseudo standard deviation.

### 5.2.1.2 Single-Dose Pharmacokinetic Profile of CX-8998

The single-dose pharmacokinetics of CX-8998 over the dose range of 1 to 24 mg were characterized by rapid absorption and biphasic elimination (Figure 7).

**Figure 7: Mean Plasma Concentrations of CX-8998 in Healthy Male Subjects After Single Oral Doses of 1 to 24 mg of CX-8998 Under Fasted Conditions (Study PN001/Part I)**



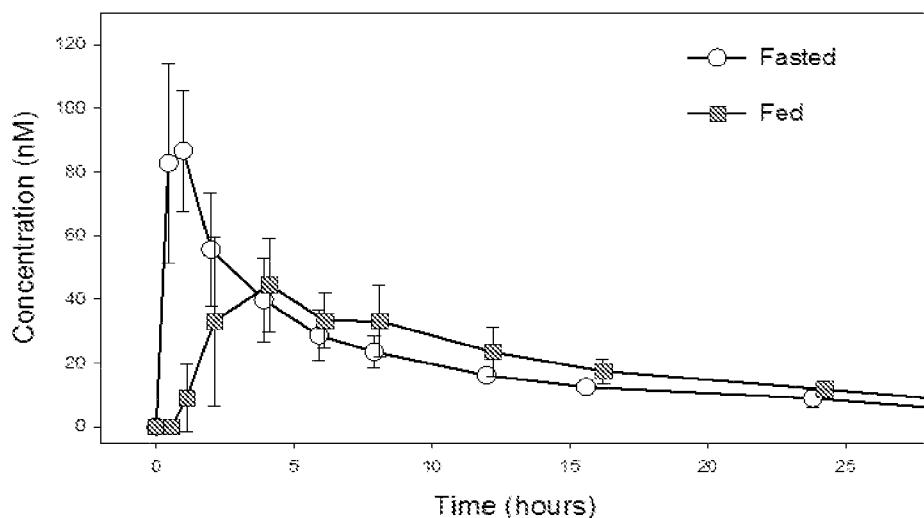
Under fasted conditions,  $C_{\max}$  of CX-8998 occurred in a median of 0.8 to 2 hours after dosing (Study PN001/Part I; Table 18). Single-dose administration of 1, 3, 4, 8, 12, 16, 20, and 24 mg of CX-8998 resulted in an approximately proportional increase in the exposure levels ( $C_{\max}$  and area under the plasma concentration-time curve from time zero to infinity [ $AUC_{\infty}$ ]) of CX-8998.

Mean terminal half-life ( $t_{1/2}$ ) of CX-8998 ranged from 9.7 to 13.5 hours in healthy young male subjects (aged 20 to 40 years; Study PN001) but was prolonged in middle-aged and elderly healthy male subjects (aged 55 to 75 years; Study PN002), with mean  $t_{1/2}$  ranging from 18.8 to 22.6 hours, and in middle-aged and elderly healthy female subjects (aged 55 to 75 years; Study PN005), with a mean  $t_{1/2}$  of 30.3 hours.

### 5.2.1.3 Food Effects

Administration of a 1 mg dose of CX-8998 with a high-fat meal resulted in a significant delay in oral absorption (Study PN001/Part I; Figure 8), which was manifested by a substantially lower mean  $C_{\max}$  (56 nM fed vs 104 nM fasted) and a delay in median  $T_{\max}$  from 0.8 hours (fasted) to 4.0 hours (fed) (Table 18).

**Figure 8: Mean Plasma Concentrations of CX-8998 in Healthy Male Subjects After a Single Oral Doses 1 mg of CX-8998 Under Fasted and Fed Conditions (Study PN001/Part I)**

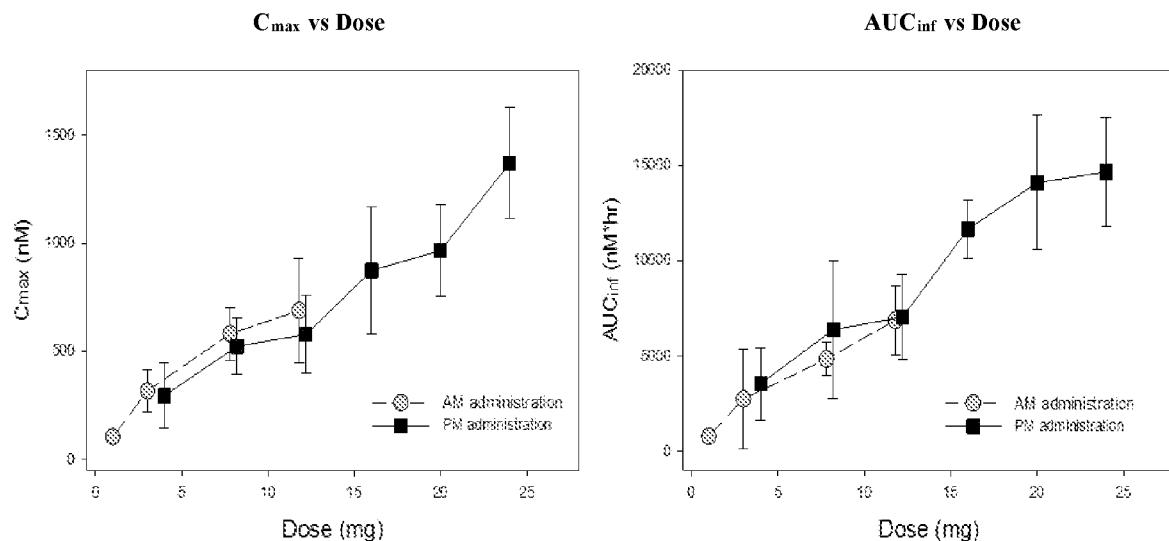


The geometric mean ratio and range of values for the geometric mean ratio for the fed/fasted conditions were 0.55 (0.40-0.76) for  $C_{max}$  and 0.95 (0.77-1.35) for  $AUC_{inf}$ . Administration of CX-8998 with food resulted in a 45% reduction in  $C_{max}$ , as compared with the fasted state, without significantly reducing the  $AUC$  of CX-8998. These results indicate that CX-8998 can be taken with food to reduce  $C_{max}$ , with the goal of improving early-exposure tolerability, without sacrificing the bioavailability of CX-8998.

#### 5.2.1.4 Dose Proportionality

Single oral doses of 1 to 24 mg of CX-8998 resulted in an approximately proportional increase in the mean exposure levels ( $C_{max}$  and  $AUC_{inf}$ ) of CX-8998 under fasted conditions, regardless of whether CX-8998 was administered in the morning or evening (Study PN001/Part I; Figure 9). Overall, the single-dose pharmacokinetics of CX-8998 were linear over the dose range of 1 to 24 mg.

**Figure 9: Mean ( $\pm$ SD) of CX-8998  $C_{\max}$  and  $AUC_{\text{inf}}$  Versus Dose After Morning or Evening Administration of CX-8998 Under Fasted Conditions (Study PN001/Part I)**

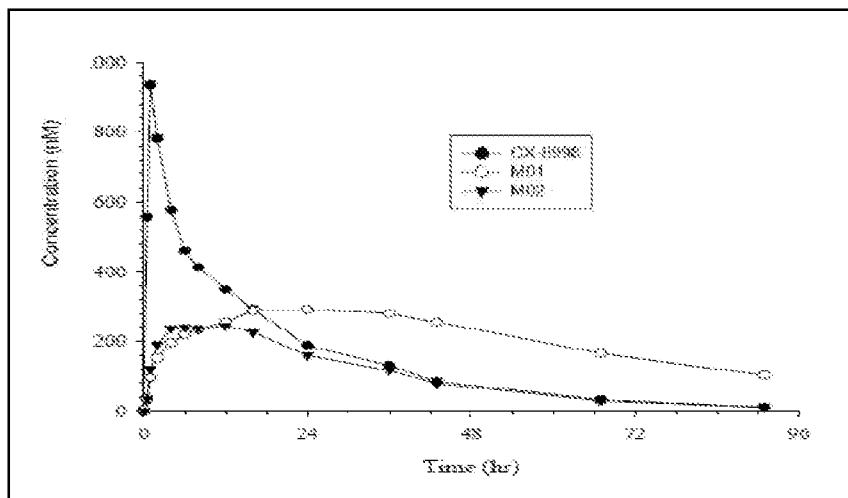


$AUC_{\text{inf}}$  = area under the plasma concentration-time curve from time zero to infinity;  $C_{\max}$  = maximum plasma drug concentration.

### 5.2.1.5 Metabolite Profiles Using an Exploratory Assay

The plasma concentrations of 2 metabolites of CX-8998 (M01 and M02) after single oral doses over the range of 1 to 24 mg (Study PN001/Part I) were quantified using an exploratory assay. Consistent with the proportionality relationship that was observed for CX-8998, single-dose administration of 12, 16, and 24 mg of CX-8998 resulted in stepwise increases in mean  $AUC_{\text{inf}}$  for M01 and M02. The single-dose plasma concentration profiles for M01 and M02, relative to CX-8998, after a 16 mg evening dose of CX-8998 are shown in Figure 10.

**Figure 10: Mean Plasma Concentration Profiles of CX-898 and Metabolites (M01 and M02) After a Single, Oral 16 mg Evening Dose of CX-8998 (Study PN001/Part I)**

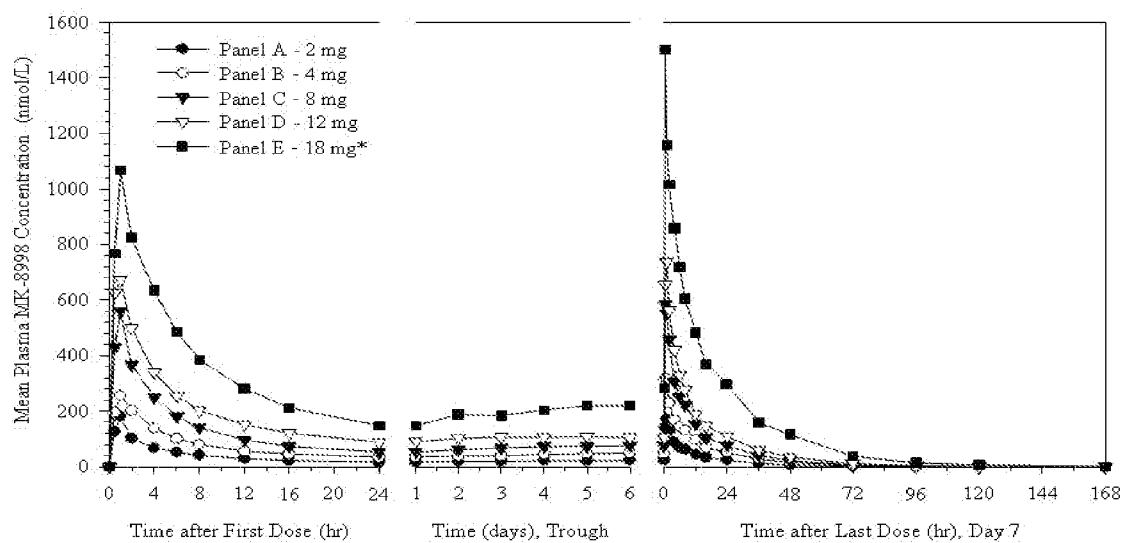


These results for M01 and M02 are consistent with metabolite findings in subsequent studies that used a more definitive metabolite assay (see Section 5.2.3).

### 5.2.2 Multiple-Dose Pharmacokinetics

The single- and multiple-dose pharmacokinetics of CX-8998 were characterized by rapid absorption and biphasic elimination after once-daily dosing with 2, 4, 8, 12, and 18 mg of CX-8998 (Study PN002/Part II; Figure 11). Steady-state trough concentrations appeared to be reached within 2 to 3 days after initiation of dosing for all dose levels.

**Figure 11: Mean Plasma Concentrations of CX-8998 After Once-Daily Dosing of CX-8998 (2, 4, 8, 12, and 18 mg) in Healthy Male Subjects (Study PN002/Part II)**



\* N=2 for the 18 mg dose on Day 8 due to premature discontinuation of 4 subjects from the study; N=6 for all other doses on Days 1 and 7 and for the 18 mg dose on Day 1.

There was an approximately proportional increase in exposure levels ( $C_{max}$  and AUC) of CX-8998 on Days 1 and 7 with increasing dose (Table 19). Mean steady-state  $C_{max}$  ranged from 215 nM after administration of 2 mg once daily to 1498 nM after administration of 18 mg once daily. The accumulation ratio for AUC<sub>24</sub> indicated a modest 24% to 36% accumulation of CX-8998 by Day 7. Mean  $t_{1/2}$  after the last dose of CX-8998 on Day 7 ranged from 11.0 to 13.5 hours, which was consistent with the single-dose estimate of  $t_{1/2}$  in healthy young male subjects (9.7-13.5 hours).

**Table 19: Mean (SD) CX-8998 Pharmacokinetic Parameters on Day 1 and Day 7 After Once-Daily Administration of CX-8998 to Healthy Male Subjects (Study PN002/Part II)**

| Time Point | CX-8998 Dose (mg) | No. of Subjects | C <sub>max</sub> (nM) | T <sub>max</sub> (hr) <sup>a</sup> | AUC <sub>24</sub> (μM•hr) | t <sub>1/2</sub> (hr) <sup>b</sup> | Accumulation Ratio (Day 7/Day 1) <sup>c</sup> |
|------------|-------------------|-----------------|-----------------------|------------------------------------|---------------------------|------------------------------------|---|
| Day 1      | 2                 | 6               | 201 (47)              | 0.75                               | 1022 (201)                |                                    |   |
|            | 4                 | 6               | 283 (67)              | 1.0                                | 1928 (463)                |                                    |   |
|            | 8                 | 6               | 575 (130)             | 1.0                                | 3467 (693)                |                                    |   |
|            | 12                | 6               | 798 (167)             | 1.0                                | 5004 (1107)               |                                    |   |
|            | 18                | 6               | 1138 (211)            | 1.0                                | 8692 (1917)               |                                    |   |
| Day 7      | 2                 | 6               | 215 (54)              | 1.0                                | 1354 (275)                | 13.3 (5.0)                         | 1.31  |
|            | 4                 | 6               | 376 (105)             | 0.75                               | 2739 (1115)               | 13.5 (3.8)                         | 1.36  |
|            | 8                 | 6               | 665 (156)             | 0.75                               | 4679 (1495)               | 11.0 (3.0)                         | 1.31  |
|            | 12                | 6               | 895 (271)             | 1.0                                | 6101 (602)                | 13.5 (3.0)                         | 1.24  |
|            | 18                | 2               | 1498 (104)            | 0.5                                | 13447 (3555)              | 11.1 (3.8)                         | 1.33  |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> Median value.

<sup>b</sup> Harmonic mean value and pseudo standard deviation.

<sup>c</sup> Geometric mean ratio of Day 7/Day 1 AUC<sub>24</sub>.

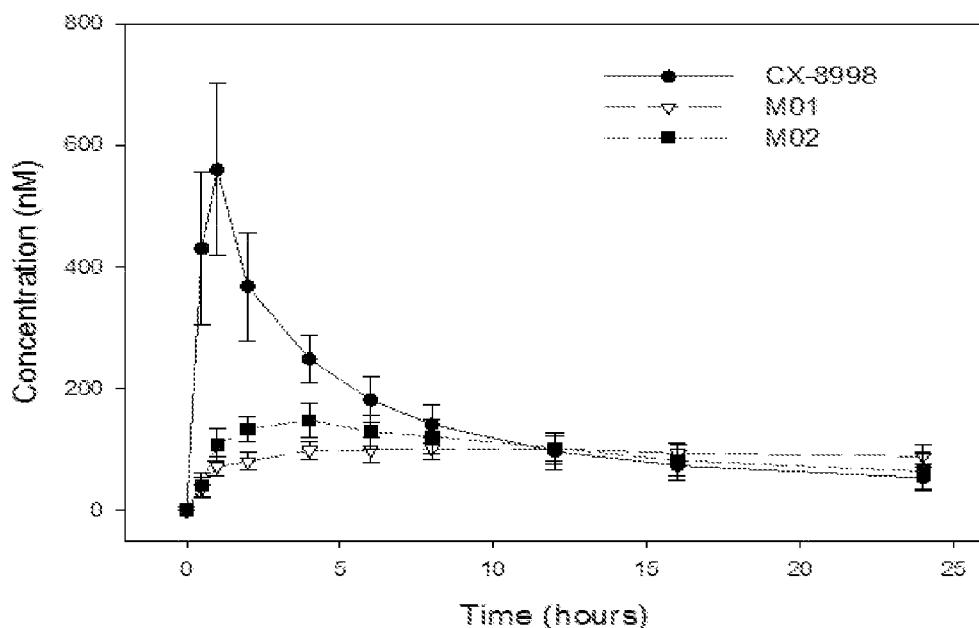
Based on the proportionality relationships between exposure level (ie, C<sub>max</sub> and AUC) and dose and the consistency of values for t<sub>1/2</sub> and the accumulation ratio across doses, the multiple-dose pharmacokinetics of CX-8998 appear to be linear over the dose range of 2 to 18 mg/day.

### 5.2.3 Metabolism

In vitro studies in human liver microsomes have shown that CX-8998 undergoes extensive CYP metabolism, predominantly by aliphatic dehydrogenation of the isopropyl moiety to give form the M01 metabolite or by hydroxylation on the isopropyl moiety to form the M02 metabolite (Section 4.3.5). The metabolism of CX-8998 is mediated by CYP3A and CYP2C enzymes. However, CX-8998 was shown to be neither an inhibitor of major CYP isoforms (IC<sub>50</sub> >25 nM in human microsomes) nor an inducer of CYP3A4 metabolism, as determined in culture of primary human hepatocytes. Likewise, CX-8998 is not a substrate of human P-glycoprotein

Plasma concentrations of M01 and M02 from samples obtained in Studies PN002, PN003, and PN005 were quantitated using a definitive (validated) assay. The plasma concentration profiles of CX-8998, M01, and M02 after the first 8 mg dose of CX-8998 in Study PN002/Part II are shown in Figure 12.

**Figure 12: Mean (SD) Concentrations of CX-8998 and Metabolites (M01 and M02) After the First 8 mg Dose of CX-8998 on Day 1 (Study PN002/Part II)**



The plasma concentration profiles of M01 and M02 after administration of the first 8 mg dose of CX-8998 in Study PN002/Part II (Figure 12) appeared consistent with the single-dose plasma concentration profiles for each analyte, as obtained from the exploratory metabolite assay in Study PN001/Part I (Figure 10), with absorption and elimination of CX-8998 more rapid relative to the slower rate of formation and elimination of M01 and M02.

Steady-state  $C_{\max}$  values for M01 and M02 were lower than for CX-8998, with the mean  $C_{\max}$  ratio ranging from 0.36 to 0.57 for M01 and from 0.26 to 0.33 for M02 (Table 20). However, the overall exposure level of M01 was higher than the overall exposure levels of M02 and CX-8998 because of the comparatively longer mean  $t_{1/2}$  for M01 (19.0-25.8 hours) than for M02 (12.2-15.4 hours) and CX-8998 (11.0-13.5 hours).

**Table 20: Mean (SD) Pharmacokinetic Parameters of CX-8998 Metabolites (M01 and M02) on Day 7 After Once-Daily Administration of CX-8998 for 7 Days (Study PN002/Part II)**

| CX-8998 Dose (mg)     | C <sub>max</sub> (nM) | C <sub>max</sub> Ratio <sup>a</sup> | AUC <sub>24</sub> (μM·hr) | AUC Ratio <sup>a</sup> | t <sub>1/2</sub> <sup>b</sup> (hr) |
|-----------------------|-----------------------|-------------------------------------|---------------------------|------------------------|------------------------------------|
| <b>Metabolite M01</b> |                       |                                     |                           |                        |                                    |
| 2                     | 76 (18)               | 0.36                                | 1522 (401)                | 1.12                   | 25.8 (8.3)                         |
| 4                     | 136 (105)             | 0.36                                | 2827 (909)                | 1.05                   | 21.6 (7.2)                         |
| 8                     | 254 (63)              | 0.38                                | 4962 (1415)               | 1.07                   | 19.3 (5.1)                         |
| 12                    | 374 (96)              | 0.42                                | 7135 (1541)               | 1.15                   | 22.6 (4.2)                         |
| 18                    | 865 (250)             | 0.57                                | 18284 (6595)              | 1.34                   | 19.0 (7.4)                         |
| <b>Metabolite M02</b> |                       |                                     |                           |                        |                                    |
| 2                     | 54 (6)                | 0.26                                | 930 (31)                  | 0.70                   | 15.0 (4.2)                         |
| 4                     | 106 (27)              | 0.28                                | 1861 (606)                | 0.69                   | 15.4 (4.5)                         |
| 8                     | 219 (50)              | 0.33                                | 3542 (1139)               | 0.76                   | 12.2 (4.0)                         |
| 12                    | 287 (52)              | 0.33                                | 4549 (655)                | 0.74                   | 14.5 (2.8)                         |
| 18                    | 481 (63)              | 0.32                                | 7966 (307)                | 0.60                   | 12.8 (3.2)                         |

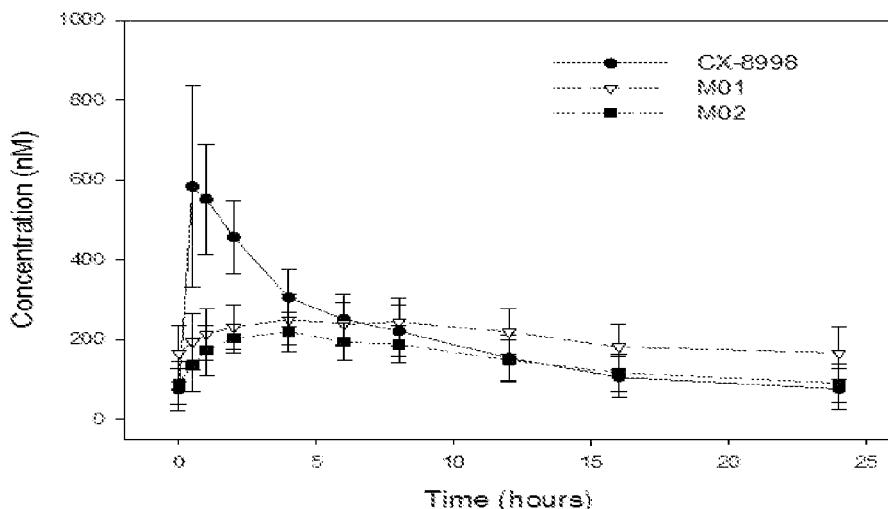
AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; C<sub>max</sub> = maximum plasma drug concentration; t<sub>1/2</sub> = terminal half-life.

<sup>a</sup> Geometric mean ratio of metabolite to parent (CX-8998).

<sup>b</sup> Harmonic mean value and pseudo standard deviation.

The plasma concentration profiles of M01 and M02 remained relatively flat, relative to that of CX-8998, over the 24-hour dosing interval on Day 7 (Figure 13). Mean plasma concentration of M01 was higher than that of CX-8998 at 12, 16, and 24 hours after administration of the last dose of CX-8998 because of the more rapid elimination of CX-8998. Mean plasma concentration of M02 was comparable to that of CX-8998 at 12, 16, and 24 hours after administration of the last dose of CX-8998, suggesting that the t<sub>1/2</sub> of M02 was more dependent on its rate of formation than on its rate of elimination (ie, flip-flop kinetics).

**Figure 13: Mean (SD) Concentrations of CX-8998 and Metabolites (M01, and M02) on Day 7 After Once-Daily Administration of 8 mg of CX-8998 for 7 Days (Study PN002/Part II)**



Based on the potency and free fraction of CX-8998, M01, and M02 and the maximum metabolite-to-parent  $C_{max}$  ratios (Table 20), the relative potency of CX-8998 to M01 would be 1.00 to 0.27 and the relative potency of CX-8998 to M02 would be 1.00 to 2.98.

Preliminary unaudited bioanalytical data from ongoing study CX-8998-CLN2-001 (T-CALM; Section 5.4.2.1) using a validated 5-in-1 method that measures CX-8998 and all 4 metabolites that have been seen in nonclinical species (M01, M02, M03, and M04) confirm the findings from the Phase 1 studies and demonstrate that M03 and M04 exposures are not significant in humans.

## 5.2.4 Pharmacokinetics in Special Populations

### 5.2.4.1 Age and Weight

Mean  $C_{max}$  and  $AUC_{inf}$  values of CX-8998 were 28% and 50% higher, respectively in middle-aged and elderly male subjects and 6% and 68% higher, respectively, in the middle-aged and elderly female subjects than in younger male subjects (Table 21). Similarly, exposures to M01 and M02 were approximately 1.5- to 2-fold (ie, 50%-100%) higher in the middle-aged and elderly male and female subjects than in the younger male subjects. However, it should be noted that an exploratory assay was used to determine the concentrations of M01 and M02 in the younger male subjects (Study PN001), whereas a definitive (validated) assay was used to determine concentrations of M01 and M02 in the middle-aged and elderly subjects (Studies PN002/Part I and PN005).

**Table 21: Mean (SD) Pharmacokinetic Parameters of CX-8998 and Metabolites (M01 and M02) After a Single 8 mg Dose of CX-8998 by Age Group (Studies PN001/Part I, PN002/Part I, and PN005)**

| Analyte | Parameter                  | Study PN001/Part I                        | Study PN002/Part I                                       | Study PN005  |
|---------|----------------------------|---|--|--|
|         |                            | Younger Male Subjects (N=12) <sup>a</sup> | Middle-aged and Elderly Male Subjects (N=6) <sup>b</sup> | Middle-aged and Elderly Female Subjects (N=7) <sup>c</sup> |
| CX-8998 | C <sub>max</sub> (nM)      | 551 (123)                                 | 708 (189)  | 582 (170)  |
|         | T <sub>max</sub> (hr)      | 1.0                                       | 0.5  | 0.5  |
|         | AUC <sub>inf</sub> (μM•hr) | 5600 (2622)                               | 8390 (3169)  | 9420 (2080)  |
|         | t <sub>1/2</sub> (hr)      | 10.6 (4.9)                                | 21.8 (6.1)   | 30.3 (10.5)  |
| M01     | C <sub>max</sub> (nM)      | 141 (48.0) <sup>d</sup>                   | 101 (23.9)   | 88.6 (15.3)  |
|         | T <sub>max</sub> (hr)      | 12  | 24   | 48   |
|         | AUC <sub>inf</sub> (μM•hr) | 7405 (2293) <sup>a</sup>                  | 11200 (5360)   | 11000 (2140)   |
|         | t <sub>1/2</sub> (hr)      | 18.6 (19.2)                               | 34.9 (12.4)  | 49.8 (16.3)  |
| M02     | C <sub>max</sub> (nM)      | 131 (47.3) <sup>d</sup>                   | 113 (11.2)   | 115 (35.9)   |
|         | T <sub>max</sub> (hr)      | 4.0                                       | 4.0  | 4.0  |
|         | AUC <sub>inf</sub> (μM•hr) | 3288 (1028) <sup>d</sup>                  | 6120 (2040)  | 5430 (1140)  |
|         | t <sub>1/2</sub> (hr)      | 10.7 (3.8)                                | 24.1 (8.5)   | 30.1 (13.4)  |

AUC<sub>inf</sub> = area under the plasma concentration-time curve from time zero to infinity; C<sub>max</sub> = maximum plasma drug concentration; t<sub>1/2</sub> = terminal half-life; T<sub>max</sub> = time of maximum plasma drug concentration.

<sup>a</sup> Mean ± SD age: 27.3 ± 6.4 years.

<sup>b</sup> Mean ± SD age: 65.8 ± 8.1 years.

<sup>c</sup> Mean ± SD age: 64.9 ± 5.6 years.

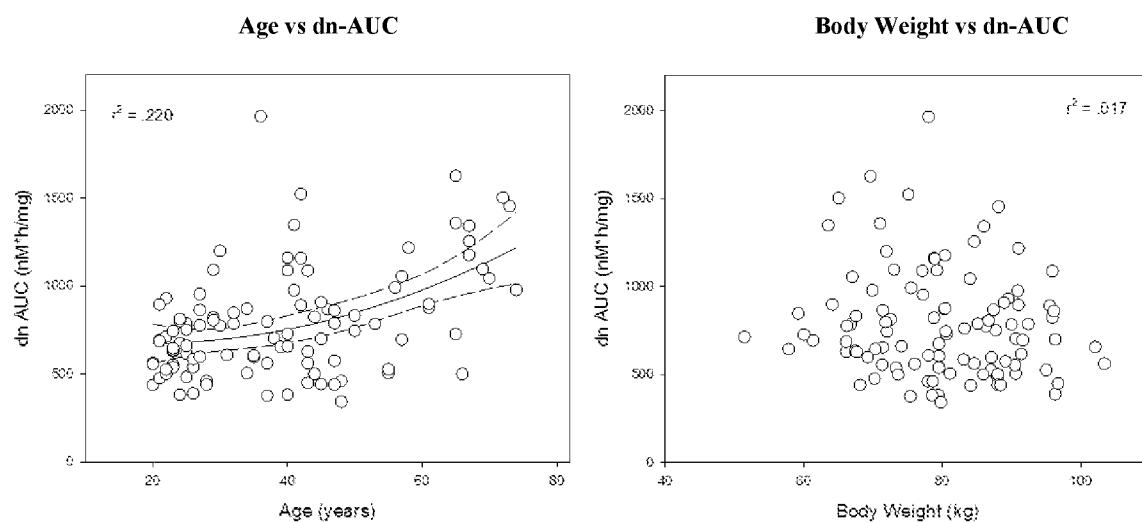
<sup>d</sup> The C<sub>max</sub> and AUC<sub>inf</sub> values for M01 and M02 were dose-normalized to 8 mg based on exploratory assay of metabolite data from the 12 mg dose of CX-8998 in Study PN001/Part I.

Source: CX-8998 Simulations Memo, 26 June 2018.

A meta-analysis of data from the 4 completed Phase 1 studies (PN001, PN002, PN003, and PN005) was performed to examine the influence of age and weight on CX-8998 exposure. Given the proportionality relationship between CX-8998 dose and AUC, dose-normalized values of AUC<sub>inf</sub> (or area under the plasma concentration-time curve over the dosing interval [AUC<sub>T</sub>], where applicable), represented collectively as the dose-normalized overall exposure (dn-AUC), from 104 subjects (34 subjects in Study PN001 who were administered 1, 3, 4, 8, 12, 16, 20, or 24 mg of CX-8998, 35 subjects from Study PN002 who were administered 2, 4, 8, 12, or 18 mg of CX-8998, 28 subjects from Study PN003 who were administered 12 mg of CX-8998, and 7 subjects from Study PN005 who were administered 8 mg of CX-8998) were used.

The results of this analysis (Figure 14) show that age accounted for approximately 22% ( $r^2=0.220$ ) of the pharmacokinetic variability associated with dn-AUC of CX-8998 using second-order polynomial, with middle-aged and elderly male and female subjects exhibiting higher CX-8998 exposure levels than younger male subjects. No clear relationship was observed between body weight and dn-AUC, with body weight accounting for less than 2% ( $r^2 = 0.017$ ) of the pharmacokinetic variability of CX-8998, regardless of the model tested.

**Figure 14: Relationship Between dn-AUC of CX-8998 and Age and Body Weight (Pooled Data from Studies PN001, PN002, PN003, and PN005)**



dn-AUC = dose-normalized area under the plasma concentration-time curve.

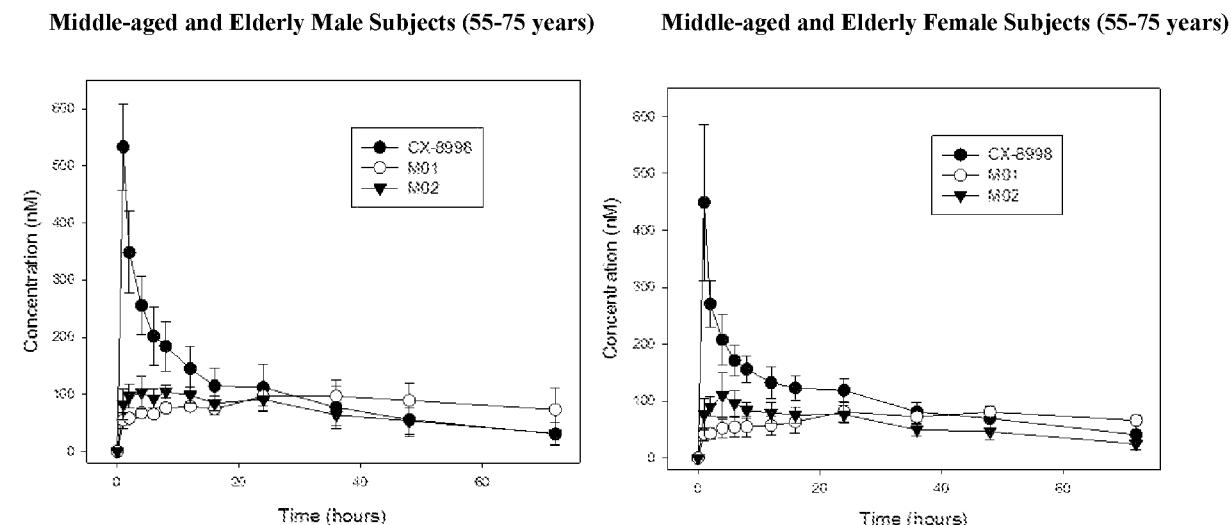
Panels illustrate the regression line and 95% confidence interval for the 2nd order polynomial ( $Y(x)=0.177*X^2-6.520*X+731$ , where  $X$  = age in years) shown in the age vs dn-AUC relationship ( $r^2=0.220$ ) and for the linear relationship ( $r^2=0.017$ ) tested between body weight and dn-AUC

The results of this meta-analysis indicate that the overall exposure levels of CX-8998 are higher in middle-aged and elderly subjects than in younger subjects, independent of the dose of CX-8998, but that body weight is not as significant contributor to the pharmacokinetic variability of CX-8998.

#### 5.2.4.2 Sex

The effects of sex on the pharmacokinetics of CX-8998 were examined by comparing plasma concentrations of CX-8998 and its metabolites (M01 and M02) after administration of an 8 mg dose of CX-8998 between middle-aged and elderly male subjects (Study PN002/Part I) and middle-aged and elderly female subjects (Study PN005). The plasma concentration profiles of CX-8998, M01, and M02 were similar in middle-aged and elderly male and female subjects, as shown in Figure 18.

**Figure 15: Mean (SD) Concentrations of CX-8998 and Metabolites (M01 and M02) in Middle-Aged and Elderly Male (Study PN002/Part I) and Middle-Aged and Elderly Female (Study PN005) Subjects After a Single 8 mg dose of CX-8998**



Maximum exposure ( $C_{\max}$ ) of CX-8998, M01, and M02 were 18% lower, 12% lower, and 2% higher, respectively, in the middle-aged and elderly female subjects than in the middle-aged and elderly male subjects (Table 21). Overall exposure ( $AUC_{\text{inf}}$ ) of CX-8998, M01, and M02 was 12% higher, 2% lower, and 11% lower, respectively, in the middle-aged and elderly female subjects than in the middle-aged and elderly male subjects. Given the comparative plasma concentration profiles and pharmacokinetic parameters between healthy middle-aged and elderly male and female subjects, there does not appear to be any clinically important sex differences in the pharmacokinetics of CX-8998, M01, or M02.

#### 5.2.4.3 Renal or Hepatic Impairment

No studies of CX-8998 have been conducted in subjects with significant renal or hepatic impairment. CX-8998 should be used with caution in subjects with a history of renal disease (creatinine clearance  $<39$  mL/min) or hepatic disease (serum alanine aminotransferase [ALT] or aspartate aminotransferase [AST] level  $>2 \times$  upper limit of normal [ULN]).

#### 5.2.5 Drug Interactions

No clinical drug-drug interaction studies have been performed with CX-8998.

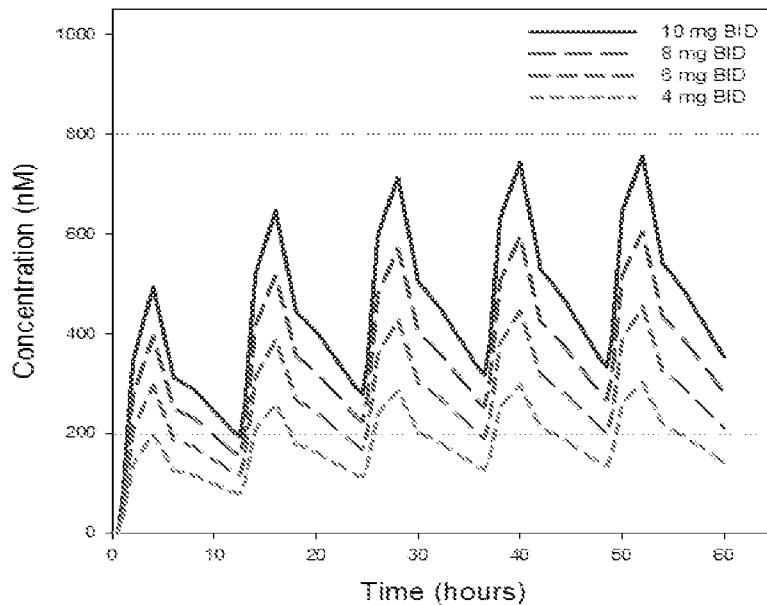
CX-8998 is metabolized principally by CYP enzymes CYP3A4 and CYP2C9. CX-8998 does not inhibit CYP3A4, CYP2C8, CYP2C9, CYP2D6, CYP1A2, CYP2C19, or CYP2B6 in human liver microsomes (concentration that produces half-maximal inhibition [ $IC_{50}$ ],  $>20-25$   $\mu$ M) and is not a time-dependent inhibitor of CYP3A4 or CYP2B6 at a concentration of 10  $\mu$ M. CX-8998 does not induce CYP3A4 but is a weak inducer of CYP2B6.

CX-8998 is not a substrate for P-glycoprotein or the BCRP and does not significantly inhibit the transport of digoxin.

### 5.2.6 Simulated Pharmacokinetic Profile of CX-8998

Modeling and simulation, using nonparametric superposition of data from a single dose of 1 mg of CX-8998 under fed conditions in healthy young male subjects (Study PN001/Part I), was performed to predict the exposure levels of CX-8998 for a clinically relevant range of BID doses of CX-8998 taken under fed conditions. The simulations were based on the assumptions that pharmacokinetic linearity would be maintained at higher doses (as shown in Study PN001/Part I; Figure 7) and that the food effect (ie, blunting of  $C_{max}$  without affecting AUC; Table 18) that was observed with the 1 mg dose would be consistent at higher doses. Simulations from first dose to steady state for the 4, 6, 8, and 10 mg BID doses of CX-8998 predict that the  $C_{max}$  of CX-8998 for each dose would fall within the potential “target exposure range” of 200 to 800 nM (Figure 16).

**Figure 16: Simulated Pharmacokinetic Profiles of CX-8998 to Steady State After Twice-Daily Dosing Under Fed Conditions**



Simulated CX-8998 pharmacokinetic profiles, based on 1 mg doses of CX-8998 under fed conditions. The AUC values for the 4, 6, 8, and 10 mg twice-daily (BID) simulated doses correspond to the observed area under the plasma concentration-time curve (AUC) values from the once-daily (QD) doses in Study PN001/Part I.

Source: CX-8998 Simulations Memo, 26 June 2018.

Estimates of the steady-state pharmacokinetic exposure parameters ( $C_{ss}$  and  $AUC_{24}$ ) for CX-8998, M01, and M02 were derived from single-dose data in younger healthy male subjects (Study PN001/Part I), older healthy male subjects (Study PN002/Part I), and older healthy female subjects (PN005). The mean, minimum, and maximum  $C_{ss}$  values for CX-8998, M01, and M02 in younger male subjects, middle-aged and elderly male subjects, and middle-aged and elderly female subjects, as predicted from a 10 mg BID dose of CX-8998, are shown in Table 22; mean, minimum, and maximum  $AUC_{24}$  values are shown in Table 23.

**Table 22: Estimated Mean (Minimum, Maximum) Steady-State Concentration of CX-8998, M01, and M02 After Administration of CX-8998 10 mg Twice Daily Under Fasted Conditions**

| Population                    | N  | Age (Mean $\pm$ SD)  | C <sub>ss</sub> (nM) <sup>a</sup> |                     |                   |
|-------------------------------|----|----------------------|-----------------------------------|---------------------|-------------------|
|                               |    |                      | CX-8998                           | M01                 | M02               |
| Young men                     | 12 | 27.3 $\pm$ 6.4 years | 583<br>[382, 1367]                | 771<br>[352, 1105]  | 343<br>[225, 543] |
| Middle-aged and elderly men   | 6  | 65.8 $\pm$ 8.1 years | 874<br>[480, 1285]                | 1167<br>[505, 1995] | 683<br>[345, 870] |
| Middle-aged and elderly women | 7  | 64.9 $\pm$ 5.6 years | 981<br>[604, 1252]                | 1146<br>[858, 1551] | 566<br>[383, 722] |

AUC<sub>inf</sub> = area under the plasma concentration-time curve from time zero to infinity; C<sub>ss</sub> = concentration at steady state.

<sup>a</sup> C<sub>ss</sub> was derived from dose-normalized AUC<sub>inf</sub> (in Table 23). C<sub>ss</sub> = 1.25  $\times$  AUC<sub>inf</sub>  $\div$   $\tau$ , where the dosing interval ( $\tau$ ) is equal to 12 hours and 10 mg/8 mg = 1.25.

Source: CX-8998 Simulations Memo, 26 June 2018.

**Table 23: Estimated Mean (Minimum, Maximum) Steady-State AUC<sub>24</sub> of CX-8998, M01, and M02 After Administration of CX-8998 10 mg Twice Daily Under Fasted Conditions**

| Population                    | N  | Age (Mean $\pm$ SD)  | AUC <sub>24</sub> (nM*hr) <sup>a</sup> |                         |                        |
|-------------------------------|----|----------------------|--|-------------------------|------------------------|
|                               |    |                      | CX-8998                                | M01                     | M02                    |
| Young men                     | 12 | 27.3 $\pm$ 6.4 years | 13992<br>[9168, 32808]                 | 18504<br>[8448, 26520]  | 8232<br>[14496, 30048] |
| Middle-aged and elderly men   | 6  | 65.8 $\pm$ 8.1 years | 20976<br>[11520, 30840]                | 28008<br>[12120, 47880] | 15312<br>[8280, 20880] |
| Middle-aged and elderly women | 7  | 64.9 $\pm$ 5.6 years | 23544<br>[14496, 30048]                | 27504<br>[20592, 37224] | 13584<br>[9192, 17328] |

AUC<sub>24</sub> = area under the plasma concentration-time curve from time zero to 24 hours after dosing; AUC<sub>inf</sub> = area under the plasma concentration-time curve from time zero to infinity; C<sub>ss</sub> = concentration at steady state.

<sup>a</sup> Steady-state AUC<sub>24</sub> was derived from dose-normalized AUC<sub>inf</sub> (in Table 21) for a 20 mg per 24-hour dose. AUC<sub>24</sub> = 1.25  $\times$  AUC<sub>inf</sub> \* 2, where the dosing interval is twice per 24 hours and 10 mg/8 mg = 1.25.

Source: CX-8998 Simulations Memo, 26 June 2018.

## 5.3 Phase 1 Studies

### 5.3.1 Study PN001 (Two-Part Study in Healthy Male Subjects)

#### 5.3.1.1 Study PN001/Part I

##### 5.3.1.1.1 Study Design

Study PN001/Part I was randomized, double-blind, placebo-controlled, 5-period, single-, rising-dose study of the safety, tolerability, and pharmacokinetics of CX-8998 in 24 healthy male subjects aged 20 to 40 years. Two alternating panels (Panel A and Panel B) of 8 subjects each were administered single, rising doses of 1, 3, 4, 8, 12, and 16 mg of CX-8998 (6 subjects per dose level) or placebo (2 subjects per dose level) in the fasted state over 5 treatment periods. Subjects in Panel A also received 1 mg of CX-8998 or placebo with a high-fat breakfast. An additional panel of 8 subjects (Panel C), received single, rising doses of 16, 20, and 24 mg of CX-8998 or placebo over 3 treatment periods, with the same 6 subjects receiving CX-8998 and

---

the same 2 subjects receiving placebo in each treatment period. CX-8998 or placebo was taken in the morning after an overnight fast in some treatment periods and in the evening (before bedtime) after a minimum 4-hour fast after the evening meal in some periods. Safety was monitored throughout by adverse events, vital signs, and repeated clinical and laboratory evaluations.

#### **5.3.1.1.2 Treatment-Emergent Adverse Events**

Single doses up to 16 mg were generally well tolerated. Nervous system-related adverse events (eg, drowsiness, relaxation, mood changes, poor concentration, visual changes, paresthesias) were observed at doses  $\geq 3$  mg. Doses of 20 and 24 mg were less well tolerated because of poor concentration, headache, mood changes, anxiety, restlessness, and vivid dreams after evening dosing. All adverse events were mild or moderate and severity and transient. The adverse events that were reported in 2 or more subjects are summarized in Table 24.

**Table 24: Treatment-Emergent Adverse Events Reported in Two or More Subjects After Single Doses of CX-8998 (Study PN001/Part I)**

| MedDRA System Organ Class/<br>Preferred Term | Placebo<br>(N=16) | CX-8998 Dose  |                            |                 |               |               |                            |                 |                             |                              |                             |                             |                                 |
|--|-------------------|---------------|----------------------------|-----------------|---------------|---------------|----------------------------|-----------------|-----------------------------|------------------------------|-----------------------------|-----------------------------|---------------------------------|
|  |                   | 1 mg<br>(N=6) | 1 mg<br>(N=6) <sup>a</sup> | 3 mg<br>(N=6)   | 4 mg<br>(N=6) | 8 mg<br>(N=6) | 8 mg<br>(N=6) <sup>b</sup> | 12 mg<br>(N=12) | 12 mg<br>(N=6) <sup>b</sup> | 16 mg<br>(N=12) <sup>b</sup> | 20 mg<br>(N=6) <sup>b</sup> | 24 mg<br>(N=6) <sup>b</sup> | Any Dose<br>(N=22) <sup>c</sup> |
|  | n (%)             | n (%)         | n (%)                      | n (%)           | n (%)         | n (%)         | n (%)                      | n (%)           | n (%)                       | n (%)                        | n (%)                       | n (%)                       | n (%)                           |
| <b>At least 1 adverse event</b>              | 6 (37.5)          | 2 (33.3)      | 0                          | 3 (50.0)        | 1 (16.7)      | 1 (16.7)      | 5 (83.3)                   | 9 (75.0)        | 4 (66.7)                    | 9 (75.0)                     | 6 (100)                     | 6 (100)                     | 19 (86.4)                       |
| <b>Nervous System Disorders</b>              | 4 (25.0)          | 2 (33.3)      | 0                          | 0               | 0             | 1 (16.7)      | 3 (50.0)                   | 5 (41.7)        | 3 (50.0)                    | 8 (66.7)                     | 6 (100)                     | 6 (100)                     | 16 (72.7)                       |
| Headache                                     | 2 (12.5)          | 2 (33.3)      | 0                          | 0               | 0             | 0             | 1 (16.7)                   | 2 (16.7)        | 1 (16.7)                    | 4 (33.3)                     | 5 (83.3)                    | 6 (100)                     | 10 (45.5)                       |
| Concentration impaired                       | 0                 | 0             | 0                          | 0               | 0             | 0             | 0                          | 0               | 0                           | 2 (16.7)                     | 3 (50.0)                    | 3 (50.0)                    | 7 (31.8)                        |
| Drowsiness                                   | 1 (6.3)           | 0             | 0                          | 0               | 0             | 0             | 1 (16.7)                   | 1 (8.3)         | 1 (16.7)                    | 1 (8.3)                      | 2 (33.3)                    | 3 (50.0)                    | 7 (31.8)                        |
| Lethargy                                     | 1 (6.3)           | 0             | 0                          | 0               | 0             | 0             | 0                          | 1 (8.3)         | 1 (16.7)                    | 1 (8.3)                      | 2 (33.3)                    | 1 (16.7)                    | 3 (13.6)                        |
| Sensory disturbance                          | 0                 | 0             | 0                          | 0               | 0             | 0             | 0                          | 0               | 0                           | 1 (8.3)                      | 2 (33.3)                    | 0                           | 3 (13.6)                        |
| Abnormal physical sensation                  | 0                 | 0             | 0                          | 0               | 0             | 0             | 1 (16.7)                   | 0               | 0                           | 0                            | 1 (16.7)                    | 0                           | 2 (9.1)                         |
| Dizziness                                    | 0                 | 0             | 0                          | 0               | 0             | 0             | 0                          | 1 (8.3)         | 0                           | 1 (8.3)                      | 0                           | 1 (16.7)                    | 2 (9.1)                         |
| Paraesthesia                                 | 0                 | 0             | 0                          | 0               | 0             | 0             | 1 (16.7)                   | 0               | 0                           | 1 (8.3)                      | 1 (16.7)                    | 1 (16.7)                    | 2 (9.1)                         |
| <b>Psychiatric Disorders</b>                 | <b>0</b>          | <b>0</b>      | <b>0</b>                   | <b>1 (16.7)</b> | <b>0</b>      | <b>0</b>      | <b>4</b>                   | <b>4 (33.3)</b> | <b>2</b>                    | <b>8 (66.7)</b>              | <b>5 (83.3)</b>             | <b>4 (66.7)</b>             | <b>15 (68.2)</b>                |
| Vivid dreams                                 | 0                 | 0             | 0                          | 0               | 0             | 0             | 1 (16.7)                   | 0               | 2                           | 8 (66.7)                     | 2 (33.3)                    | 2 (33.3)                    | 11 (50.0)                       |
| Euphoric mood                                | 0                 | 0             | 0                          | 1 (16.7)        | 0             | 0             | 2                          | 2 (16.7)        | 0                           | 3 (25.0)                     | 3 (50.0)                    | 1 (16.7)                    | 8 (36.4)                        |
| Elevated mood                                | 0                 | 0             | 0                          | 0               | 0             | 0             | 2                          | 1 (8.3)         | 0                           | 3 (25.0)                     | 1 (16.7)                    | 0                           | 6 (27.3)                        |
| Racing thoughts                              | 0                 | 0             | 0                          | 0               | 0             | 0             | 1 (16.7)                   | 1 (8.3)         | 0                           | 2 (16.7)                     | 0                           | 1 (16.7)                    | 4 (18.2)                        |
| Indifference                                 | 0                 | 0             | 0                          | 0               | 0             | 0             | 0                          | 0               | 0                           | 2 (16.7)                     | 0                           | 0                           | 2 (9.1)                         |
| Insomnia                                     | 0                 | 0             | 0                          | 0               | 0             | 0             | 0                          | 0               | 0                           | 0                            | 1 (16.7)                    | 1 (16.7)                    | 2 (9.1)                         |

**Table 24: Treatment-Emergent Adverse Events Reported in Two or More Subjects After Single Doses of CX-8998 (Study PN001/Part I)**

| MedDRA System Organ Class/<br>Preferred Term                | Placebo<br>(N=16) | CX-8998 Dose  |                            |               |               |               |                            |                 |                             |                              |                             |                             |                                 |
|---|-------------------|---------------|----------------------------|---------------|---------------|---------------|----------------------------|-----------------|-----------------------------|------------------------------|-----------------------------|-----------------------------|---------------------------------|
|   |                   | 1 mg<br>(N=6) | 1 mg<br>(N=6) <sup>a</sup> | 3 mg<br>(N=6) | 4 mg<br>(N=6) | 8 mg<br>(N=6) | 8 mg<br>(N=6) <sup>b</sup> | 12 mg<br>(N=12) | 12 mg<br>(N=6) <sup>b</sup> | 16 mg<br>(N=12) <sup>b</sup> | 20 mg<br>(N=6) <sup>b</sup> | 24 mg<br>(N=6) <sup>b</sup> | Any Dose<br>(N=22) <sup>c</sup> |
|   | n (%)             | n (%)         | n (%)                      | n (%)         | n (%)         | n (%)         | n (%)                      | n (%)           | n (%)                       | n (%)                        | n (%)                       | n (%)                       | n (%)                           |
| <b>General Disorders and Administration Site Conditions</b> | 2 (12.5)          | 0             | 0                          | 1 (16.7)      | 1 (16.7)      | 0             | 1 (16.7)                   | 7 (58.3)        | 0                           | 7 (58.3)                     | 4 (66.7)                    | 3 (50.0)                    | 15 (68.2)                       |
| Relaxed   | 1 (6.3)           | 0             | 0                          | 0             | 0             | 0             | 0                          | 4 (33.3)        | 0                           | 2 (16.7)                     | 4 (66.7)                    | 0                           | 9 (40.9)                        |
| Feeling abnormal  | 0                 | 0             | 0                          | 0             | 1 (16.7)      | 0             | 1 (16.7)                   | 2 (16.7)        | 0                           | 0                            | 0                           | 1 (16.7)                    | 4 (18.2)                        |
| Fatigue   | 0                 | 0             | 0                          | 0             | 0             | 0             | 0                          | 0               | 0                           | 2 (16.7)                     | 0                           | 0                           | 2 (9.1)                         |
| Floating feeling  | 0                 | 0             | 0                          | 0             | 0             | 0             | 0                          | 0               | 0                           | 1 (8.3)                      | 0                           | 1 (16.7)                    | 2 (9.1)                         |
| Hangover effect   | 0                 | 0             | 0                          | 0             | 0             | 0             | 0                          | 0               | 0                           | 2 (16.7)                     | 0                           | 0                           | 2 (9.1)                         |
| Irritability  | 0                 | 0             | 0                          | 0             | 0             | 0             | 0                          | 0               | 0                           | 1 (8.3)                      | 1 (16.7)                    | 0                           | 2 (9.1)                         |
| <b>Eye Disorders</b>  | 0                 | 0             | 0                          | 0             | 1 (16.7)      | 1 (16.7)      | 1 (16.7)                   | 1 (8.3)         | 3 (50.0)                    | 1 (8.3)                      | 1 (16.7)                    | 2 (33.3)                    | 9 (40.9)                        |
| Vision blurred  | 0                 | 0             | 0                          | 0             | 0             | 0             | 1 (16.7)                   | 0               | 0                           | 1 (8.3)                      | 1 (16.7)                    | 1 (16.7)                    | 4 (18.2)                        |
| Visual disturbance  | 0                 | 0             | 0                          | 0             | 1 (16.7)      | 1 (16.7)      | 0                          | 1 (8.3)         | 3 (50.0)                    | 0                            | 0                           | 0                           | 4 (18.2)                        |
| <b>Gastrointestinal Disorders</b>                           | 0                 | 0             | 0                          | 0             | 0             | 1 (16.7)      | 0                          | 3 (25.0)        | 1 (16.7)                    | 1 (8.3)                      | 0                           | 0                           | 4 (18.2)                        |
| Paraesthesia oral   | 0                 | 0             | 0                          | 0             | 0             | 1 (16.7)      | 0                          | 1 (8.3)         | 0                           | 0                            | 0                           | 0                           | 2 (9.1)                         |
| Paraesthesia tongue   | 0                 | 0             | 0                          | 0             | 0             | 0             | 0                          | 2 (16.7)        | 1 (16.7)                    | 0                            | 0                           | 0                           | 2 (9.1)                         |
| <b>Injury, Poisoning and Procedural Complications</b>       | 0                 | 0             | 0                          | 0             | 0             | 0             | 0                          | 0               | 0                           | 0                            | 2 (33.3)                    | 0                           | 2 (9.1)                         |
| Intoxication  | 0                 | 0             | 0                          | 0             | 0             | 0             | 0                          | 0               | 0                           | 0                            | 2 (33.3)                    | 0                           | 2 (9.1)                         |

MedDRA = Medical Dictionary for Regulatory Activities.

<sup>a</sup> CX-8998 was administered after a high-fat breakfast. All other doses were administered in a fasting state.

<sup>b</sup> CX-8998 was administered 4 hours after the evening meal. All other doses were administered in the morning.

<sup>c</sup> The “any dose” column is based on the number of subjects who received any dose of CX-8998. Subjects who experienced the same event more than once in any treatment group were counted only once for the event.

---

No serious adverse events were reported in the subjects who received CX-8998. One placebo-treated subject experienced a serious adverse event (peritonsillar abscess). The subject was admitted to the hospital for treatment with oral and intravenous antibiotics and was discontinued from the study because of this event.

#### **5.3.1.1.3 Other Safety Assessments**

No clinically important trends were observed in vital signs, safety laboratory assessments, ECG parameters, or forced expiratory volume in 1 second (FEV<sub>1</sub>) as assessed by bedside spirometry.

#### **5.3.1.1.4 Conclusions**

Single oral doses of up to 16 mg were well tolerated by the healthy male subjects in this study. Doses of 20 and 24 mg were less well tolerated due to poor concentration, headache, mood changes, anxiety, restlessness, and vivid dreams with evening dosing.

### **5.3.1.2 Study PN001/Part II**

#### **5.3.1.2.1 Study Design**

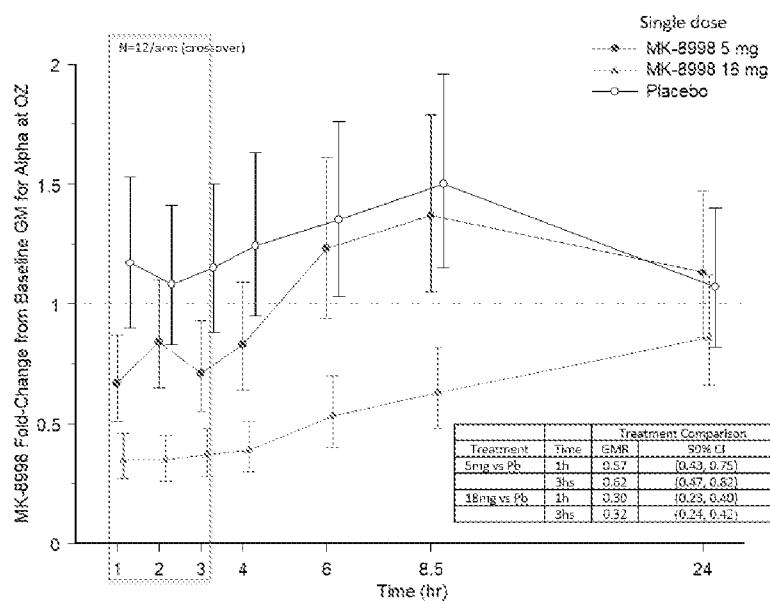
Study PN001/Part II was a randomized, double-blind, placebo-controlled, 3-period crossover study of the effects of a single dose of CX-8998 on quantitative EEG parameters in 12 awake, healthy male subjects aged 22 to 39 years. Subjects were randomized to a sequence of 3 treatments: placebo, 5 mg CX-8998, and 18 mg CX-8998. Each treatment period was separated from the previous one by an approximate 2-week washout, and all treatments were administered in the morning after an overnight fast. Electroencephalograms were recorded before and at selected time points for up to 24 hours after dosing in each treatment period. Cognitive and subjective assessments, including the Karolinska Sleepiness Scale and Bond-Lader visual analog scale, were also performed.

#### **5.3.1.2.2 Pharmacodynamic Data**

Alpha rhythm is seen posterior brain regions in healthy adults during quiet wakefulness. It originates in the thalamus and is driven by Ca<sub>v</sub>3 channel activity (Schreckenberger, 2004). Agitated, awake individuals may not display an alpha rhythm.

Analysis of awake EEGs revealed statistically significant, dose-dependent changes in EEG power density spectra in the alpha frequency band (Figure 17). Reductions in alpha power during the eyes closed position, were generally observed throughout the 24-hour postdose evaluation period for the 18 mg dose and were generally consistent across electrode sites.

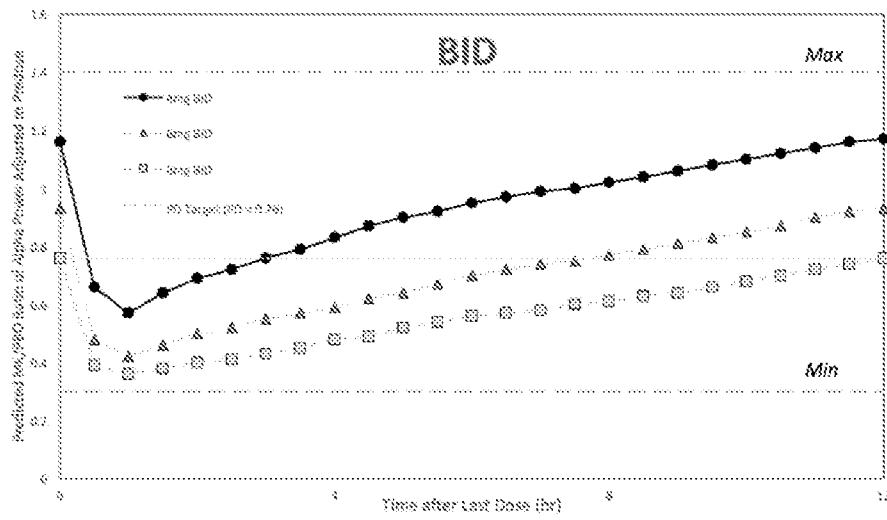
**Figure 17: Analysis of Awake EEG Absolute Power for Alpha Band (Electrode Site Oz, Eyes Closed Condition) (Study PN001/Part II)**



CI = confidence interval; EEG – electroencephalogram; GM = geometric mean; MK-8998 = CX-8998; Pb = placebo.

Dose-response analyses (Figure 18) suggested that reductions of alpha power of about 25% or greater occurred in a dose- and concentration- dependent manner at plasma CX-8998 concentrations greater than 200 to 300 nM (4 mg BID).

**Figure 18: Pharmacokinetic/Pharmacodynamic Analysis of EEG Alpha Power (Study PN001/Part II)**



BID = twice daily; EEG = electroencephalogram; MK = CX-8998; PBO = placebo; PD = pharmacodynamic.

In addition to the EEG pharmacodynamic effects, dose-dependent trends consistent with an increase in sleepiness were observed on the Bond and Lader Visual Analog Scale, the Karolinska

Sleepiness Scale, and the Cognitive Drug Research Sedation Battery (which includes reaction time tests and digit vigilance tests) after the 5 and 18 mg doses of CX-8998. The dose-dependent reductions in alpha rhythm and trends that were seen in the clinical scales are consistent with  $\text{Ca}_v3$  channel (target) engagement and serve as proof of central biological activity of CX-8998.

### 5.3.1.2.3 Safety Data

#### 5.3.1.2.3.1 Treatment-Emergent Adverse Events

Single doses of 5 and 18 mg of CX-8998 were generally well tolerated, with nervous system, psychiatric, and general disorders the most frequently reported events. The adverse events that were reported in 2 or more subjects are summarized in Table 25.

**Table 25: Treatment-Emergent Adverse Events Reported in Two or More Subjects After Single Doses of CX-8998 (Study PN001/Part II)**

| MedDRA System Organ Class/<br>Preferred Term <sup>a</sup>   | Placebo<br>(N=12) | CX-8998 Dose <sup>b</sup> |                  |
|---|-------------------|---------------------------|------------------|
|   |                   | 5 mg<br>(N=12)            | 18 mg<br>(N=12)  |
|   | n (%)             | n (%)                     | n (%)            |
| <b>At least 1 adverse event</b>                             | <b>5 (41.7)</b>   | <b>8 (66.7)</b>           | <b>11 (91.7)</b> |
| <b>Nervous System Disorders</b>                             | <b>3 (25.0)</b>   | <b>4 (33.3)</b>           | <b>8 (66.7)</b>  |
| Drowsiness  | 2 (16.7)          | 3 (25.0)                  | 3 (25.0)         |
| Headache  | 0                 | 1 (8.3)                   | 3 (25.0)         |
| Dizziness   | 0                 | 1 (8.3)                   | 3 (25.0)         |
| Intermittent headache                                       | 0                 | 0                         | 2 (16.7)         |
| <b>Psychiatric Disorders</b>                                | <b>1 (8.3)</b>    | <b>4 (33.3)</b>           | <b>6 (50.0)</b>  |
| Euphoric mood   | 0                 | 1 (8.3)                   | 3 (25.0)         |
| Sleep disturbance   | 0                 | 1 (8.3)                   | 2 (16.7)         |
| Vivid dreams  | 1 (8.3)           | 2 (16.7)                  | 2 (16.7)         |
| <b>General Disorders and Administration Site Conditions</b> | <b>0</b>          | <b>4 (33.3)</b>           | <b>5 (41.7)</b>  |
| Feeling of relaxation                                       | 0                 | 1 (8.3%)                  | 3 (25.0)         |
| Floating feeling  | 0                 | 1 (8.)                    | 1 (8.3)          |
| <b>Gastrointestinal Disorders</b>                           | <b>0</b>          | <b>2 (16.7)</b>           | <b>1 (8.3)</b>   |
| Nausea  | 0                 | 2 (16.7)                  | 1 (8.3)          |

MedDRA = Medical Dictionary for Regulatory Activities.

<sup>a</sup> Subjects who experienced the same event more than once were counted only once for the event.

<sup>b</sup> Study mediation was administered in the morning under fasting conditions.

All adverse events were mild or moderate in intensity. No serious adverse events were reported.

#### 5.3.1.2.3.2 Other Safety Assessments

No clinically important trends were observed in vital signs, safety laboratory assessments, or ECG parameters

---

### 5.3.1.2.4 Conclusions

Single doses of 5 and 18 mg were well tolerated by the healthy male subjects in this study. The awake EEGs demonstrated 25% or greater reduction in absolute power for the alpha band in a dose-dependent manner at CX-8998 concentrations of 200 to 800 nM.

## 5.3.2 Study PN002 (Two-Part Study in Healthy Male Subjects)

### 5.3.2.1 Study PN002/Part I

#### 5.3.2.1.1 Study Design

Study PN002/Part I was a randomized, double-blind, placebo-controlled, 5-period, rising-, single-dose study of the safety and pharmacokinetics of CX-8998 in 9 healthy middle-aged and elderly males (aged 55-75 years).\* Subjects were randomized to receive single oral doses of 2, 4, 8, 12, and 18 mg of CX-8998 or matching placebo after an overnight fast in Periods 1 through 5, starting with the lowest dose and proceeding to the highest dose. Within each period, allocation to treatment with CX-8998 (N=6) or placebo (N=2) was assigned according to a computer-generated randomization schedule. Treatment periods were separated by a minimum 1-week washout period after administration of the 2 mg dose in Period 1 and by a minimum 2-week washout after subsequent treatment periods. Clinical safety was monitored throughout the study by adverse events, clinical laboratory tests, vital signs, ECGs, and ECG telemetry

#### 5.3.2.1.2 Safety Data

##### 5.3.2.1.2.1 Treatment-Emergent Adverse Events

Single doses of up to 18 mg of CX-8998 were generally well tolerated. The most frequently reported adverse events were relaxation, fuzzy head, headache, lightheadedness, dizziness, and mood alteration, all of which were transient and generally mild or moderate in severity. The adverse events that were reported in 2 or more subjects are summarized in Table 26.

---

\* The study was planned to include 8 subjects. A ninth subject was randomized to replace a subject who was discontinued after Period 1 (because of a prolonged QTc interval after administration of the 2 mg dose, which was considered by the investigator to be unrelated to the study drug).

**Table 26: Treatment-Emergent Adverse Events Reported in Two or More Middle-Aged or Elderly Male Subjects After Single Doses of CX-8998 (Study PN002/Part I)**

| MedDRA System Organ Class/<br>Preferred Term <sup>a</sup>   | Placebo<br>(N=8) | CS-8998 Dose    |                 |                  |                 |                  |                  |
|---|------------------|-----------------|-----------------|------------------|-----------------|------------------|------------------|
|   |                  | 2 mg<br>N=7     | 4 mg<br>N=6     | 8 mg<br>N=6      | 12 mg<br>N=6    | 18 mg<br>N=6     | Any Dose<br>N=9  |
|   | n (%)            | n (%)           | n (%)           | n (%)            | n (%)           | n (%)            | n (%)            |
| <b>At least 1 adverse event</b>                             | <b>5 (62.5)</b>  | <b>5 (71.4)</b> | <b>5 (83.3)</b> | <b>6 (100)</b>   | <b>5 (83.3)</b> | <b>6 (100.0)</b> | <b>9 (100.0)</b> |
| <b>General Disorders and Administration Site Conditions</b> | <b>1 (12.5)</b>  | <b>2 (28.6)</b> | <b>4 (66.7)</b> | <b>4 (66.7)</b>  | <b>4 (66.7)</b> | <b>6 (100.0)</b> | <b>8 (88.9)</b>  |
| Feeling of relaxation                                       | 0                | 1 (14.3)        | 1 (16.7)        | 0                | 2 (33.3)        | 2 (33.3)         | 5 (55.6)         |
| Fuzzy head  | 0                | 0               | 1 (16.7)        | 2 (33.3)         | 0               | 2 (33.3)         | 3 (33.3)         |
| Tiredness   | 0                | 0               | 1 (16.7)        | 2 (33.3)         | 0               | 1 (16.7)         | 3 (33.3)         |
| Feeling drunk   | 0                | 0               | 0               | 0                | 1 (16.7)        | 1 (16.7)         | 2 (22.2)         |
| Feeling hot   | 0                | 0               | 0               | 2 (33.3)         | 0               | 2 (33.3)         | 2 (22.2)         |
| Feeling of warmth   | 0                | 0               | 0               | 0                | 0               | 2 (33.3)         | 2 (22.2)         |
| Floating feeling  | 0                | 1 (14.3)        | 1 (16.7)        | 1 (16.7)         | 0               | 2 (33.3)         | 2 (22.2)         |
| <b>Nervous System Disorders</b>                             | <b>2 (25.0)</b>  | <b>2 (28.6)</b> | <b>5 (83.3)</b> | <b>6 (100.0)</b> | <b>4 (66.7)</b> | <b>6 (100.0)</b> | <b>8 (88.8)</b>  |
| Headache  | 0                | 2 (28.6)        | 3 (50.0)        | 3 (50.0)         | 3 (50.0)        | 2 (33.3)         | 7 (77.8)         |
| Lightheadedness   | 0                | 0               | 1 (16.7)        | 3 (50.0)         | 0               | 1 (16.7)         | 4 (44.4)         |
| Dizziness   | 0                | 0               | 0               | 2 (33.3)         | 0               | 2 (33.3)         | 3 (33.3)         |
| Dizziness upon standing                                     | 0                | 0               | 0               | 1 (16.7)         | 0               | 1 (16.7)         | 2 (22.2)         |
| Paraesthesia of fingers                                     | 0                | 0               | 0               | 0                | 0               | 2 (33.3)         | 2 (22.2)         |
| <b>Gastrointestinal Disorders</b>                           | <b>0</b>         | <b>1 (14.3)</b> | <b>1 (16.7)</b> | <b>4 (66.7)</b>  | <b>1 (16.7)</b> | <b>3 (50.0)</b>  | <b>6 (66.7)</b>  |
| Dry mouth   | 0                | 0               | 0               | 4 (66.7)         | 1 (16.7)        | 0                | 4 (44.4)         |
| <b>Eye Disorders</b>  | <b>0</b>         | <b>0</b>        | <b>1 (16.7)</b> | <b>2 (33.3)</b>  | <b>1 (16.7)</b> | <b>2 (33.3)</b>  | <b>4 (44.4)</b>  |
| Vision blurred  | 0                | 0               | 1 (16.7)        | 1 (16.7)         | 1 (16.7)        | 0                | 3 (33.3)         |
| Visual disturbance  | 0                | 0               | 0               | 1 (16.7)         | 0               | 2 (33.3)         | 3 (33.3)         |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>      | <b>0</b>         | <b>1 (14.3)</b> | <b>1 (16.7)</b> | <b>3 (50.0)</b>  | <b>1 (16.7)</b> | <b>2 (33.3)</b>  | <b>4 (44.4)</b>  |
| Breathing difficult   | 0                | 0               | 0               | 1 (16.7)         | 0               | 2 (33.3)         | 2 (22.2)         |
| Dry throat  | 0                | 0               | 0               | 1 (16.7)         | 0               | 1 (16.7)         | 2 (22.2)         |
| Nasal congestion  | 0                | 0               | 1 (16.7)        | 1 (16.7)         | 0               | 0                | 2 (22.2)         |

MedDRA = Medical Dictionary for Regulatory Activities.

<sup>a</sup> Subjects who experienced the same event more than once were counted only once for the event.

---

No serious adverse events were reported.

### **5.3.2.1.2.2 Other Safety Assessments**

No dose-dependent effects were observed on clinical laboratories, vital signs, ECGs, or ECG telemetry.

### **5.3.2.1.3 Conclusions**

Single doses of CX-8998 ranging from 2 to 18 mg were generally well tolerated by the middle-aged and elderly male subjects (aged 55-75 years) in this study. No dose-limiting toxicity was observed even at the highest single dose of 18 mg.

## **5.3.2.2 Study PN002/Part II**

### **5.3.2.2.1 Study Design**

Study PN002/Part II was a randomized, double-blind, placebo-controlled, rising-, multiple-dose study of the safety and pharmacokinetics of multiple doses of CX-8998 in 40 healthy male subjects (aged 18-45 years). Subjects were randomized to 1 of 5 multiple-dosing treatment panels and received doses of 2, 4, 8, 12, or 18 mg of CX-8998 or placebo in Panels A, B, C, D, or E, respectively, once daily, after an overnight fast, for 7 days. Within each treatment panel, 6 subjects were randomized to CX-8998 and 2 subjects were randomized to placebo. Clinical safety was monitored throughout the study by adverse events, clinical laboratory tests, vital signs, ECGs, and ECG telemetry.

### **5.3.2.2.2 Safety Data**

#### **5.3.2.2.2.1 Treatment-Emergent Adverse Events**

Multiple doses of up to 12 mg once daily for 7 days were generally well tolerated. The most common drug-related adverse events were headache, lightheadedness, tiredness, feeling happy or pleasant, feeling emotional, tiredness, somnolence, relaxation, abnormal or vivid dreams or daydreams, and paresthesia/hypoesthesia. Adverse events of mood or perceptual disturbance were more frequent and intense at the 18 mg/day dose, and 4 of the 6 subjects who were exposed to that dose prematurely discontinued treatment because of adverse events. The adverse events that were reported in at least 2 subjects are summarized in Table 27.

**Table 27: Treatment-Emergent Adverse Events Reported in Two or More Subjects After Single Doses of CX-8998 (Study PN002/Part II)**

| MedDRA System Organ Class/<br>Preferred Term <sup>a</sup>   | Placebo<br>(N=10) | CX-8998                    |                            |                            |                             |                             |                  | Any dose<br>(N = 30) |
|---|-------------------|----------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|------------------|----------------------|
|   |                   | Panel A<br>2 mg/d<br>(N=6) | Panel B<br>4 mg/d<br>(N=6) | Panel C<br>8 mg/d<br>(N=6) | Panel D<br>12 mg/d<br>(N=6) | Panel E<br>18 mg/d<br>(N=6) |                  |                      |
|   | n                 | %                          | n                          | %                          | n                           | %                           | n                | %                    |
| <b>At least 1 adverse event</b>                             | <b>9 (90.0)</b>   | <b>4 (66.7)</b>            | <b>5 (83.3)</b>            | <b>6 (100)</b>             | <b>6 (100)</b>              | <b>6 (100)</b>              | <b>27 (90.0)</b> |                      |
| <b>General Disorders and Administration Site Conditions</b> | <b>6 (60.0)</b>   | <b>3 (50.0)</b>            | <b>5 (83.3)</b>            | <b>6 (100)</b>             | <b>6 (100)</b>              | <b>5 (83.3)</b>             |                  | <b>25 (83.3)</b>     |
| Tiredness   | 4 (40.0)          | 1 (16.7)                   | 2 (33.3)                   | 3 (50.0)                   | 5 (83.3)                    | 2 (33.3)                    |                  | 13 (43.3)            |
| Feeling of relaxation                                       | 1 (10.0)          | 0                          | 4 (66.7)                   | 1 (16.7)                   | 2 (33.3)                    | 0                           |                  | 7 (23.3)             |
| Application site erythema                                   | 1 (10.0)          | 0                          | 0                          | 3 (50.0)                   | 1 (16.7)                    | 0                           |                  | 4 (13.3)             |
| Floating feeling  | 0                 | 0                          | 1 (16.7)                   | 2 (33.3)                   | 0                           |                             |                  | 3 (10.0)             |
| Fuzzy head  | 0                 | 0                          | 1 (16.7)                   | 1 (16.7)                   | 0                           |                             | 1 (16.7)         | 3 (10.0)             |
| Spaced out  | 1 (10.0)          | 0                          | 0                          | 1 (16.7)                   | 0                           |                             | 2 (33.3)         | 3 (10.0)             |
| Application site pruritus                                   | 0                 | 0                          | 0                          | 1 (16.7)                   | 1 (16.7)                    | 0                           |                  | 2 (6.7)              |
| Feeling drunk   | 0                 | 0                          | 0                          | 0                          | 0                           |                             | 2 (33.3)         | 2 (6.7)              |
| Sensation of pressure                                       | 0                 | 0                          | 0                          | 2 (33.3)                   | 0                           |                             | 0                | 2 (6.7)              |
| <b>Nervous System Disorders</b>                             | <b>7 (70.0)</b>   | <b>1 (16.7)</b>            | <b>5 (83.3)</b>            | <b>6 (100)</b>             | <b>2 (33.3)</b>             | <b>6 (100)</b>              |                  | <b>20 (66.7)</b>     |
| Headache  | 5 (50.0)          | 1 (16.7)                   | 3 (50.0)                   | 5 (83.3)                   | 1 (16.7)                    | 4 (66.7)                    |                  | 14 (46.7)            |
| Lightheadedness   | 4 (40.0)          | 0                          | 4 (66.7)                   | 4 (66.7)                   | 0                           |                             | 1 (16.7)         | 9 (30.0)             |
| Drowsiness  | 1 (10.0)          | 0                          | 2 (33.3)                   | 1 (16.7)                   | 0                           |                             | 2 (33.3)         | 5 (15.7)             |
| Dizziness   | 0                 | 0                          | 0                          | 0                          | 1 (16.7)                    | 2 (33.3)                    |                  | 3 (10.0)             |
| Hyperactivity   | 0                 | 0                          | 0                          | 2 (33.3)                   | 1 (16.7)                    | 0                           |                  | 3 (10.0)             |
| Intermittent headache                                       | 0                 | 0                          | 1 (16.7)                   | 1 (16.7)                   | 1 (16.7)                    | 0                           |                  | 3 (10.0)             |
| Lethargy  | 0                 | 0                          | 1 (16.7)                   | 1 (16.7)                   | 0                           |                             | 1 (16.7)         | 3 (10.0)             |
| Somnolence  | 1 (10.0)          | 0                          | 1 (16.7)                   | 2 (33.3)                   | 0                           |                             | 0                | 3 (10.0)             |
| Abnormal physical sensation                                 | 0                 | 0                          | 0                          | 0                          | 0                           |                             | 2 (33.3)         | 2 (6.7)              |
| Abnormal sensation of limbs                                 | 0                 | 0                          | 0                          | 0                          | 0                           |                             | 2 (33.3)         | 2 (6.7)              |
| Heaviness of head   | 0                 | 0                          | 0                          | 0                          | 1 (16.7)                    | 1 (16.7)                    |                  | 2 (6.7)              |
| Paraesthesia generalized                                    | 0                 | 0                          | 0                          | 1 (16.7)                   | 0                           |                             | 1 (16.7)         | 2 (6.7)              |

**Table 27: Treatment-Emergent Adverse Events Reported in Two or More Subjects After Single Doses of CX-8998 (Study PN002/Part II)**

| MedDRA System Organ Class/<br>Preferred Term <sup>a</sup> | Placebo<br>(N=10) | CX-8998                    |                            |                            |                             |                             |                  | Any dose<br>(N = 30) |
|---|-------------------|----------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|------------------|----------------------|
|   |                   | Panel A<br>2 mg/d<br>(N=6) | Panel B<br>4 mg/d<br>(N=6) | Panel C<br>8 mg/d<br>(N=6) | Panel D<br>12 mg/d<br>(N=6) | Panel E<br>18 mg/d<br>(N=6) |                  |                      |
|   | n                 | %                          | n                          | %                          | n                           | %                           | n                | %                    |
| Sedation  | 0                 | 0                          | 0                          |                            | 2 (33.3)                    | 0                           | 0                | 2 (6.7)              |
| Syncope   | 0                 |                            | 1 (16.7)                   | 0                          | 0                           |                             | 1 (16.7)         | 2 (6.7)              |
| Taste change  | 0                 |                            | 0                          |                            | 1 (16.7)                    | 0                           | 1 (16.7)         | 2 (6.7)              |
| Tingling  | 0                 |                            | 1 (16.7)                   | 0                          | 1 (16.7)                    | 0                           | 0                | 2 (6.7)              |
| <b>Psychiatric Disorders</b>                              | <b>3 (30.0)</b>   | <b>1 (16.7)</b>            | <b>3 (50.0)</b>            | <b>3 (50.0)</b>            | <b>2 (33.3)</b>             | <b>6 (100)</b>              | <b>15 (50.0)</b> |                      |
| Euphoric mood   | 0                 |                            | 1 (16.7)                   | 2 (33.3)                   | 0                           |                             | 1 (16.7)         | 4 (13.3)             |
| Vivid dreams  | 2 (20.0)          | 0                          | 2 (33.3)                   | 2 (33.3)                   | 0                           |                             | 0                | 4 (13.3)             |
| Daydreaming   | 1 (10.0)          | 0                          | 0                          |                            | 1 (16.7)                    | 0                           | 2 (33.3)         | 3 (10.0)             |
| Anger   | 0                 |                            | 0                          |                            | 0                           |                             | 2 (33.3)         | 2 (6.7)              |
| Disorientation  | 0                 |                            | 1 (16.7)                   | 0                          | 0                           |                             | 1 (16.7)         | 2 (6.7)              |
| Hallucination   | 0                 |                            | 0                          |                            | 0                           |                             | 2 (33.3)         | 2 (6.7)              |
| Increased state of alertness                              | 0                 |                            | 1 (16.7)                   | 1 (16.7)                   | 0                           |                             | 0                | 2 (6.7)              |
| Mood altered  | 0                 |                            | 0                          |                            | 1 (16.7)                    | 1 (16.7)                    | 0                | 2 (6.7)              |
| Mood change   | 0                 |                            | 0                          |                            | 2 (33.3)                    | 0                           | 0                | 2 (6.7)              |
| Paranoia  | 0                 |                            | 0                          |                            | 0                           |                             | 2 (33.3)         | 2 (6.7)              |
| Sleep difficult   | 0                 |                            | 0                          |                            | 0                           |                             | 1 (16.7)         | 1 (16.7)             |
| Sleep disturbance   | 0                 |                            | 0                          |                            | 1 (16.7)                    | 0                           | 1 (16.7)         | 2 (6.7)              |
| Temporal disorientation                                   | 0                 |                            | 0                          |                            | 2 (33.3)                    | 0                           | 0                | 2 (6.7)              |
| <b>Gastrointestinal Disorders</b>                         | <b>1 (10.0)</b>   | <b>2 (33.3)</b>            | <b>1 (16.7)</b>            | <b>3 (50.0)</b>            | <b>1 (16.7)</b>             | <b>4 (66.7)</b>             | <b>11 (36.7)</b> |                      |
| Nausea  | 0                 | 2 (33.3)                   | 0                          | 1 (16.7)                   | 0                           | 2 (33.3)                    | 5 (16.7)         |                      |
| Vomiting  | 0                 | 1 (16.7)                   | 0                          | 1 (16.7)                   | 0                           | 1 (16.7)                    | 3 (10.0)         |                      |
| Dyspepsia   | 0                 | 0                          | 0                          | 2 (33.3)                   | 0                           | 0                           | 2 (6.7)          |                      |
| Hypoesthesia mouth  | 0                 | 0                          | 0                          | 0                          | 0                           | 2 (33.3)                    | 2 (6.7)          |                      |

**Table 27: Treatment-Emergent Adverse Events Reported in Two or More Subjects After Single Doses of CX-8998 (Study PN002/Part II)**

| MedDRA System Organ Class/<br>Preferred Term <sup>a</sup> | Placebo<br>(N=10) | CX-8998                    |                            |                            |                             |                             |                 | Any dose<br>(N = 30) |                 |
|---|-------------------|----------------------------|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------|----------------------|-----------------|
|   |                   | Panel A<br>2 mg/d<br>(N=6) | Panel B<br>4 mg/d<br>(N=6) | Panel C<br>8 mg/d<br>(N=6) | Panel D<br>12 mg/d<br>(N=6) | Panel E<br>18 mg/d<br>(N=6) |                 |                      |                 |
|   | n                 | %                          | n                          | %                          | n                           | %                           | n               | %                    | N (%)           |
| <b>Musculoskeletal and Connective Tissue Disorders</b>    | <b>1 (10.0)</b>   | <b>2 (33.3)</b>            | <b>0</b>                   |                            | <b>1 (16.7)</b>             | <b>1 (16.7)</b>             | <b>4 (66.7)</b> |                      | <b>8 (26.7)</b> |
| Backache  | 0                 | 0                          | 0                          |                            | 0                           | 0                           | 2 (33.3)        |                      | 2 (6.7)         |
| Sensation of heaviness                                    | 0                 | 0                          | 0                          |                            | 1 (16.7)                    | 0                           | 1 (16.7)        |                      | 2 (6.7)         |
| <b>Eye Disorders</b>                                      | <b>1 (10.0)</b>   | <b>0</b>                   | <b>1 (16.7)</b>            | <b>2 (33.3)</b>            | <b>1 (16.7)</b>             | <b>2 (33.3)</b>             | <b>6 (20.0)</b> |                      |                 |
| Visual disturbance  | 0                 | 0                          | 1 (16.7)                   | 1 (16.7)                   | 0                           | 2 (33.3)                    |                 |                      | 4 (13.3)        |
| <b>Skin and Subcutaneous Tissue Disorders</b>             | <b>0</b>          | <b>0</b>                   | <b>1 (16.7)</b>            | <b>1 (16.7)</b>            | <b>1 (16.7)</b>             | <b>3 (50.0)</b>             | <b>6 (20.0)</b> |                      |                 |
| Clamminess  | 0                 | 0                          | 0                          |                            | 1 (16.7)                    | 0                           | 1 (16.7)        |                      | 2 (6.7)         |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>    | <b>4 (40.0)</b>   | <b>1 (16.7)</b>            | <b>0</b>                   |                            | <b>3 (50.0)</b>             | <b>0</b>                    | <b>1 (16.7)</b> |                      | <b>5 (16.7)</b> |
| Sore throat   | 0                 | 1 (16.7)                   | 0                          |                            | 1 (16.7)                    | 0                           | 1 (16.7)        |                      | 3 (10.0)        |
| Nasal obstruction   | 1 (10.0)          | 1 (16.7)                   | 0                          |                            | 1 (16.7)                    | 0                           | 0               |                      | 2 (6.7)         |

MedDRA = Medical Dictionary for Regulatory Activities.

<sup>a</sup> Subjects who experienced the same event more than once were counted only once for the event.

---

One subject experienced a serious adverse event (mood swings) after administration of the first of the planned 7 daily doses of 18 mg of CX-8998 and was discontinued from treatment. An additional 3 subjects also prematurely discontinued treatment after receiving fewer than the planned 7 daily doses of 18 mg of CX-8998 because of adverse events. Narratives for these 4 subjects appear below:

**Subject 0001-1020 (mood swings)** was a 44-year-old healthy white man who reported multiple nervous system-related adverse events, including feeling spaced out, hands and feet feeling clammy, feeling drunk, legs restless, shaking all over body, not feeling happy (emotional), and feeling electrical impulses through body, after receiving a single 18 mg dose of CX-8998. Additional adverse events, including mood swings, feeling frightened, laughing intermittently, difficulty moving hands, feeling weak, enhanced taste, loss of fine sensation in fingertips, some loss of sensation at skin level (all over body), and out of body feeling, were reported as the day progressed. All adverse events were mild or moderate in severity. Most events began minutes to hours after dosing, and all had resolved by 3 days after dosing. The adverse events that the subject experienced were described as “mood swings” and led to discontinuation of dosing. The event of mood swings was classified as a serious adverse event because it resulted in prolonged inpatient monitoring in the clinical research unit.

**Subject 0001-1021 (aggression)** was a 25-year-old healthy white man who reported feeling aggressive after receiving the sixth of 7 planned 18 mg doses of CX-8998. In addition, he reported feeling angry towards another subject, feeling dizzy/drunk, intense daydreams, shaking/trembling, and sweating. All adverse events were mild in severity, and all were considered possibly related to the study drug. The last dose of CX-8998 was not administered. All adverse events resolved after discontinuation of the study drug.

**Subject 0001-1114 (emotional disorder)** was a 28-year-old healthy white man who received 18 mg of CX-8998 for 6 of the planned 7 days of treatment. The subject experienced nervous system-related events of gradually increasing severity, including lightheadedness, euphoria, tiredness, headache, hard to follow thoughts, vulnerable thoughts and emotions, feeling flat, and weak in the muscles. All adverse events were mild or moderate in severity, and all were considered possibly related to the study drug. The last dose of CX-8998 was not administered. All adverse events resolved after discontinuation of the study drug.

**Subject 0001-1115 (syncope)** was a 25-year-old healthy white man who experienced a syncopal episode, associated with nausea and vomiting, approximately 2 hours after receiving the first of 7 planned doses of 18 mg of CX-8998. Oxygen saturation and serum glucose levels were within normal limits, but the subject’s blood pressure was low at the time of the event (76/43 mmHg, with a pulse rate of 59 bpm). Telemetry monitoring showed no evidence of cardiac dysrhythmia or clinically important bradycardia. The event was judged by the investigator as moderate in severity and as probably related to the study drug. The subject was discontinued from the study because of ongoing nausea and feelings of weakness and lethargy.

An additional subject felt nauseous and fainted upon standing approximately 2 hours after the first of the 7 planned doses of 2 mg of CX-8998. His blood pressure was 131/64 mmHg, his pulse rate was 50 bpm, his oxygen saturation was 97%, and his serum glucose level was within normal limits 1 minute after fainting. The subject was not on telemetry at the time. The investigator considered the event to be a vasovagal reaction (moderate in severity) and assessed the event as unrelated to the study drug. The subject continued in the study and completed the planned 7 days of treatment.

---

---

### 5.3.2.2.2 Other Safety Assessments

No clinically important trends were observed in vital signs, safety laboratories, or ECG parameters.

### 5.3.2.3 Conclusions

Multiple oral doses of 2, 4, 8, and 12 mg administered once daily for 7 days were well tolerated by the healthy male subjects in this study. Multiple doses of 18 mg once daily were not well tolerated, with 4 of the 6 subjects discontinuing treatment because of adverse events before completing the 7-day treatment period. Based on these results, the maximum tolerated dose of CX-8998 was 12 mg when administered once daily for 7 days.

## 5.3.3 Study PN003 (Two-Part Study in Healthy Male Subjects)

### 5.3.3.1 Study Design

Study PN-003 was a multicenter, 2-part, adaptive-design, randomized, double-blind, placebo-controlled, single-dose, crossover study of the effects of CX-8998 on polysomnogram (PSG) endpoints, including slow wave activity and rapid eye movement sleep, in 28 healthy male subjects aged 40 to 80 years.

Subjects received open-label treatment with 12 mg of CX-8998, without PSG recording, in Part I/Period 1 of the study. In Part I/Periods 2 and 3, subjects received a single oral 12 mg dose of CX-8998 in one period and placebo in the other period according to a randomized, double-blind, 2-period, crossover design to compare the effects of CX-8998 with those of placebo on the PSG endpoints. A washout period of at least 2 weeks separated the treatment periods. CX-8998 or placebo was taken 30 minutes before each subject's usual bedtime (as determined by sleep diary) and 4 hours after completion of an evening meal. The PSG recordings were initiated at each subject's habitual bedtime and continued for 8 hours. In addition to PSG recordings, subjects were evaluated on the next day with subjective measures of sleep quality (Leeds Sleep Evaluation Questionnaire) and sleepiness (Karolinska Sleepiness Scale) and with cognitive and motor tasks to assess next-morning residual effects.

An interim analysis of the primary endpoint (slow wave activity in the first one-third of sleep) was performed after 24 subjects had completed Part I of the study (Section 5.3.3.1.2). The study was adaptively designed to allow a re-estimation of the sample size after the interim analysis. Based on the results of the interim analysis, the study could be stopped if the efficacy criterion (increase in slow wave activity,  $p < 0.05$ ) or futility criterion ( $p > 0.25$ ) was achieved. If neither criterion was met, a re-estimation of the sample size was specified, with the ability to enroll up to 24 additional subjects. The pharmacodynamic endpoint met the futility criterion (ie, slow wave activity in the first one-third of the sleep cycle did not increase but, in fact, decreased on average by 30%); therefore, additional subjects were not enrolled.

All 28 of the enrolled subjects completed Part I of the study and, after a washout period of at least 2 weeks, were re-randomized in Part II of the study to receive a single dose of CX-8998 (4 or 8 mg) or placebo. CX-8998 or placebo was taken 30 minutes before each subject's usual bedtime and 4 hours after completion of an evening meal. As in Part I of the study, PSG recordings were initiated at each subject's habitual bedtime and continued for 8 hours, and subjects were evaluated on the next day with subjective measures of sleep quality (Leeds Sleep

Evaluation Questionnaire) and sleepiness (Karolinska Sleepiness Scale) and with cognitive and motor tasks to assess next-morning residual effects.

### 5.3.3.1.2 Pharmacodynamic Data

Single 12 mg doses of CX-8998 significantly decreased slow wave activity in the first one-third of the night, with approximately a 30% reduction in slow wave activity relative to placebo (Table 28).

**Table 28: Observed Summary Statistics for Slow Wave Activity ( $\mu\text{V}^2/\text{Hz}$ ) during the First One-Third of the Sleep Period (Study PN003)**

| Treatment     | No. of Subjects | Raw Value |       | Geometric Mean |                | Geometric Mean Ratio |              |
|---------------|-----------------|-----------|-------|----------------|----------------|----------------------|--------------|
|               |                 | Mean      | SD    | Mean           | 95%CI          | Mean                 | 90% CI       |
| Placebo       | 24              | 43.21     | 37.68 | 37.68          | (29.58, 48.01) | 0.70                 | (0.62, 0.79) |
| CX-8998 12 mg | 24              | 30.51     | 14.23 | 26.36          | (20.69, 33.59) |                      |              |

CI = confidence interval.

Between-treatment P-value = 0.9999 (tests null hypothesis of no treatment difference versus one-sided alternative that CX-8998 > placebo).

The observed geometric mean ratio (CX-8998 12 mg/placebo) of fold-change from baseline was 0.70 with a 90% confidence interval (0.62, 0.79), and the corresponding p-value was 0.9999 (tests the null hypothesis of no treatment difference versus one-sided alternative that CX-8998 > placebo).

### 5.3.3.1.3 Safety Data

#### 5.3.3.1.3.1 Treatment-Emergent Adverse Events

Single doses up to 12 mg of CX-8998 were generally well tolerated in this study. All reported adverse experiences were temporary and generally of mild intensity. The adverse events that were reported in at least 2 subjects after administration of CX-8998 (Parts I and II) are summarized in Table 29.

**Table 29: Treatment-Emergent Adverse Events Reported in Two or More Subjects After Single Doses of CX-8998 (Study PN003/Part I and Part II)**

| MedDRA System Organ Class/<br>Preferred Term <sup>a</sup> | Placebo<br>(N=30) <sup>b</sup> | CX-8998 Dose                |                            |                              |                                 |
|---|--------------------------------|-----------------------------|----------------------------|------------------------------|---------------------------------|
|   |                                | 4 mg<br>(N=12) <sup>b</sup> | 8 mg<br>(N=9) <sup>b</sup> | 12 mg<br>(N=54) <sup>b</sup> | Any Dose<br>(N=75) <sup>b</sup> |
|   |                                | n (%)                       | n (%)                      | n (%)                        | n (%)                           |
| <b>At least 1 adverse event</b>                           | <b>11 (36.7)</b>               | <b>4 (33.3)</b>             | <b>2 (22.2)</b>            | <b>27 (50.0)</b>             | <b>33 (44.0)</b>                |
| <b>Psychiatric Disorders</b>                              | <b>1 (3.3)</b>                 | <b>3 (25.0)</b>             | <b>0</b>                   | <b>14 (25.9)</b>             | <b>17 (22.7)</b>                |
| Hallucinations visual                                     | 0                              | 2 (16.7)                    | 0                          | 2 (3.7)                      | 4 (5.3)                         |
| Vivid dreams  | 1 (3.3)                        | 0                           | 0                          | 4 (7.4)                      | 4 (5.3)                         |
| Disorientation  | 0                              | 0                           | 0                          | 3 (5.6)                      | 3 (4.0)                         |
| Insomnia  | 0                              | 1 (8.3)                     | 0                          | 2 (3.7)                      | 3 (4.0)                         |
| <b>Nervous System Disorders</b>                           | <b>2 (6.7)</b>                 | <b>2 (16.7)</b>             | <b>1 (11.1)</b>            | <b>12 (22.2)</b>             | <b>15 (20.0)</b>                |
| Headache  | 1 (3.3)                        | 1 (8.3)                     | 0                          | 8 (14.8)                     | 9 (12.0)                        |
| Somnolence  | 0                              | 1 (8.3)                     | 1 (11.1)                   | 4 (7.4)                      | 6 (8.0)                         |
| <b>Gastrointestinal Disorders</b>                         | <b>4 (13.4)</b>                | <b>1 (8.3)</b>              | <b>1 (11.1)</b>            | <b>5 (9.3)</b>               | <b>7 (9.3)</b>                  |
| Dry mouth   | 2 (6.7)                        | 0                           | 0                          | 2 (3.7)                      | 2 (2.7)                         |
| Nausea  | 0                              | 1 (8.3)                     | 0                          | 1 (1.9)                      | 2 (2.7)                         |

MedDRA = Medical Dictionary for Regulatory Activities.

<sup>a</sup> Only events that were reported in 2 or more subjects who were exposed to CX-8998 are included in the table.

<sup>b</sup> N = the number of exposures to study drug, not the number of subjects. Subjects in each column were considered individual observations. Subjects who experienced the same event more than once during an exposure were counted only once; however, if a subject experienced the same event in multiple exposures, the event was counted for each exposure.

The visual and/or auditory disturbances or hallucinations (reported after single evening doses of 4 or 12 mg of CX-8998) were typically described as seeing geometric shapes, colors, lights, and/or movement and hearing tones like from a telephone or electronic music. The visual disturbances tended to cease with eye opening and to recur with eye closure and were generally not disturbing to the subjects. The study treatments were administered 30 minutes before the subject's usual bedtime, and the visual and/or auditory disturbances or hallucinations usually had an onset of approximately 30 minutes after dosing (generally near T<sub>max</sub>) and resolved within minutes or during the night.

No serious adverse events were reported, and none of the subjects discontinued treatment because of an adverse event. Four subjects did not complete all 4 treatment periods for the following reasons: withdrawal of consent after Period 1 (1 subject), withdrawal by sponsor after Period 2 because the enrollment goal had been met (1 subject), withdrawal after Period 3 because the study objective had been met (1 subject), and vomiting after administration of the 12 mg dose resulting in low exposure to study drug (1 subject).

### 5.3.3.1.3.2 Other Safety Assessments

No clinically significant trends in safety laboratory parameters or vital signs were observed. One of the 9 exposures at the 8 mg dose (11.1% of exposures) and 3 of the 54 exposures at the 12 mg dose (5.6% of exposures) resulted in an increase from baseline of  $\geq 30$  and  $\leq 60$  msec in QTc interval. No changes of  $\geq 60$  msec from baseline occurred, and no subject has a QTc interval  $\geq 500$  msec.

---

### 5.3.3.1.4 Conclusions

Single doses of 4, 8, and 12 mg of CX-8998 were well tolerated. The most common adverse events were headache, vivid dreams, and visual and/or auditory disturbances or hallucinations (typically described as seeing geometric shapes, colors, lights, and/or movement and hearing tones like from a telephone or electronic music). A decrease of 30% in slow wave activity, delayed sleep onset, and decreased sleep maintenance were observed after single 12 mg doses of CX-8998. The hypothesis that slow wave activity would increase after administration of CX-8998 was not met. The pattern observed with a single 12 mg dose of CX-8998 dose was not consistent with a beneficial effect on sleep onset and maintenance.

### 5.3.4 Study PN005 (Single-Dose Study in Healthy Female Subjects)

#### 5.3.4.1.1 Study Design

Study PN005 was a randomized, double-blind, placebo-controlled, single-dose study of the safety, tolerability, and pharmacokinetics of CX-8998 in 9 middle-aged and elderly female subjects (aged 55-75 years). Subjects were randomized to receive either a single oral 8 mg dose of CX-8998 (N=7) or placebo (N=2) after an overnight fast. Clinical safety was monitored throughout the study by adverse events, clinical laboratory tests, vital signs, ECGs, and ECG telemetry.

#### 5.3.4.1.2 Safety Data

##### 5.3.4.1.2.1 Treatment-Emergent Adverse Events

Single 8 mg doses of CX-8998 were generally well tolerated by the healthy middle-aged and elderly women in this study. Psychiatric-related events, including mild laughing (2 subjects), nervousness (1 subject), racing thoughts (1 subject), and annoyed (1 subject), were the most commonly reported adverse events after administration of CX-8998. The adverse events that were reported during the study are summarized in Table 30.

**Table 30: Treatment-Emergent Adverse Events Reported in After a Single Dose of CX-8998 in Middle-Aged and Elderly Female Subjects (Study PN005)**

| MedDRA System Organ Class/<br>Preferred Term <sup>a</sup>   | Placebo<br>(N=2) | CX-8998 8 mg<br>(N=7) |
|---|------------------|-----------------------|
|   | n (%)            | n (%)                 |
| <b>At least 1 adverse event</b>                             | 0                | 6 (85.7)              |
| <b>Psychiatric Disorders</b>                                | 0                | 4 (57.1)              |
| Inappropriate laughter                                      | 0                | 2 (28.6)              |
| Nervousness   | 0                | 1 (14.3)              |
| Racing thoughts   | 0                | 1 (14.3)              |
| <b>Gastrointestinal Disorders</b>                           | 0                | 3 (42.9)              |
| Dry mouth   | 0                | 1 (14.3)              |
| Hypoaesthesia oral  | 0                | 1 (14.3)              |
| Nausea  | 0                | 1 (14.3)              |
| Vomiting  | 0                | 1 (14.3)              |
| <b>Eye Disorders</b>  | 0                | 1 (14.3)              |
| Vision blurred  | 0                | 1 (14.3)              |
| <b>General Disorders and Administration Site Conditions</b> | 0                | 1 (14.3)              |
| Irritability  | 0                | 1 (14.3)              |
| <b>Infections and Infestations</b>                          | 0                | 1 (14.3)              |
| Shingles  | 0                | 1 (14.3)              |
| <b>Investigations</b>                                       | 0                | 1 (14.3)              |
| Alanine aminotransferase increased                          | 0                | 1 (14.3)              |
| <b>Vascular Disorders</b>                                   | 0                | 1 (14.3)              |
| Hot flush   | 0                | 1 (14.3)              |

MedDRA = Medical Dictionary for Regulatory Activities.

<sup>a</sup> Subjects who experienced the same event more than once were counted only once for the event.

No serious adverse events were reported.

#### 5.3.4.1.2.2 Other Safety Assessments

No clinically important trends were observed in vital signs, safety laboratories, or ECG parameters.

One subject had an elevated value for serum ALT at 1 and 4 days after administration of CX-8998 (from 28 IU/L at baseline, to 41 IU/L at 1 day after dosing, to 59 IU/L at 4 days after dosing; reference range, 6-40 IU/L), which the investigator assessed as possibly related to the study drug. Values for serum AST, alkaline phosphatase, and bilirubin were within normal limits at each evaluation, and the subject's serum ALT value had returned to within normal limits by 2 weeks after dosing.

#### 5.3.4.1.3 Conclusions

A single 8 mg dose of CX-8998 was well tolerated by the middle-aged and elderly women (aged 55-75 years) in this study.

---

## 5.4 Phase 2 Studies

### 5.4.1 Study PN004 (Acutely Psychotic Patients With Schizophrenia)

#### 5.4.1.1 Study Design

Study PN004 was a Phase 2A, 4-week, multicenter, randomized, double-blind (with in-house blinding), placebo- and active-controlled, parallel-group study to evaluate the safety and efficacy of CX-8998 in acutely psychotic patients with schizophrenia. Subjects completed a placebo lead-in period and were then randomized in a 2:2:1 ratio to receive:

- CX-8998 6 mg BID orally with food on Days 1 to 7 and then 8 mg of CX-8998 BID on Days 8 to 28 (N=86), with a reduction in dose to 6 mg BID on Day 9 or after, at the discretion of the investigator, based on individual subject tolerability,
- placebo BID on Days 1 through 28 (N=83), or
- olanzapine 5 mg BID on Days 1 to 7 and then 5 mg in the morning and 10 mg in the evening on Days 8 to 28 (N=47).

The primary efficacy endpoint was the mean change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 4; secondary efficacy endpoints included responder rates on the PANSS total score at Week 4 and the change from baseline in the Clinical Global Impressions – Severity of Illness Scale at Week 4. Safety was monitored by adverse events, laboratory evaluations, ECGs, Holter monitoring, vital signs, the Simpson-Angus Scale, the Barnes Akathisia Rating Scale, the Abnormal Involuntary Movement Scale, and the Columbia Suicide-Severity Rating scale (C-SSRS).

#### 5.4.1.2 Efficacy Data

No statistically significant differences were observed between CX-8998 or the active comparator olanzapine and placebo on the primary efficacy endpoint of the mean change from baseline in the PANSS total score at Week 4 or on any of the secondary endpoints.

#### 5.4.1.3 Safety Data

##### 5.4.1.3.1 Treatment-Emergent Adverse Events

Psychiatric-, nervous system-, and gastrointestinal-related adverse events were the most commonly reported events after administration of CX-8998; however, only insomnia was reported at a frequency of  $\geq 5$  in the CX-8998 treatment group. The adverse events that were reported in at least 2 subjects during the study are summarized in Table 31.

**Table 31: Treatment-Emergent Adverse Events Reported in Two or More Subjects With Schizophrenia (Study PN004)**

| MedDRA Preferred Term <sup>a</sup> | Treatment Group  |                   |                  |
|------------------------------------|------------------|-------------------|------------------|
|                                    | CX-8998 (N=86)   | Olanzapine (N=47) | Placebo (N=83)   |
| <b>At least 1 adverse event</b>    | <b>41 (47.7)</b> | <b>23 (48.9)</b>  | <b>33 (39.8)</b> |
| Insomnia                           | 13 (15.1)        | 5 (10.6)          | 7 (8.4)          |
| Schizophrenia                      | 3 (3.5)          | 1 (2.1)           | 1 (1.2)          |
| Anxiety                            | 2 (2.3)          | 0 (0.0)           | 0 (0.0)          |
| Chronic pharyngitis                | 2 (2.3)          | 0 (0.0)           | 0 (0.0)          |
| Dizziness                          | 2 (2.3)          | 1 (2.1)           | 0 (0.0)          |
| Headache                           | 2 (2.3)          | 3 (6.4)           | 3 (3.6)          |
| Rhinopharyngitis                   | 2 (2.3)          | 0 (0.0)           | 0 (0.0)          |
| Sinus tachycardia                  | 2 (2.3)          | 3 (6.4)           | 1 (1.2)          |
| Somnolence                         | 2 (2.3)          | 3 (6.4)           | 1 (1.2)          |

MedDRA = Medical Dictionary for Regulatory Activities.

<sup>a</sup> Subjects who experienced the same event more than once were counted only once for the event.

Dizziness and vertigo were reported in 4 of the 86 subjects (4.7%). Review of Holter monitoring reports for these subjects did not reveal any data to confirm clinically significant rhythm abnormalities or bradycardia that could have been the reason for the dizziness and vertigo. The dizziness and vertigo resolved spontaneously in all 4 subjects and did not require administration of concomitant therapies. The subjects did not discontinue treatment with CX-8998 because of these events.

No serious adverse events were reported among the CX-8998-treated subjects. Nine of the CX-8998-treated subjects (10.5%), compared with 1 of the placebo-treated subjects (1.2%), discontinued treatment because of adverse events; however, 4 of the 9 discontinuations in the CX-8998 treatment group were due to worsening of schizophrenia. Narratives for the CX-8998-treated subjects who discontinued treatment because of adverse events are provided below:

**Subject 0006-00007 (generalized weakness)** was a 55-year-old white man in the CX-8998 treatment group who was diagnosed with schizophrenia at age 22 years and who had 4 prior psychiatric hospitalizations. The subject was a previous cigarette smoker but had no history of substance abuse. The first dose of CX-8998 (6 mg) was taken on 11 December 2009. The subject reported generalized weakness beginning on 18 December 2009, and treatment with the study drug was discontinued. The adverse event resolved on 21 December 2009. The investigator assessed the adverse event as moderate in intensity and related to the study drug. No other adverse events were reported for this subject.

**Subject 0013-00002 (general tonic-clonic seizure)** was a 33-year-old white man in the CX-8998 treatment group who was diagnosed with schizophrenia at age 13 years and who had 5 prior psychiatric hospitalizations. The subject had no history of tobacco use or substance abuse. The first dose of study drug (6 mg) was taken on 02 June 2009. The subject had an adverse event of generalized tonic-clonic seizure on 11 June 2009, which resolved on the same day. Study drug was discontinued. The investigator classified the adverse event as severe in intensity and related to the study drug. The subject also had an adverse event of insomnia on 07 June 2009 (moderate in intensity and not related to the study drug).

---

**Subject 0014-00007 (right bundle branch block)** was a 22-year-old white man who was diagnosed with schizophrenia at age 15 years and who had 3 prior psychiatric hospitalizations. The subject was a current cigarette smoker but had no history of substance abuse. At the screening visit (Day -9), his ECG showed “rSr in V1” and a QRS duration of 103 msec. Prior to the placebo run-in dosing on Day-3, his ECG showed sinus tachycardia (heart rate, 95 bpm; QRS duration, 104 msec) and intraventricular conduction defect (machine interpretation). The first dose of CX-8998 (6 mg) was taken on 19 October 2009. The subject had adverse event of right bundle branch block on 22 October 2009, with a QRS duration of 144 msec. Study drug was discontinued on 23 October 2009. An ECG on 26 October 2009 showed resolution of the adverse event, with a QRS duration of 88 msec. The investigator classified the adverse event as mild in intensity and related to the study drug. No other adverse events were reported for this subject.

**Subject 0017-00005 (electrocardiogram QTc interval prolonged)** was a 49-year-old white woman in the CX-8998 treatment group who was diagnosed with schizophrenia at age 40 years and who had 7 prior psychiatric hospitalizations. The subject had no history of tobacco use or substance abuse. At screening (Day -8), her QT interval was measured with lead V5 (because of lead misplacement), and the following values were recorded: QTcF interval, 420 msec; QTcB interval, 422 msec; and heart rate, 62 bpm. On the day before dosing (Day -1), her ECG showed a QTcF interval of 452 msec, a QTcB interval of 439 msec, and a heart rate of 51 bpm. After administration of the first dose of CX-8998 (6 mg) on 16 July 2009, an ECG showed a QTcF interval of 458 msec, a QTcB interval of 441 msec, and a heart rate of 48 bpm, which were comparable to the measurements on Day -1. This was reported as adverse event of QTcF prolongation (mild, related to study drug) and sinus bradycardia (mild, related to study drug). An ECG on Day 4 showed a QTcF interval of 454 msec, a QTcB interval of 448 msec, and a heart rate of 55 bpm. Another ECG on Day 6 showed that the subject had a prolonged QTc interval, with a QTcF interval of 483 msec, a QTcB interval of 477 msec, and a heart rate of 56 bpm. Prolonged QTc interval was reported as an adverse event (moderate, related to study drug), and the study drug was discontinued. This adverse event resolved on 23 July 2009 (QTcF interval, 440 msec; QTcB interval, 432 msec; and heart rate, 54 bpm). The subject also experienced the following adverse events: QTcF prolongation on 16 July 2009 (mild, resolved 21 July 2009, related to study drug); sinus bradycardia on 16 July 2009 (mild, resolved 20 Jul 2009, related to study drug); venipuncture site hematoma on 22 July 2009 (mild, resolved, not related to study drug); red blood cell count decreased on 22 Jul 2009 (mild, resolved 28 July 2009, related to study drug); decreased hemoglobin on 22 July 2009 (mild, resolved 28 July 2009, related to study drug); and decreased hematocrit on 22 July 2009 (mild, resolved 28 July 2009, related to study drug).

**Subject 0017-0008 (schizophrenia)** was a 43-year-old white woman in the CX-8998 treatment group who was diagnosed with schizophrenia at age 24 years and who had 10 prior psychiatric hospitalizations. The subject had no history of tobacco use or substance abuse. The first dose of study drug (6 mg) was taken on 24 September 2009. The subject had an adverse event of schizophrenia (investigator term: worsening schizophrenia) on 15 October 2009, which resolved on 20 October 2009. Study drug was discontinued on 06 October 2009. The investigator classified the adverse event as moderate in intensity and related to the study drug. The subject also had an adverse event of (worsening) schizophrenia on 01 October 2009 (mild, resolved 04 October 2009, related to study drug).

**Subject 0019-00008 (schizophrenia)** was a 43-year-old white male in the CX-8998 treatment group who was diagnosed with schizophrenia at age 26 years and who had 12 prior psychiatric hospitalizations. The subject was a current cigarette smoker but had no history of substance abuse. The first dose of study drug (6 mg) was taken on 22 September 2009. The subject had an adverse event of schizophrenia (investigator term: worsening schizophrenia) on

---

30 September 2009, which resolved on 12 October 2009. The subject was discontinued from the study. The investigator classified the adverse event as moderate in intensity and not related to the study drug. The subject also had an adverse event of insomnia on 22 September 2009 (mild, resolved 14 October 2009, not related to the study drug).

**Subject 0019-00009 (schizophrenia)** was a 41-year-old white woman in the CX-8998 treatment group who was diagnosed with schizophrenia at age 24 years and who had 6 prior psychiatric hospitalizations. The subject had no history of tobacco use or substance abuse. The first dose of study drug (6 mg) was taken on 01 October 2009. The subject had an adverse event of schizophrenia (investigator term: worsening schizophrenia) on 19 October 2009, which resolved on 31 October 2009. The subject was discontinued from the study. The investigator classified the adverse event as moderate in intensity and not related to the study drug. The subject also had an adverse event of insomnia on 25 September 2009 (mild, resolved 25 October 2009, not related to study drug).

**Subject 0020-00002 (psychomotor excitability)** was 23-year-old white man in the CX-8998 treatment group who was diagnosed with schizophrenia at age 19 years and who had 5 prior psychiatric hospitalizations. The subject was a current cigarette smoker but had no history of substance abuse. The first dose of study drug (6 mg) was taken on 01 October 2009. The subject had an adverse event of psychomotor excitability on 25 October 2009, which was resolved on 24 December 2009. The subject was discontinued from the study. The investigator classified the adverse event as moderate in intensity and not related to the study drug. No other adverse events were reported for this subject.

**Subject 0021-00006 (schizophrenia)** was a 43-year-old white man in the CX-8998 treatment group who was diagnosed with schizophrenia at age 22 years and who had 10 prior psychiatric hospitalizations. The subject had no history of tobacco use or substance abuse. The first dose of study drug (6 mg) was taken on 27 October 2009. The subject had an adverse event of acute schizophrenic episode on 20 November 2009, which was resolved on 24 December 2009. The subject was discontinued from the study. The investigator classified the adverse event as mild in intensity and related to the study drug. No other adverse events were reported for this subject.

#### 5.4.1.3.2 Other Safety Assessments

No clinically important trends were observed in vital signs, safety laboratories, or ECG parameters.

#### 5.4.1.4 Conclusions

CX-8998 was well tolerated by the acutely psychotic subjects with schizophrenia who participated in this study when administered in doses of 8 mg BID according to a titration dosing regimen (6 mg BID for 7 days, increased to 8 mg BID for 21 days). Psychiatric- and nervous system-related events were the most commonly reported, but only insomnia was reported in  $\geq 5\%$  of the CX-8998-treated subjects. The results of the study did not provide evidence to suggest that CX-8998 provides improvement in schizophrenia, as measured by the primary endpoint of the change in the PANSS total score at Week 4 or any of the secondary efficacy endpoints.

### 5.4.2 Ongoing Studies

#### 5.4.2.1 Study CX-8998-CLN2-001 (T-CALM; Patients With Essential Tremor)

Study CX-8998-CLN2-001 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-titration study to assess the efficacy and safety of CX-8998 in doses up

---

to 10 mg BID for reducing the severity of tremor (as assessed by The Essential Tremor Rating Assessment Scale [TETRAS] and Kinesia ONE accelerometry) associated with essential tremor. The study included a screening period of up to 4 weeks; a 4-week, double-blind, dose-titration, treatment period; a 1-week follow-up period after the last dose of study medication; and a follow-up phone call 1 week later. Up to 106 subjects were to be randomized in a 1:1 ratio to receive CX-8998 or placebo. Subjects who were randomized to CX-8998 were to receive 4 mg of CX-8998 BID in Week 1 (8 mg/day), 8 mg of CX-8998 BID in Week 2 (16 mg/day), and 10 mg of CX-8998 BID in Weeks 3 and 4 (20 mg/day); subjects who were randomized to placebo were to receive the corresponding number of placebo capsules. Safety assessments included adverse events, laboratory assessments, vital signs, ECGs, C-SSRS, and the Epworth Sleepiness Scale. As of the date of this document (27 June 2018), the study had been completed in the clinic, with 95 subjects randomized.

#### **5.4.2.2 Study CX-8998-CLN2-002 (T-WAVE; Patients With Generalized Epileptic Syndromes With Absence Seizures)**

Study CX-8998-CLN2-002 is an ongoing Phase 2A, multicenter, open-label, dose-titration study to assess the safety, tolerability, and efficacy of CX-8998 in doses up to 10 mg BID in adolescents and young adults (aged 16-55 years) with generalized epileptic syndromes with absence seizures. The study includes a screening period of up to 4 weeks; a 4-week, double-blind, dose-titration, treatment period; and a 1-week follow-up period after the last dose of study medication. Up to 15 subjects will be enrolled. Subjects will receive 2 mg of CX-8998 BID on Days 1 and 2, 4 mg of CX-8998 BID on Days 3 through 8, 6 mg of CX-8998 BID on Days 9 through 14, 8 mg of CX-8998 BID on Days 15 through 20, 10 mg of CX-8998 BID on Days 21 through 26, and then 10 mg of CX-8998 in the morning on Day 27. Safety assessments include adverse events, laboratory assessments, vital signs, and ECGs.

#### **5.4.3 Planned Studies**

##### **5.4.3.1 Study CX-8998-CLN2-001, Open-label Digital Substudy #2**

Study CX-8998-CLN2-001, Open-label Digital Substudy #2 is a component of the primary T-CALM essential tremor study (CX-8998-CLN2-001; Section 5.4.2.1). The study is designed to assess the utility of digital assessment tools in the objective measurement of PDT using a schedule of assessments like that used in the primary T-CALM essential tremor study. Three digital tools will be assessed: 1) the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPRDS), 2) the iMotor application, and 3) a continuous wearable tremor monitoring device (optional assessment based on availability of the devices). The purpose of the study is to identify the most appropriate PDT-specific digital monitoring biomarker(s) before initiation of the study CX-8998-CLN2-003 (Section 5.4.3.2). Specifically, this study will initiate the process of digital drug development tool (dDDT) evaluation by exploring the following:

- correlations between clinical measures and the biometric monitoring tool parameters,
- correlations among biometric monitoring tool variables, and
- the ability of the different biometric monitoring tools to detect treatment effects.

---

Approximately 12 subjects with PDT will be recruited for the digital substudy. Subjects will receive 4 mg of CX-8998 BID in Week 1 (8 mg/day), 8 mg of CX-8998 BID in Week 2 (16 mg/day), and 10 mg of CX-8998 BID in Weeks 3 and 4 (20 mg/day).

#### **5.4.3.2      Study CX-8998-CLN2-003 (T-CALM-PDT; Patients With Parkinson's Disease Tremor)**

Study CX-8998-CLN2-003 is a planned, Phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-titration study to assess the efficacy and safety of CX-8998 in doses up to 10 mg BID for reducing the severity of PDT (as assessed by the MDS-UPRDS, TETRAS, and Kinesia ONE accelerometry). The study includes a screening period of up to 4 weeks; a 4-week, double-blind, dose-titration, treatment period; a 1-week follow-up period after the last dose of study medication; and a follow-up phone call 3 weeks later. Up to 60 subjects will be randomized to receive CX-8998 or placebo. Subjects who are randomized to CX-8998 will receive 4 mg of CX-8998 BID in Week 1 (8 mg/day), 8 mg of CX-8998 BID in Week 2 (16 mg/day), and 10 mg of CX-8998 BID in Weeks 3 and 4 (20 mg/day); subjects who are randomized to placebo will receive the corresponding number of placebo capsules. Safety assessments include adverse events, laboratory assessments, vital signs, ECGs, C-SSRS, and the Epworth Sleepiness Scale.

**WHAT IS CLAIMED IS:**

1. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof,

wherein the dosage form comprises a controlled release component comprising said Cav3 antagonist, and wherein the dosage form optionally contains an immediate release component comprising said Cav3 antagonist;

wherein said oral dosage form, when administered a human of about 35 years of age or older, is effective to provide:

a maximum plasma concentration ( $C_{max}$ ) of said Cav3 antagonist at steady state of no greater than twice the mean plasma concentration over 24 hours; and

a plasma concentration of said Cav3 antagonist at steady state of from about 400 nM to about 1000 nM for at least 18 hours.

2. The oral dosage form of claim 1, wherein said oral dosage form, when administered to said human, is effective to maintain said  $C_{max}$  of said Cav3 antagonist at steady state of from 1 to 2 times the mean plasma concentration over 24 hours.

3. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof,

wherein the dosage form comprises a controlled release component comprising said Cav3 antagonist, and wherein the dosage form optionally contains an immediate release component comprising said Cav3 antagonist;

wherein said oral dosage form, when administered a human less than about 35 years of age, is effective to provide:

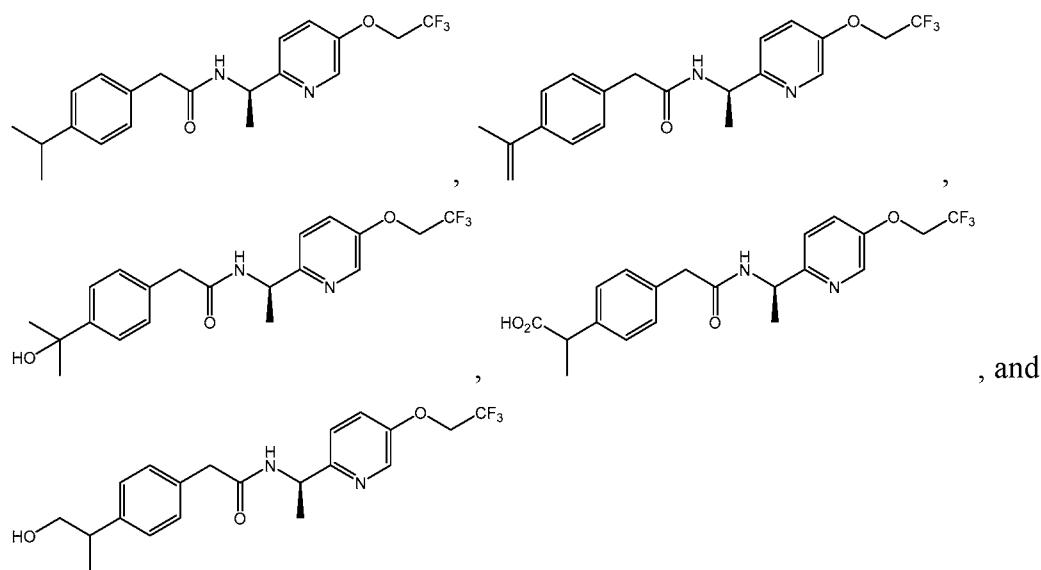
a maximum plasma concentration ( $C_{max}$ ) of said Cav3 antagonist at steady state of no greater than 2.5 times the mean plasma concentration over 24 hours; and

a plasma concentration of said Cav3 antagonist at steady state of from about 400 nM to about 1000 nM for at least 15 hours.

4. The oral dosage form of claim 3, wherein said oral dosage form, when administered to said human, is effective to maintain said Cmax of said Cav3 antagonist at steady state of from 1 to 2.5 times the mean plasma concentration over 24 hours.

5. The oral dosage form of any one of claims 1 - 4, wherein said oral dosage form is administered to said human once daily.

6. The oral dosage form of any one of claims 1 - 5, wherein said Cav3 antagonist has a structure selected from the group consisting of:



7. The oral dosage form of any one of claims 1 - 6, wherein said Cav3 antagonist comprises a hydrochloride salt.

8. The oral dosage form of any one of claims 1 - 7, wherein said oral dosage form is selected from the group consisting of a capsule, a pill, a tablet, and a suspension.

9. The oral dosage form of any one of claims 1 - 8, wherein said controlled release component comprises particles, a tablet, a mini-tablet, a solution, a suspension, a capsule, or a mixture thereof.

10. The oral dosage form of claim 9, wherein said particles are granules, pellets, beads, microparticles, or nanoparticles, or a mixture thereof.

11. The oral dosage form of any one of claims 1 - 10, wherein said oral dosage form comprises a capsule.

12. The oral dosage form of claim 11, wherein said capsule is a gelatin capsule or a hydroxypropyl methylcellulose capsule.

13. The oral dosage form of any one of claims 1 - 12, wherein at least one particle in a plurality of particles comprising said Cav3 antagonist in said controlled release component comprises a coating comprising a pH-sensitive enteric polymer.

14. The oral dosage form of claim 13, wherein at least a portion of said pH-sensitive enteric polymer coating can dissolve at a pH of about 6.

15. The oral dosage form of claim 14, wherein said pH-sensitive enteric polymer comprises, by weight, about 6.25% methacrylic acid copolymer L, about 6.25% methacrylic acid copolymer S, about 1.25% triethyl citrate, and about 6.25% talc.

16. The oral dosage form of claim 13, wherein at least a portion of said pH-sensitive enteric polymer coating can dissolve at a pH of about 7.

17. The oral dosage form of claim 16, wherein said pH-sensitive enteric polymer comprises, by weight, about 17.4% EUDRAGIT® FS 30 D, and about 2.6% PlasACRYL® T20.

18. The oral dosage form of any one of claims 1 - 17, wherein said controlled release component comprises, by weight, about 5.0% of said Cav3 antagonist, about 57.7% lactose monohydrate, about 25.0% crospovidone, about 8.0% citric acid anhydrous, about 2.0% sodium lauryl sulfate (SLS), about 2.0% hydroxypropyl cellulose (HPC), about 0.3% butylated hydroxyanisole (BHA), and about 0.1% butylated hydroxytoluene (BHT).

19. The oral dosage form of any one of claims 1 - 18, further comprising said immediate release component, wherein said immediate release component comprises a plurality of particles comprising said Cav3 antagonist.

20. The oral dosage form of claim 19, wherein one or more of said particles in said immediate release component comprises, by weight, about 5.0% of said Cav3 antagonist, about 57.7% lactose monohydrate, about 25.0% crospovidone, about 8.0% citric acid anhydrous, about 2.0% sodium lauryl sulfate (SLS), about 2.0% hydroxypropyl cellulose (HPC), about 0.3% butylated hydroxyanisole (BHA), and about 0.1% butylated hydroxytoluene (BHT).

21. The oral dosage form of claim 19 or claim 20, wherein one or more of said particles in said immediate release component, when said oral dosage form is administered to a human, releases at least 80% of said Cav3 antagonist present in the immediate release component within 45 minutes of administration.

22. The oral dosage form of any one of claims 19 - 21, wherein said oral dosage form comprises about 30% of said Cav3 antagonist in said immediate release component and about 70% of said Cav3 antagonist in said controlled release component.

23. The oral dosage form of any one of claims 19 - 22, wherein said oral dosage form, when administered to a human, is effective to reach at least 25% of a maximum concentration ( $C_{max}$ ) of said Cav3 antagonist within 30 minutes.

24. The oral dosage form of any one of claims 1 - 23, wherein said Cav3 antagonist reduces activity of a T-type calcium channel.

25. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, wherein the dosage form comprises a capsule comprising:

a) an immediate release component comprising one or more granules comprising said Cav3 antagonist, and

b) a controlled release component comprising one or more granules comprising said Cav3 antagonist;

wherein said oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours.

26. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, wherein the dosage form comprises a tablet comprising:

a) an immediate release component comprising one or more granules comprising said Cav3 antagonist, and

b) a controlled release component comprising one or more granules comprising said Cav3 antagonist;

wherein said oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours.

27. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, wherein the dosage form comprises a capsule containing:

a) an immediate release component comprising said Cav3 antagonist, and

b) a controlled release component comprising one or more tablets comprising said Cav3 antagonist;

wherein said oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours.

28. The oral dosage capsule of claim 27, wherein said immediate release component comprises a plurality of granules.

29. The oral dosage capsule of claim 27, wherein said immediate release component comprises a plurality of beads and/or pellets.

30. The oral dosage capsule of any one of claims 27 - 29, wherein said one or more tablets comprise one or more mini-tablets.

31. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, wherein the dosage form comprises a capsule containing:

- a) an immediate release component comprising said Cav3 antagonist, wherein said immediate release component is a liquid, and
- b) a controlled release component comprising said Cav3 antagonist, wherein said controlled release component comprises one or more solid components selected from the group consisting of granules, beads, pellets, and mini-tablets;

wherein said oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours.

32. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, wherein the dosage form comprises a capsule containing an interior capsule, wherein said interior capsule fits within said oral dosage capsule such that a space is present between an outer surface of said interior capsule and an inner surface of said oral dosage capsule;

wherein said space present between said outer surface of said interior capsule and said inner surface of said oral dosage capsule contains an immediate release component comprising said Cav3 antagonist, wherein said immediate release component is a liquid;

wherein said interior capsule contains a controlled release component comprising said Cav3 antagonist; and

wherein said oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours.

33. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, wherein the dosage form comprises a suspension comprising:

a) an immediate release component comprising said Cav3 antagonist, wherein said immediate release component is a liquid, and

b) a controlled release component comprising said Cav3 antagonist, wherein said controlled release component comprises one or more solid components selected from the group consisting of granules, beads, pellets, and mini-tablets;

wherein said one or more solid components are suspended within said liquid; and

wherein said oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours.

34. An oral dosage form comprising a Cav3 antagonist or a pharmaceutically acceptable salt thereof, wherein the dosage form comprises a suspension comprising:

a) a liquid phase,

b) an immediate release component comprising said Cav3 antagonist, wherein said immediate release component comprises one or more solid components selected from the group consisting of granules, beads, pellets, and mini-tablets; wherein said one or more solid components are suspended within said liquid, and

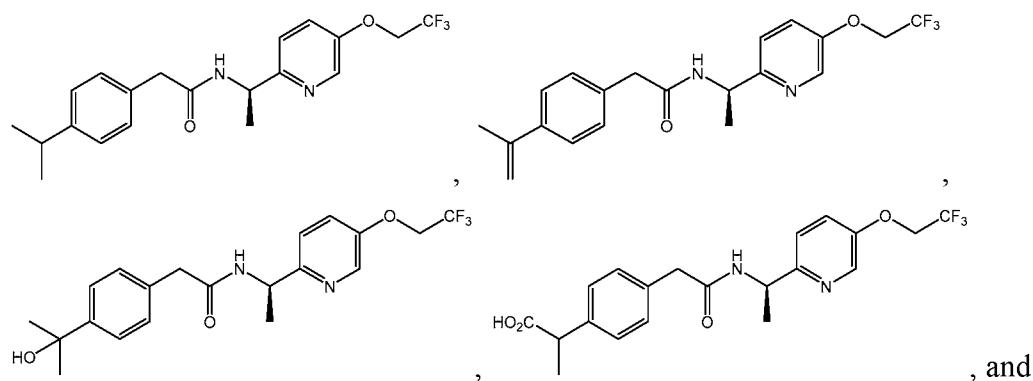
c) a controlled release component comprising said Cav3 antagonist, wherein said controlled release component comprises one or more solid components selected from the group consisting of granules, beads, pellets, and mini-tablets;

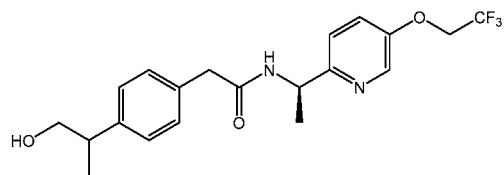
wherein said one or more solid components are suspended within said liquid; and wherein said oral dosage form, when administered to a human, is effective to maintain a mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 12 hours.

35. The oral dosage form of any one of claims 25 - 34, wherein said oral dosage form, when administered to a human, is effective to maintain said mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for at least 18 hours.

36. The oral dosage form of any one of claims 25 - 34, wherein said oral dosage form, when administered to a human, is effective to maintain said mean plasma concentration of said Cav3 antagonist of from about 400 nM to about 1000 nM for from about 12 hours to about 24 hours.

37. The oral dosage form of any one of claims 25 - 36, wherein said Cav3 antagonist has a structure selected from the group consisting of:





38. The oral dosage form of any one of claims 25 - 37, wherein said Cav3 antagonist comprises a hydrochloride salt.

39. The oral dosage form of any one of claims 25 - 38, wherein said Cav3 antagonist reduces activity of a T-type calcium channel.

40. A method of treating a patient having a movement disorder, said method comprising administering to said patient an oral dosage form of any one of claim 1 to claim 34.

41. The method of claim 40, wherein said patient is a human adult 35 years of age or older.

42. The method of claim 40, wherein said patient is human adult is less than about 35 years of age.

43. The method of any one of claims 40 - 42, wherein said movement disorder is selected from the group consisting of essential tremor, idiopathic generalized epilepsy with absence seizures, and tremor associated with Parkinson's disease.

44. The method of any one of claims 40 - 43, wherein said oral dosage form is administered to the patient between 6 am and noon.

45. The method of any one of claims 40 - 44, wherein said oral dosage form is administered to the patient within 4 hours of waking.

46. The method of any one of claims 40 - 45, wherein said controlled release component comprises a plurality of particles comprising said Cav3 antagonist, wherein at least one particle in said plurality of particles comprising said Cav3 antagonist in said controlled release component comprises a coating comprising a pH-sensitive enteric polymer, and wherein at least a portion of said pH-sensitive enteric polymer coating dissolves at an intestinal pH.

47. The method of any one of claims 40 - 46, wherein said patient has fasted for at least 4 hours prior to being administered said oral dosage form.

48. The method of any one of claims 40 - 47, wherein said Cav3 antagonist is effective to reduce or eliminate tremors associated with the movement disorder.

49. The method of any one of claims 40 - 48, wherein said patient experiences reduced adverse events as compared to a human that is administered only an immediate release component of said Cav3 antagonist.

50. The method of claim 49, wherein said adverse event is selected from the group consisting of dizziness, headache, euphoria, disturbance in attention, paresthesia, hallucination, insomnia, dry mouth, dysguesia, hypoesthesia, somnolence, lethargy, sleep disturbance, nausea, vomiting, akathisia, decreased level of consciousness, syncope, memory impairment, anxiety, restlessness, fatigue, irritability, constipation, tinnitus, anorexia, emotional disturbances, sexual impotency, diplopia, nystagmus, drowsiness, morbilliform skin eruptions, granulocytopenia, agranulocytosis, red-cell hypoplasia, and aplasia.

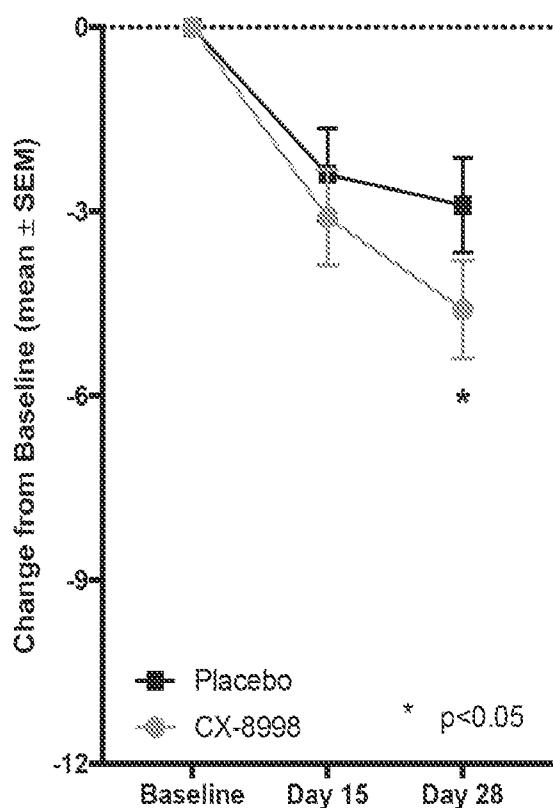


FIG. 1

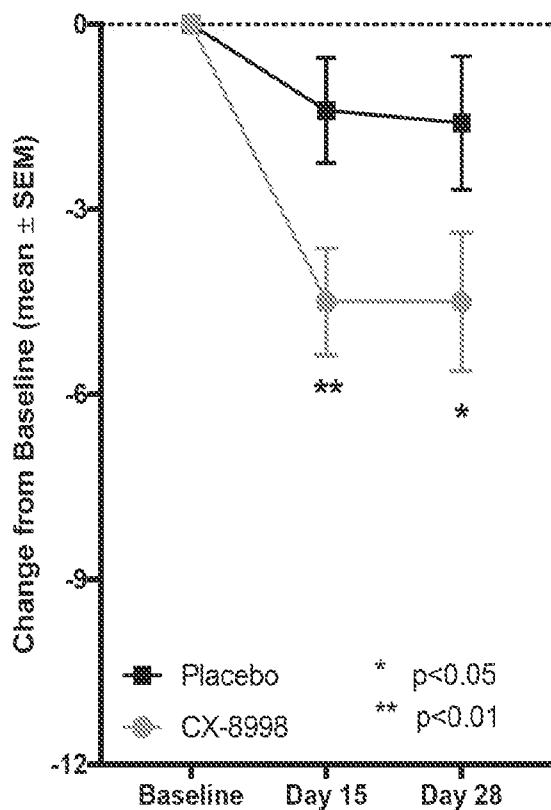


FIG. 2

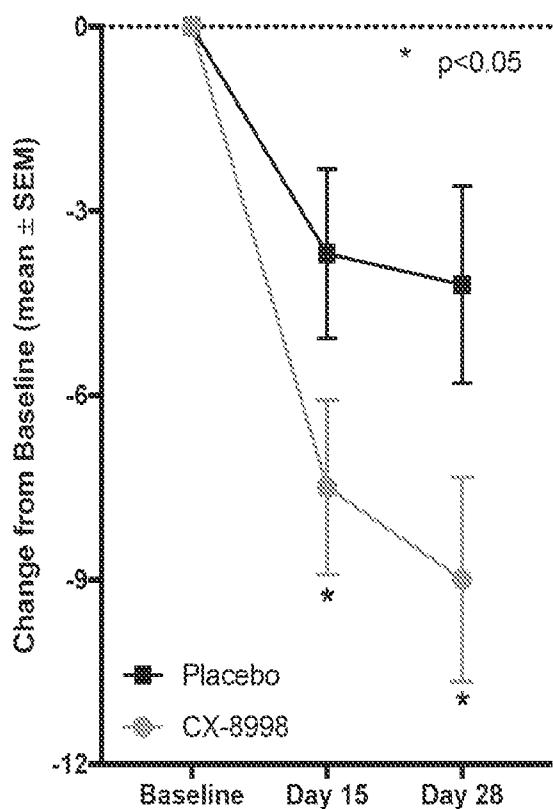


FIG. 3

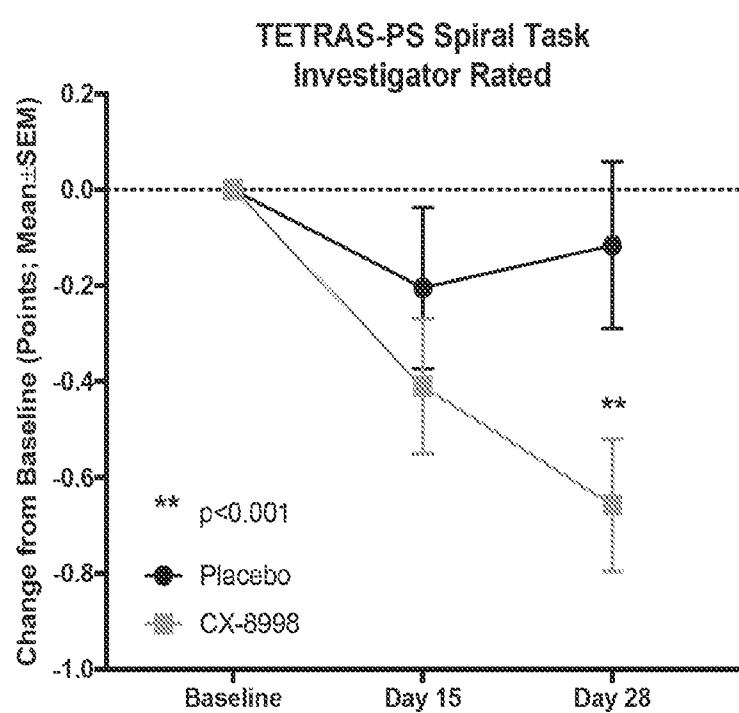


FIG. 4

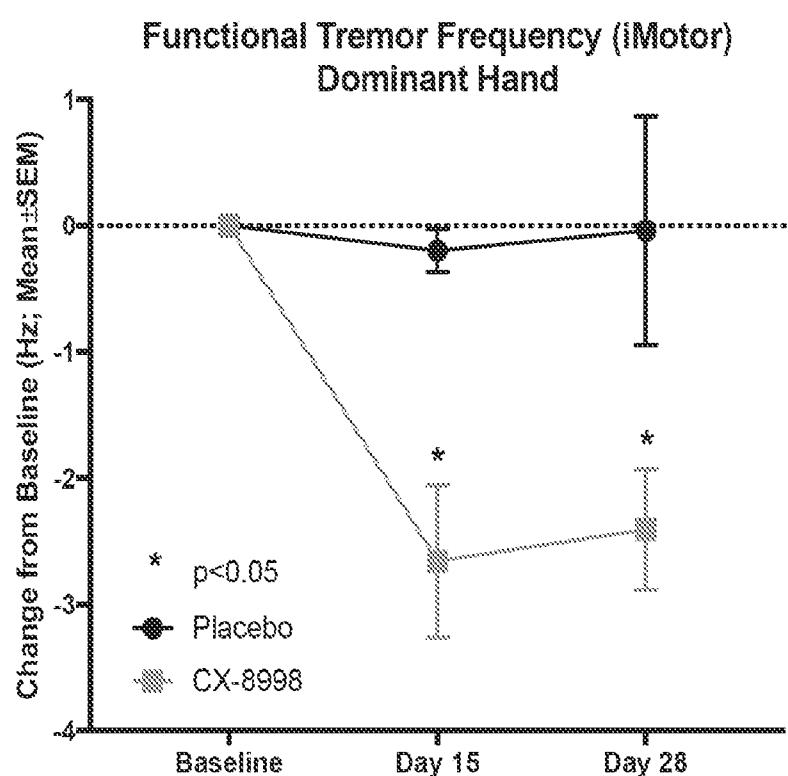


FIG. 5

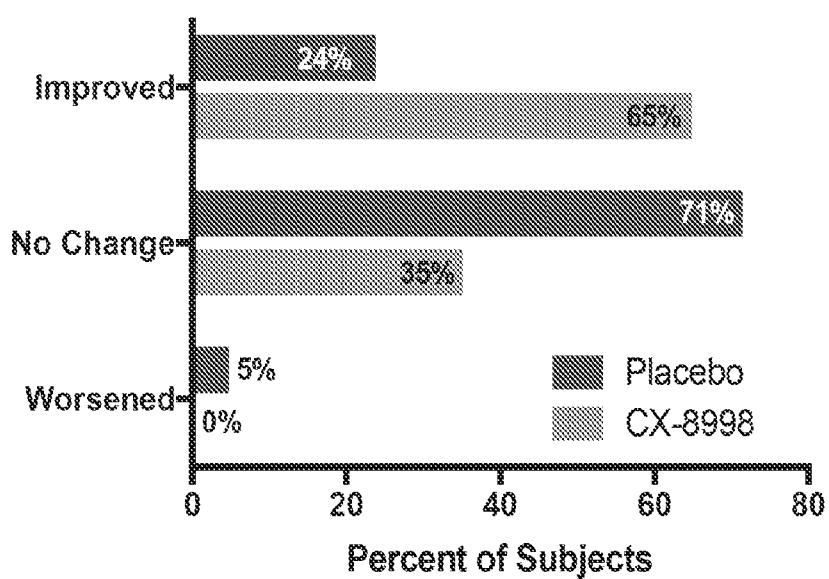


FIG. 6

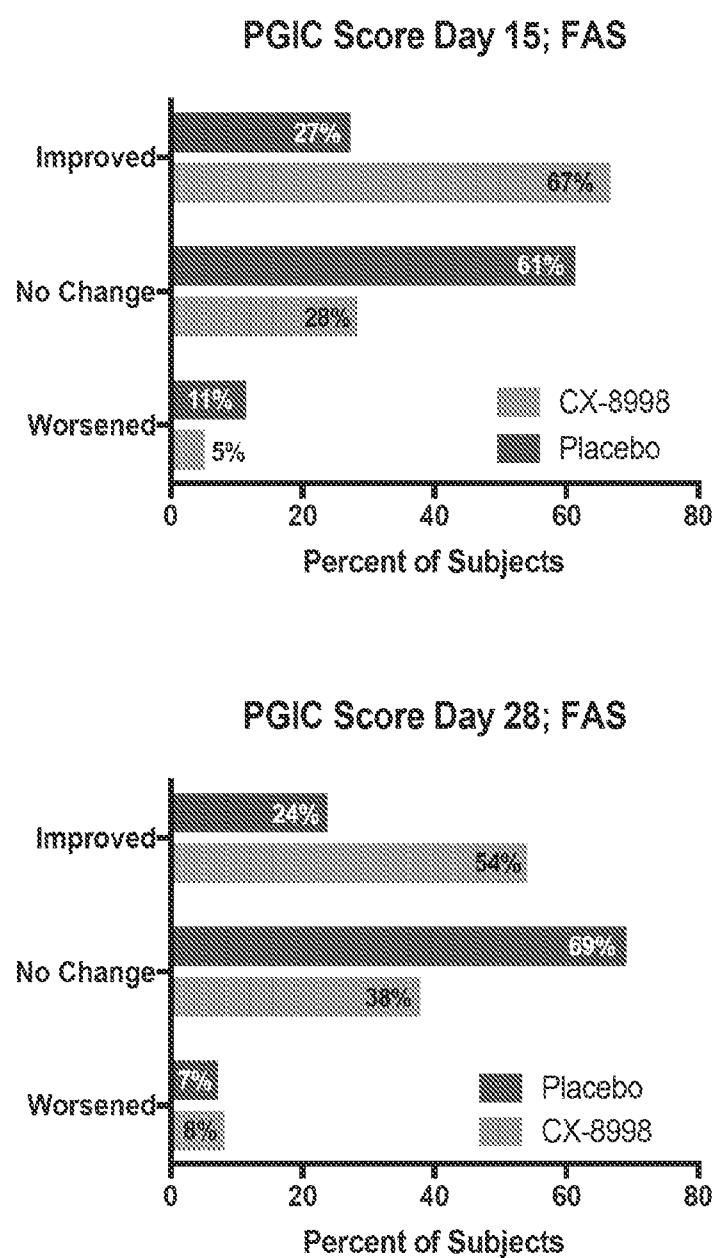


FIG. 7

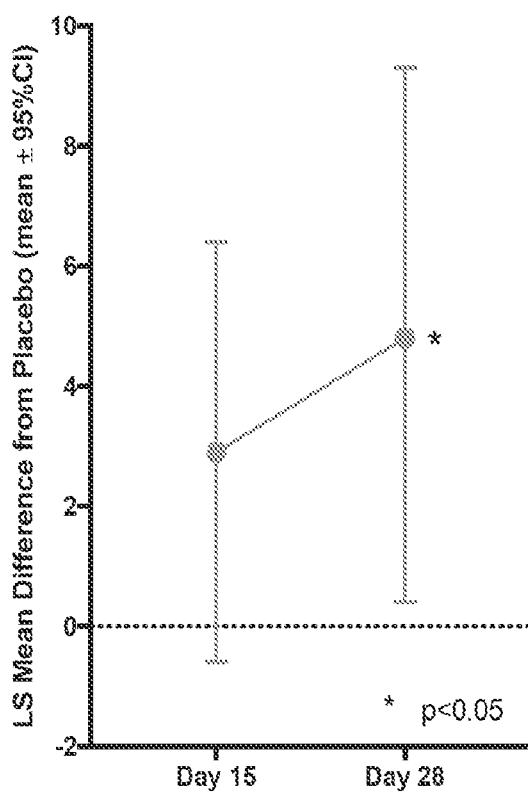


FIG. 8

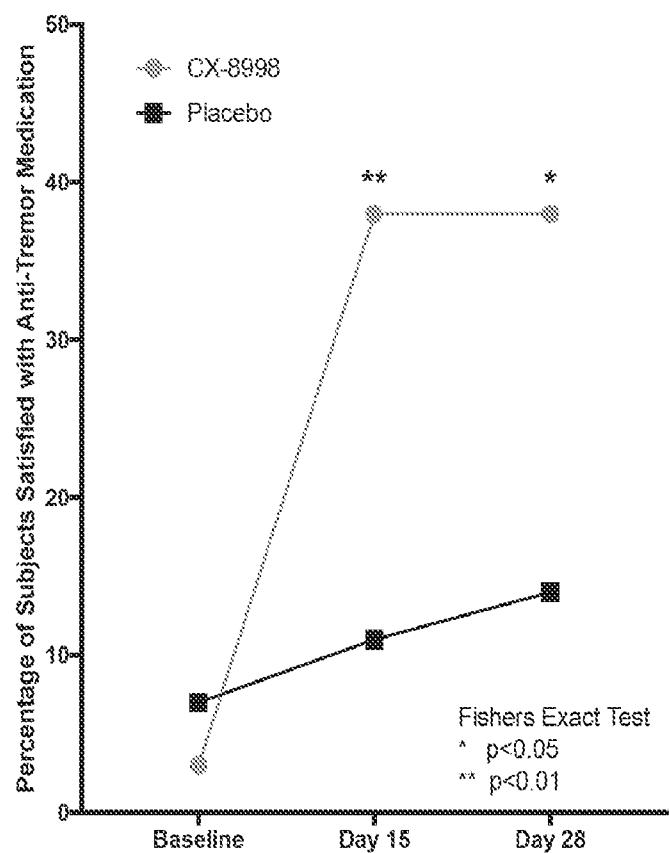


FIG. 9

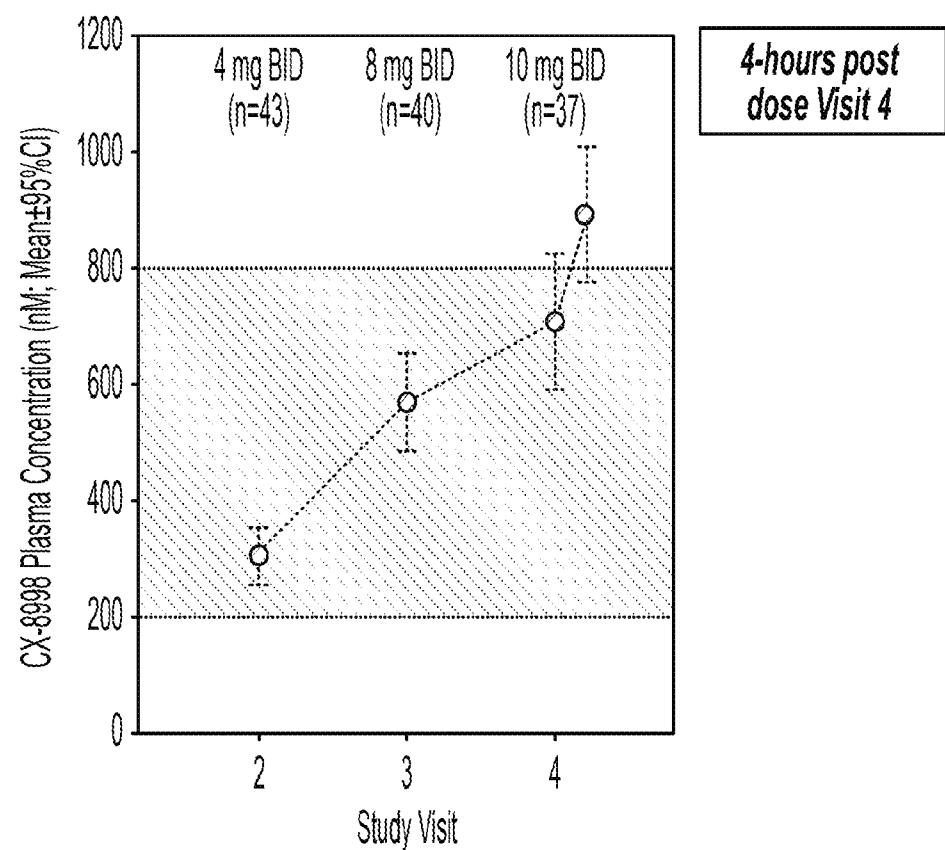


FIG. 10

11/83

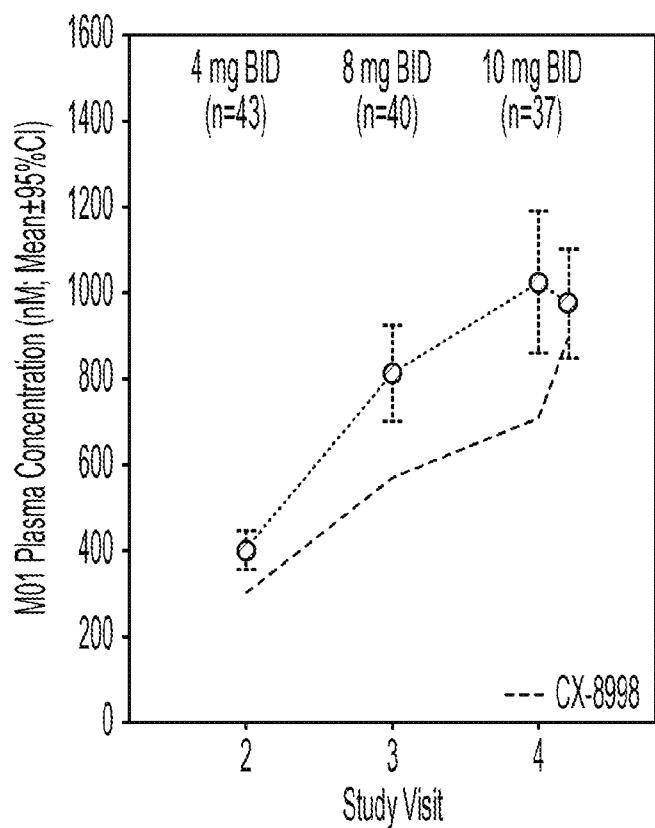


FIG. 11A

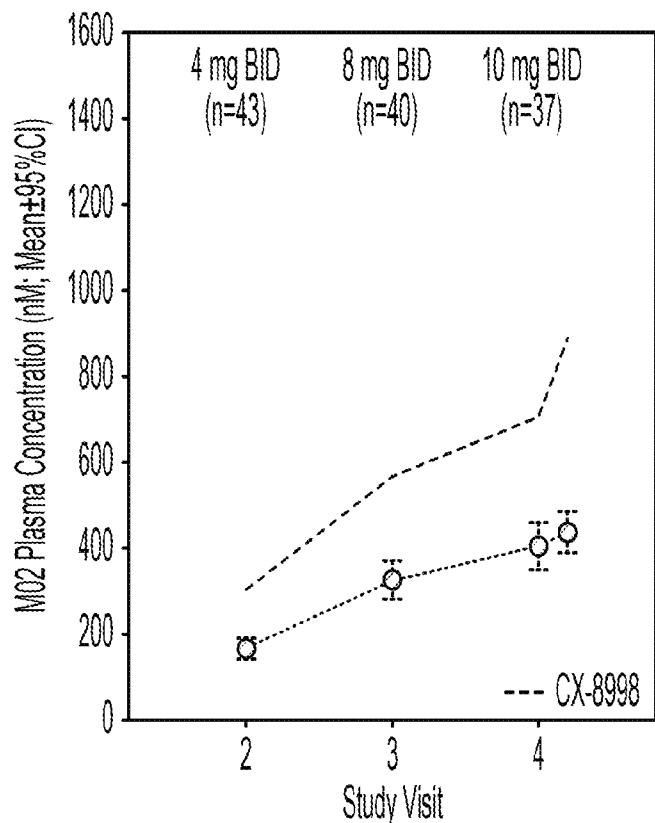


FIG. 11B

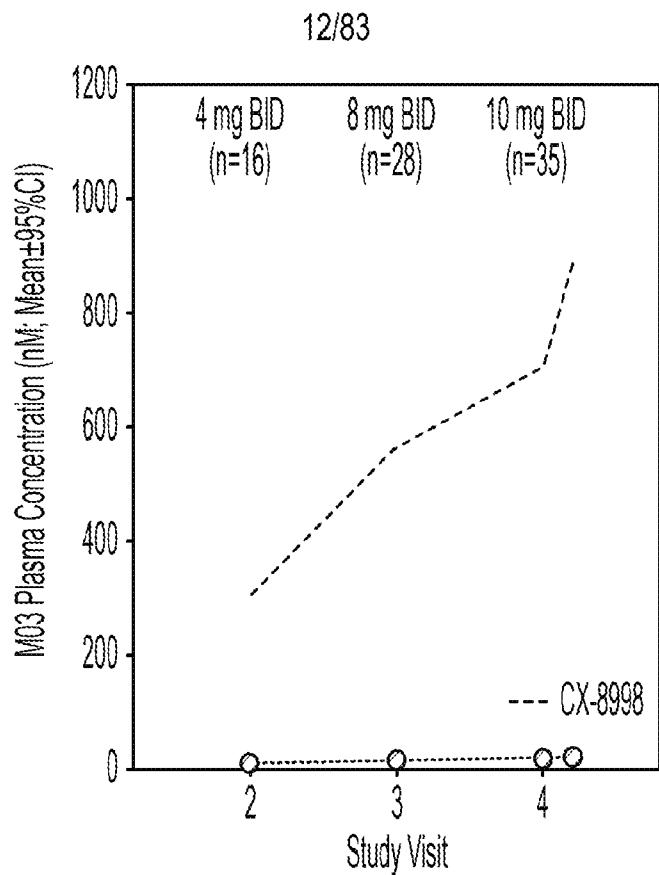


FIG. 11C

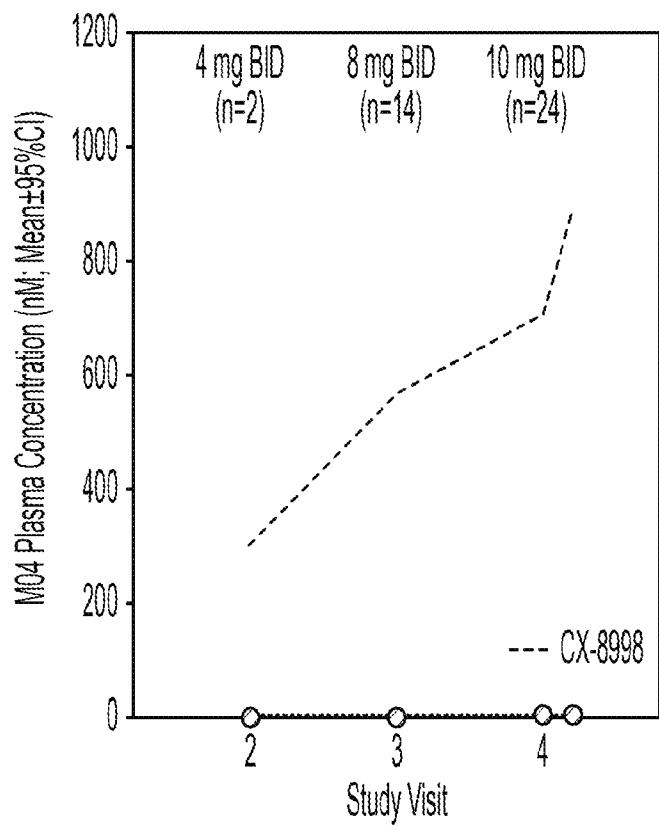


FIG. 11D

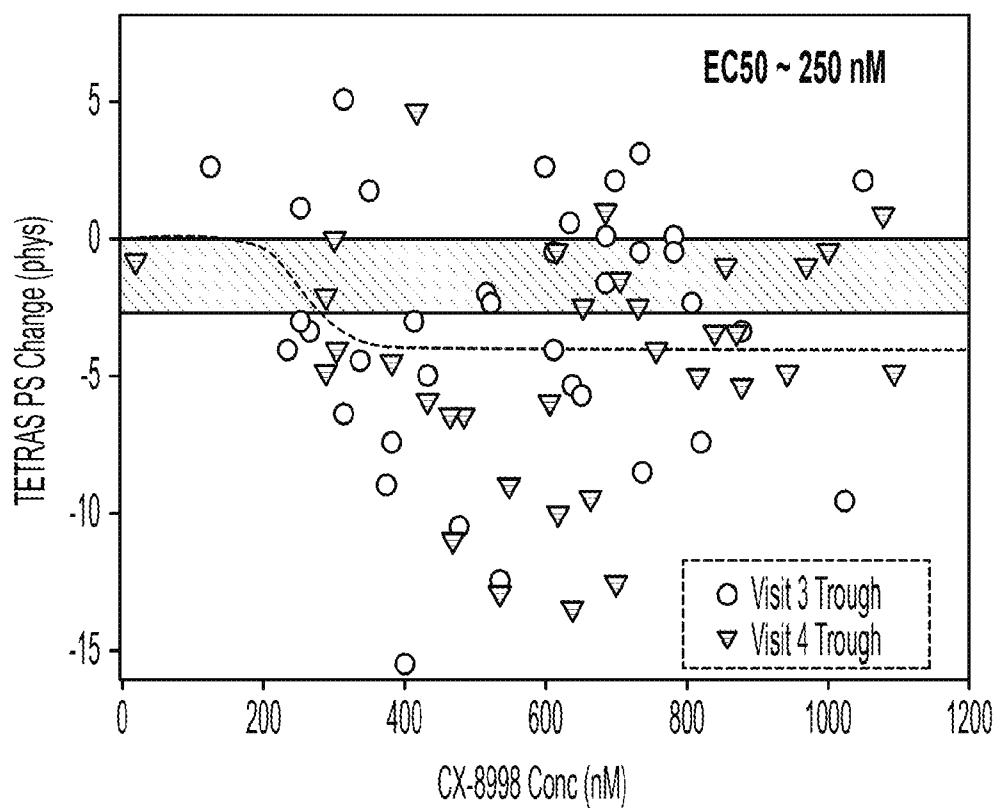


FIG. 12

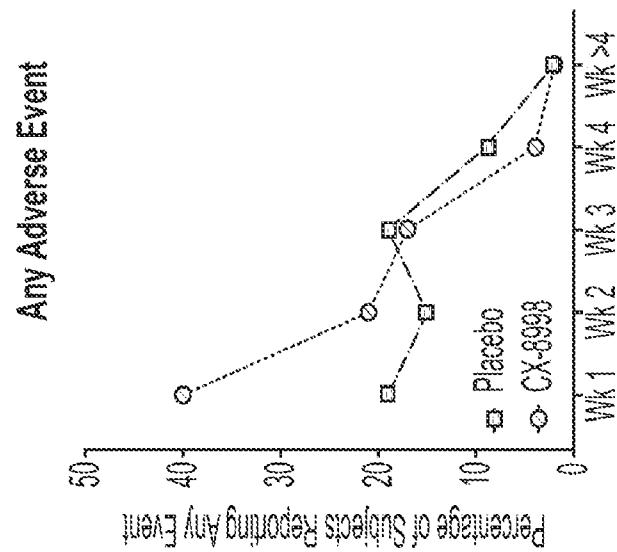
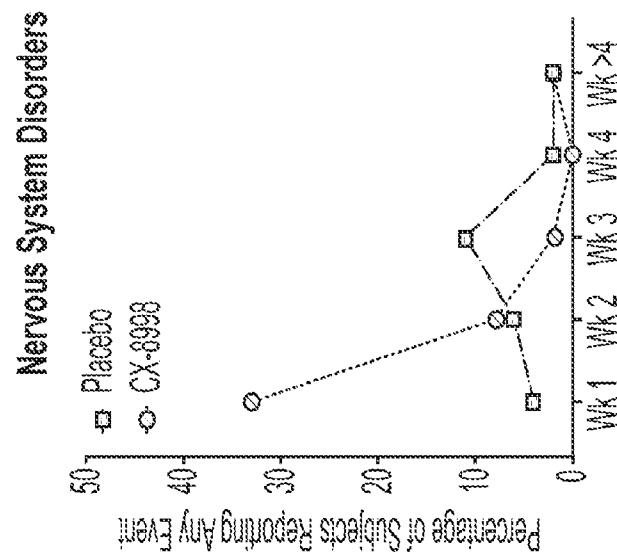
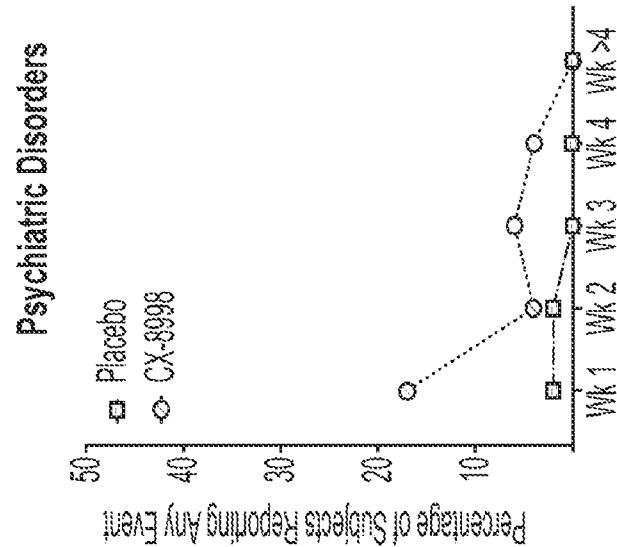


FIG. 13

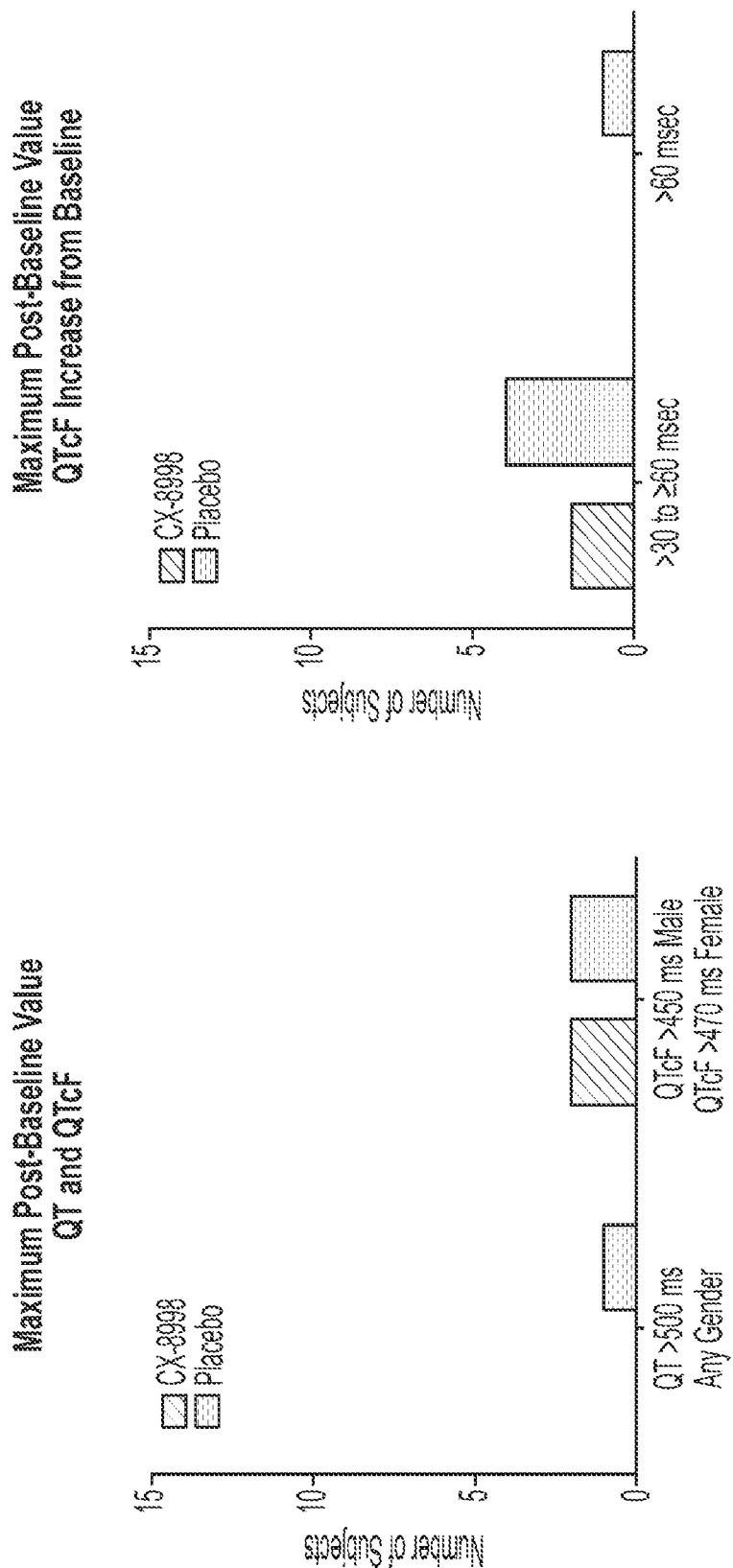
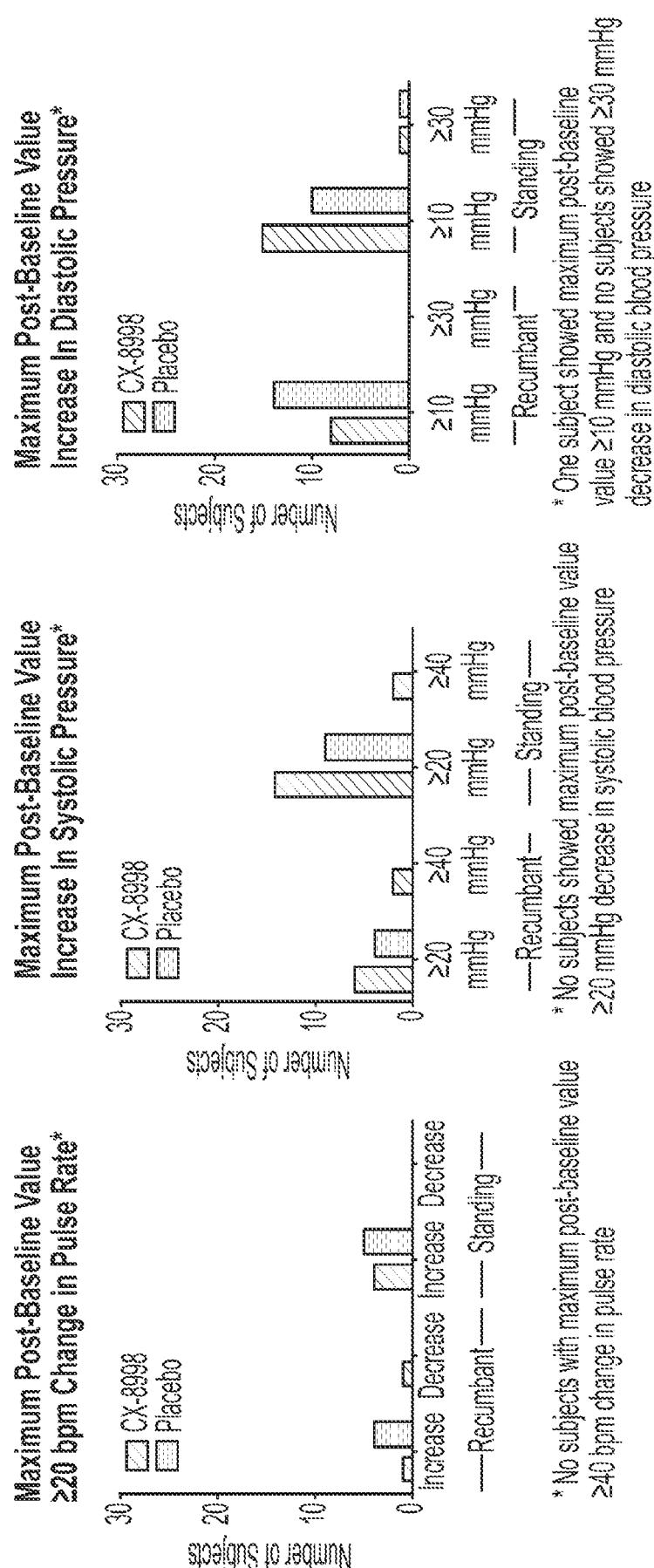
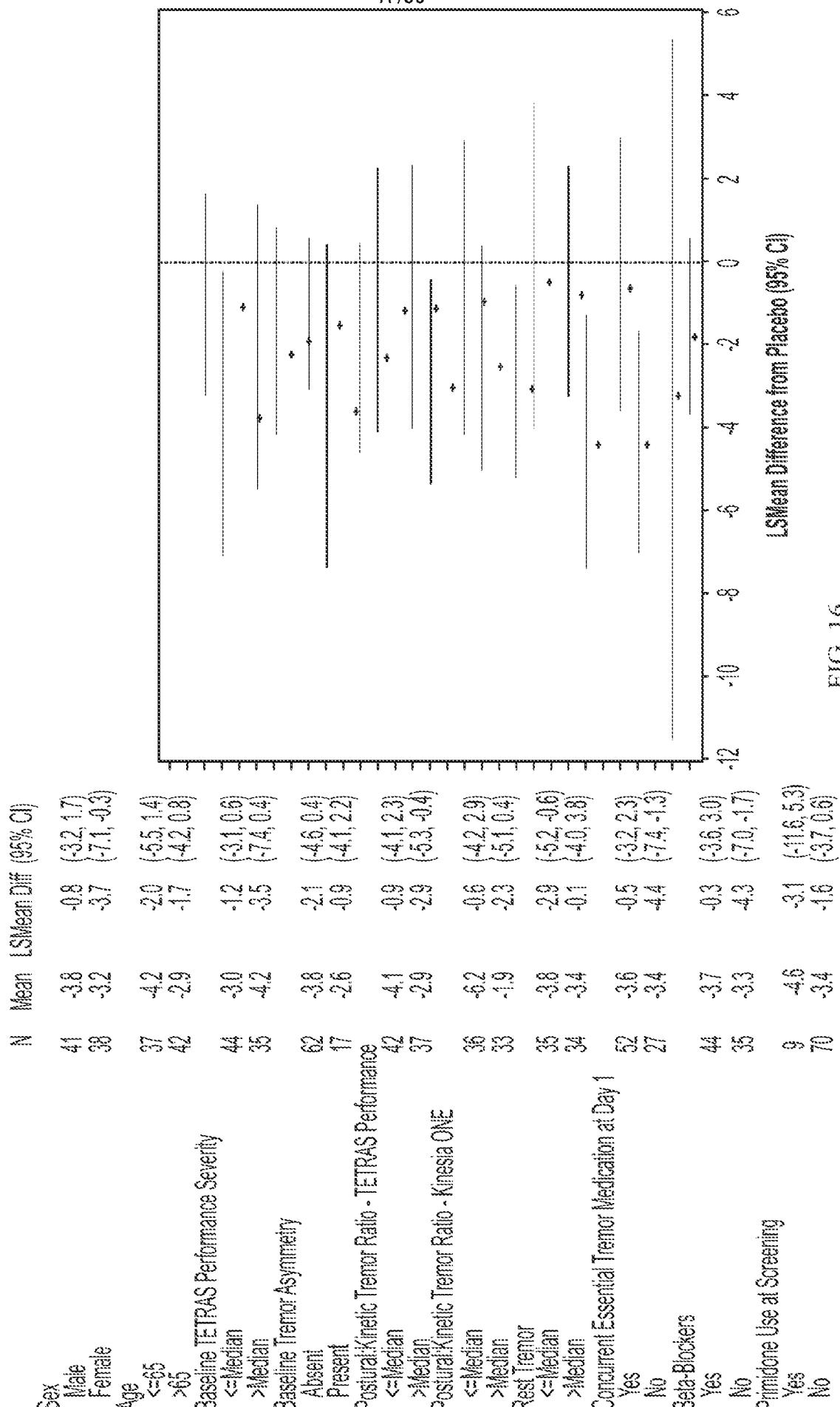


FIG. 14



17/83



SUBSTITUTE SHEET (RULE 26)

FIG. 16

18/83

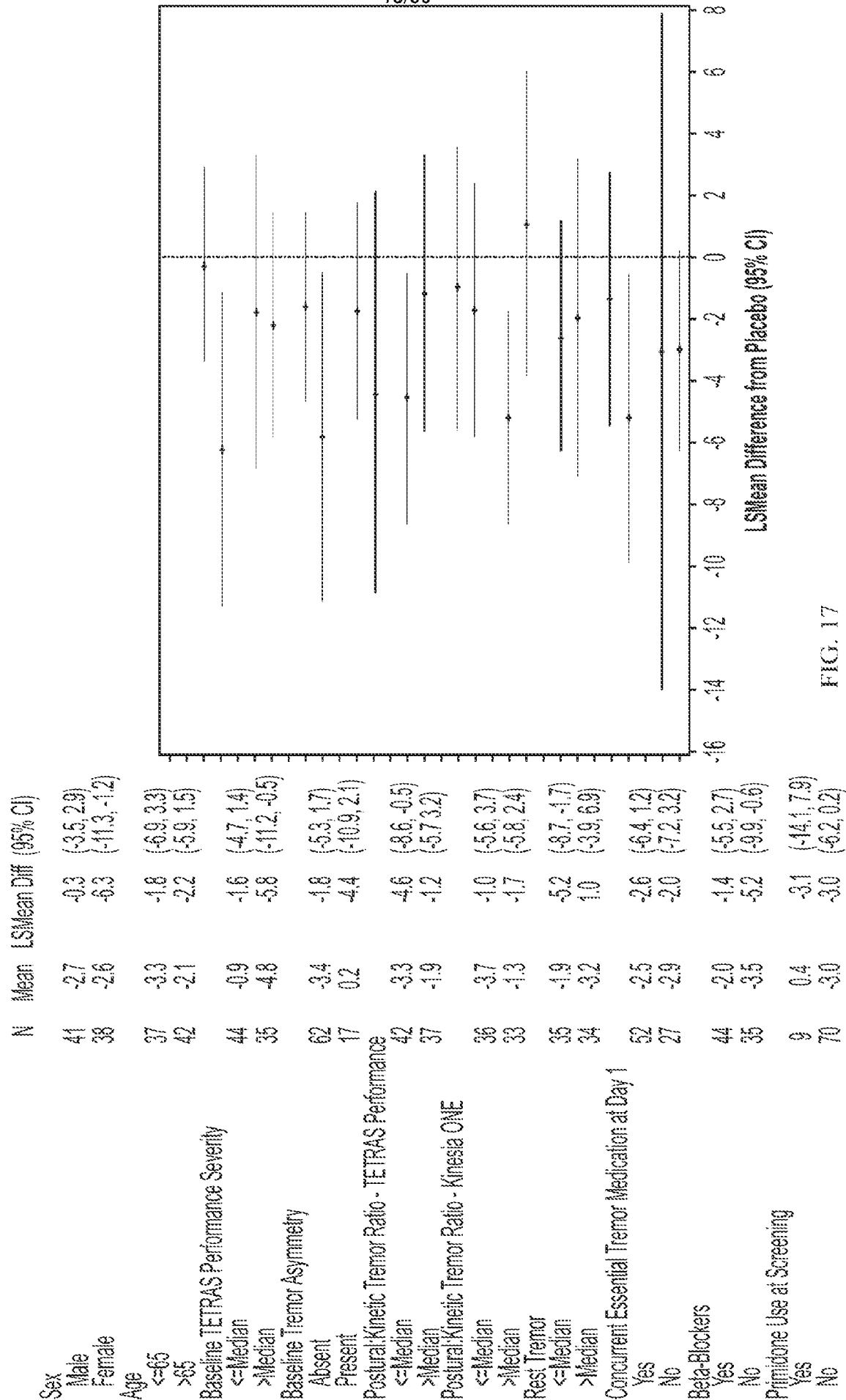


FIG. 17

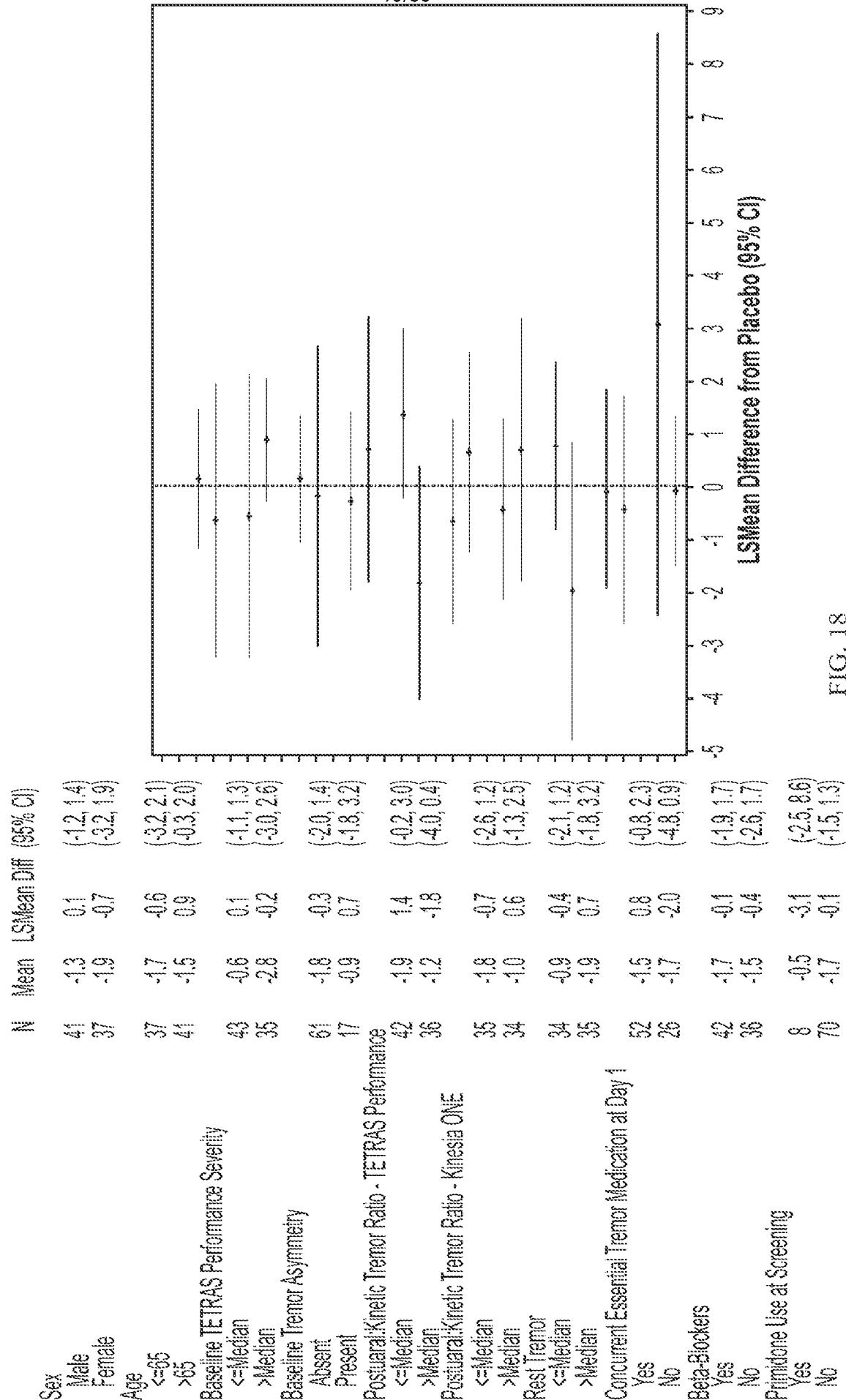
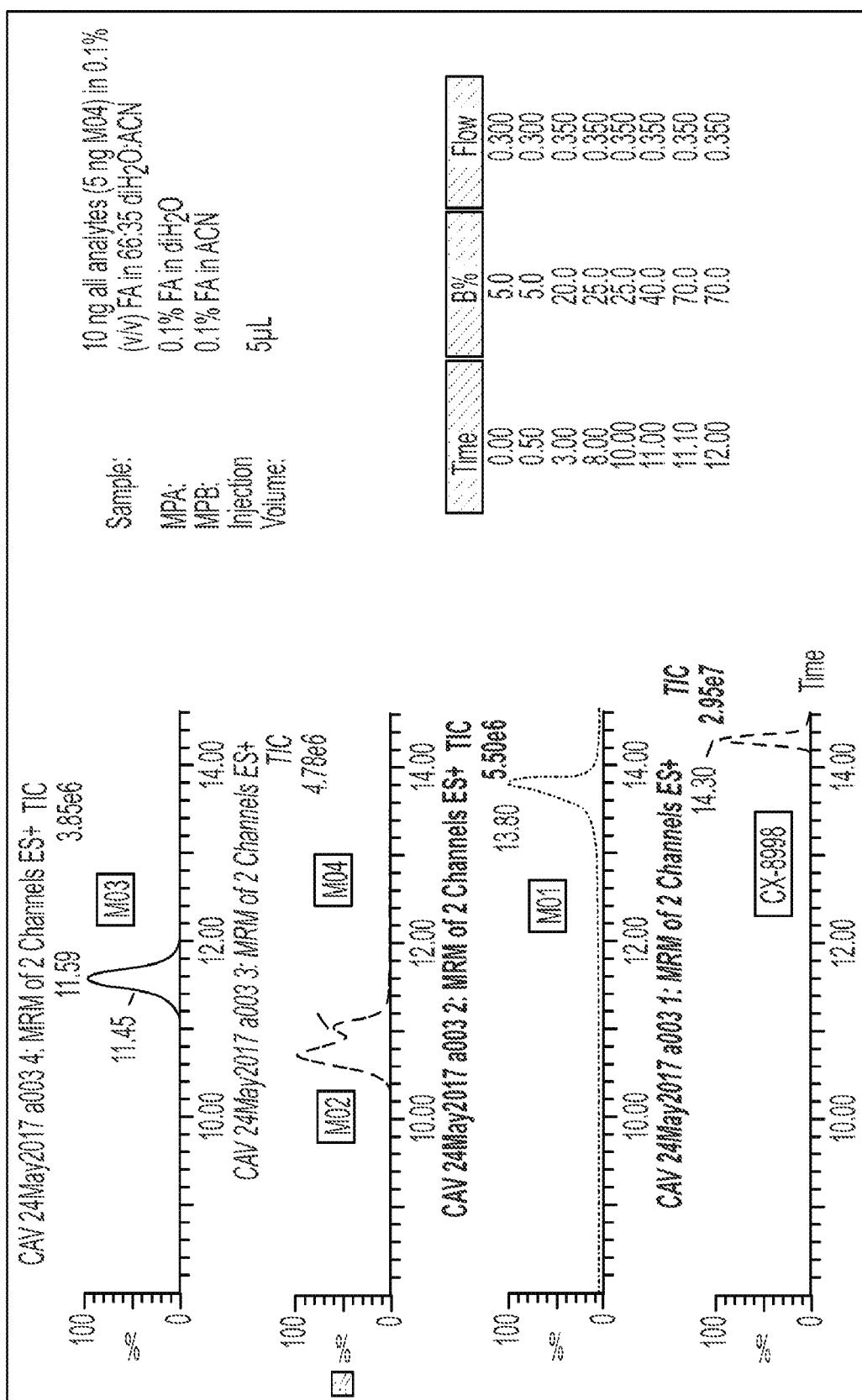
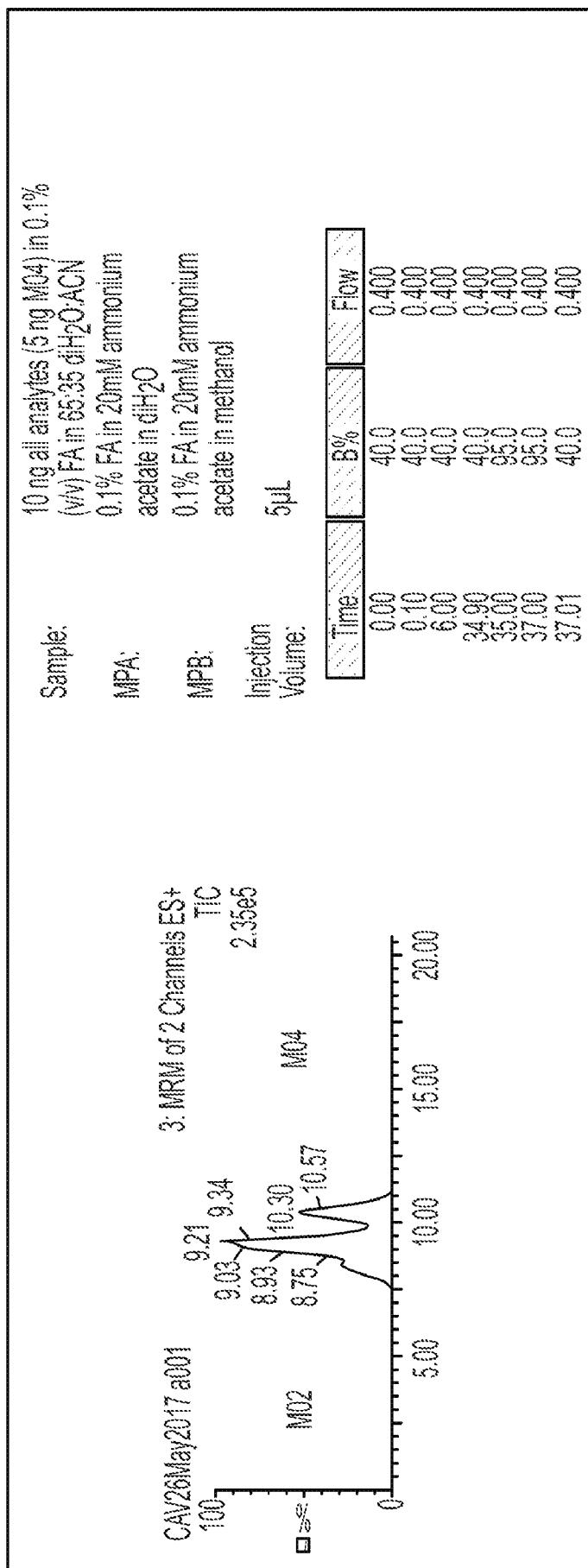


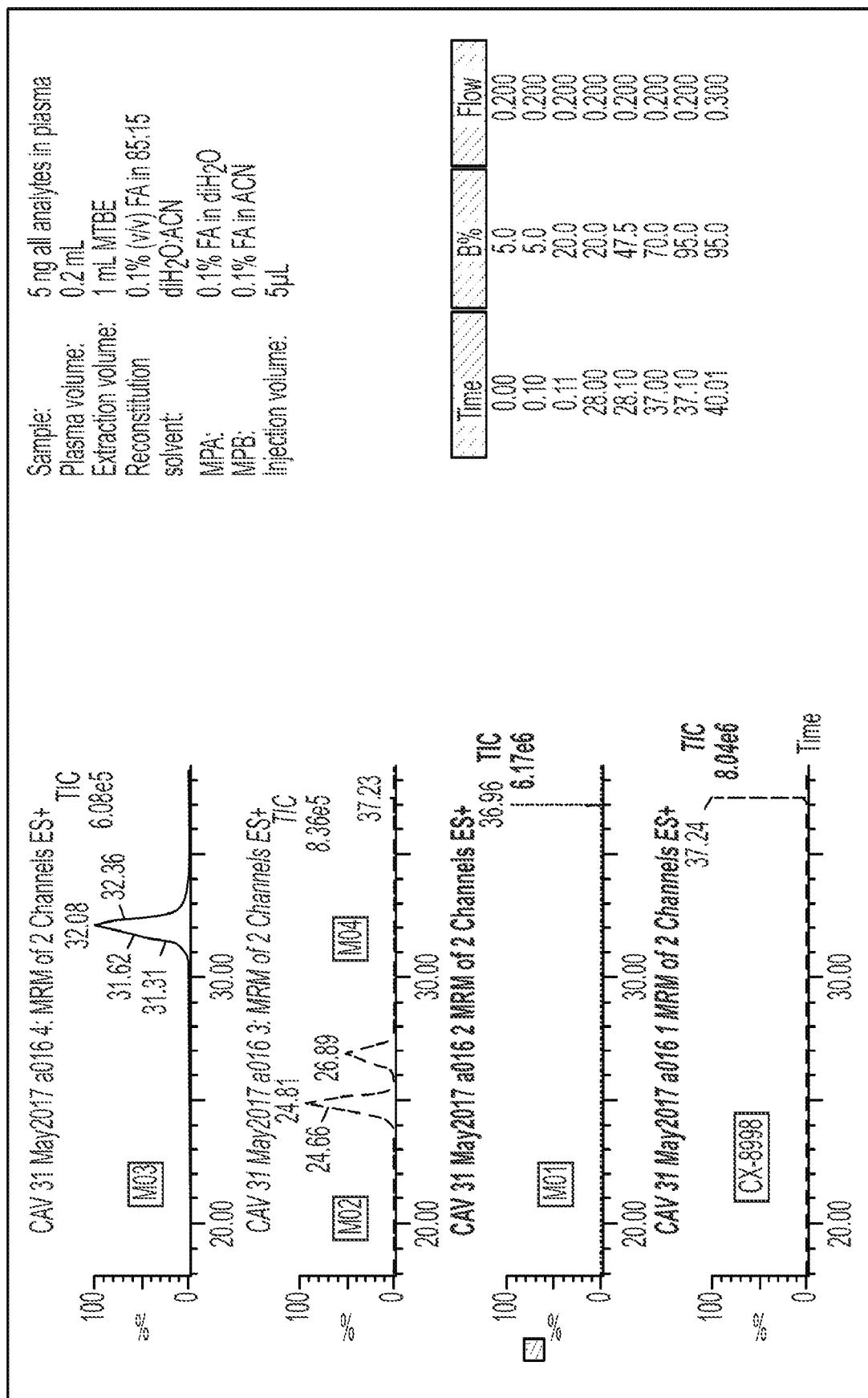
FIG. 18



61



EIC. 20



23/83

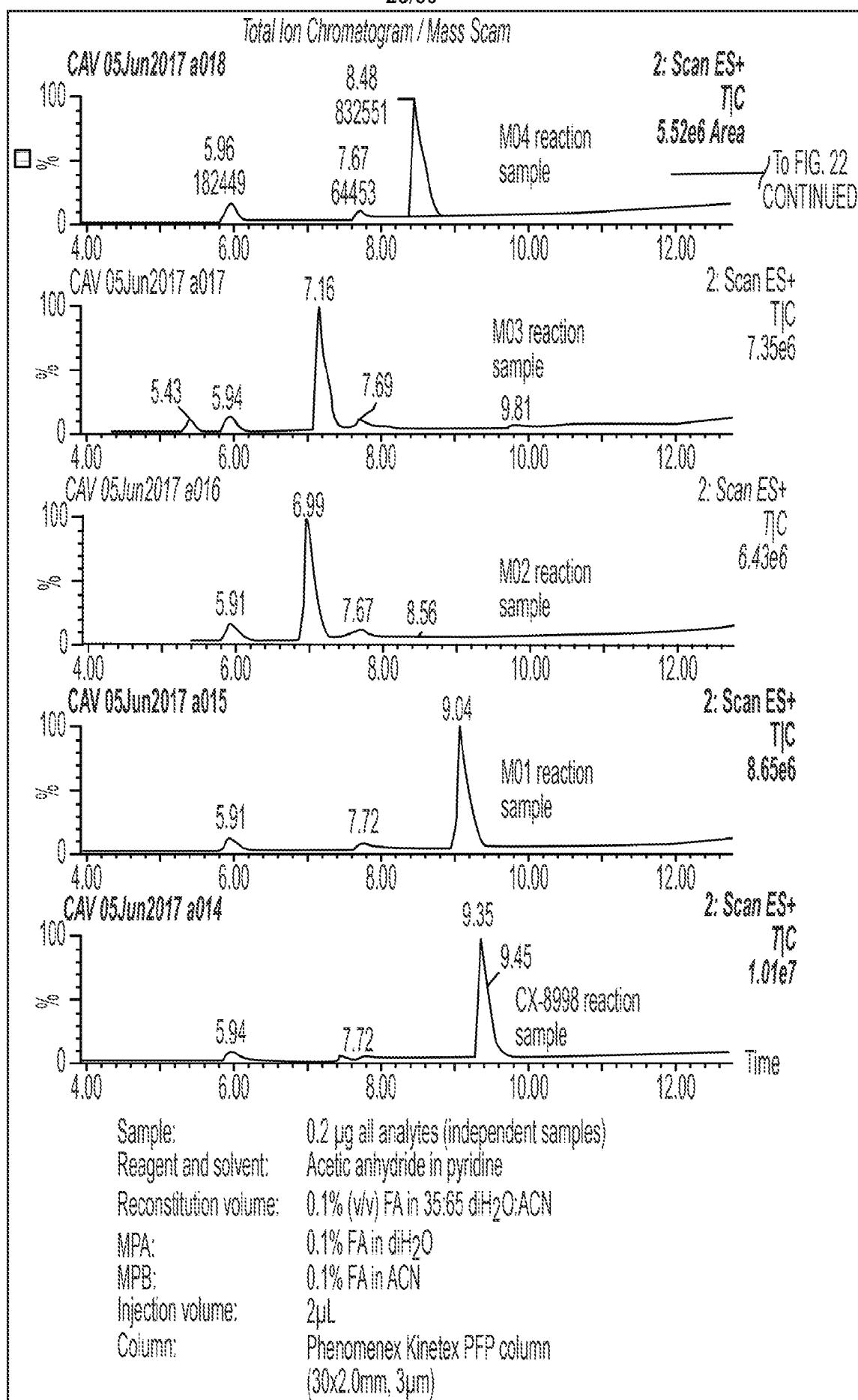
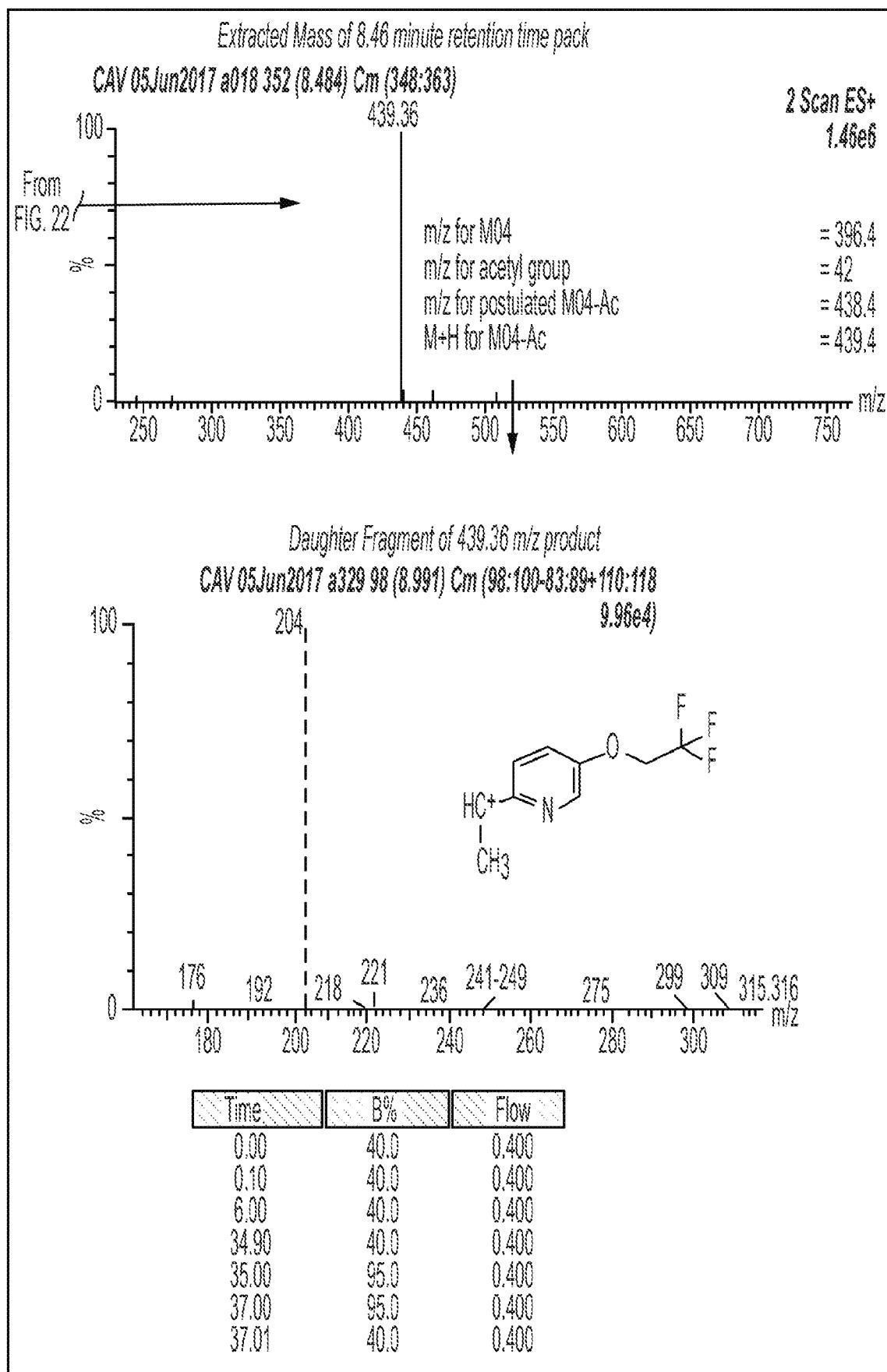


FIG. 22

24/83

FIG. 22  
CONTINUED

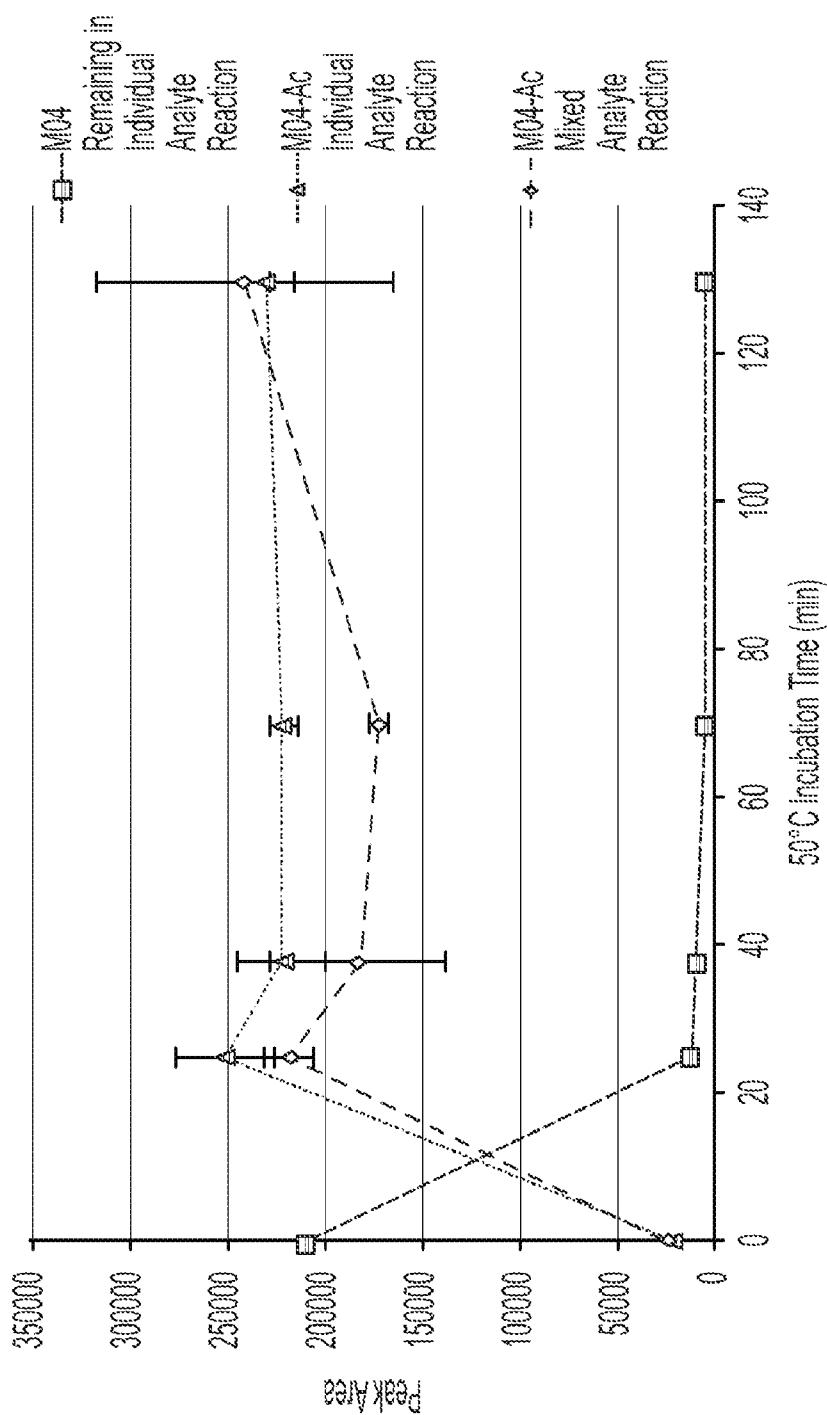


FIG. 23

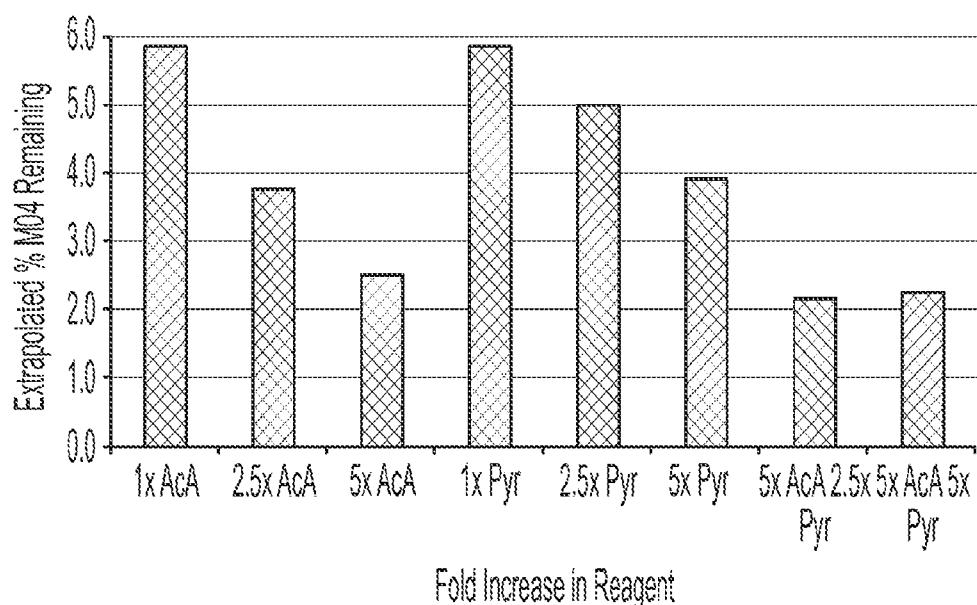


FIG. 24

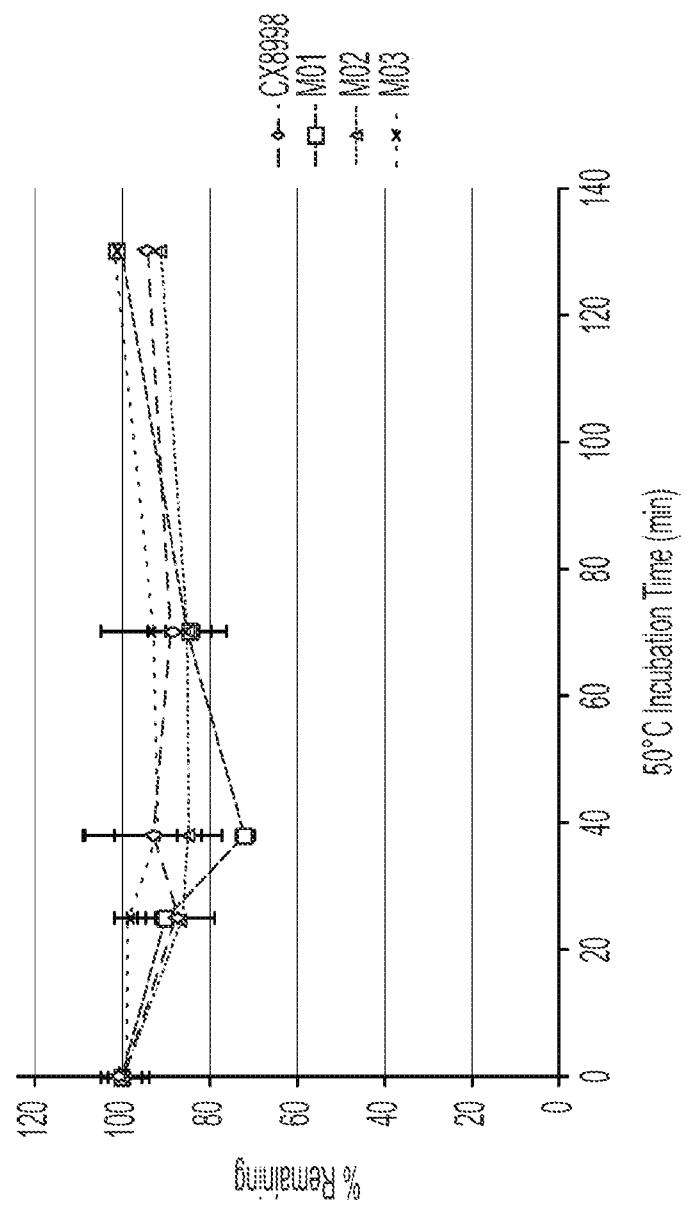


FIG. 25

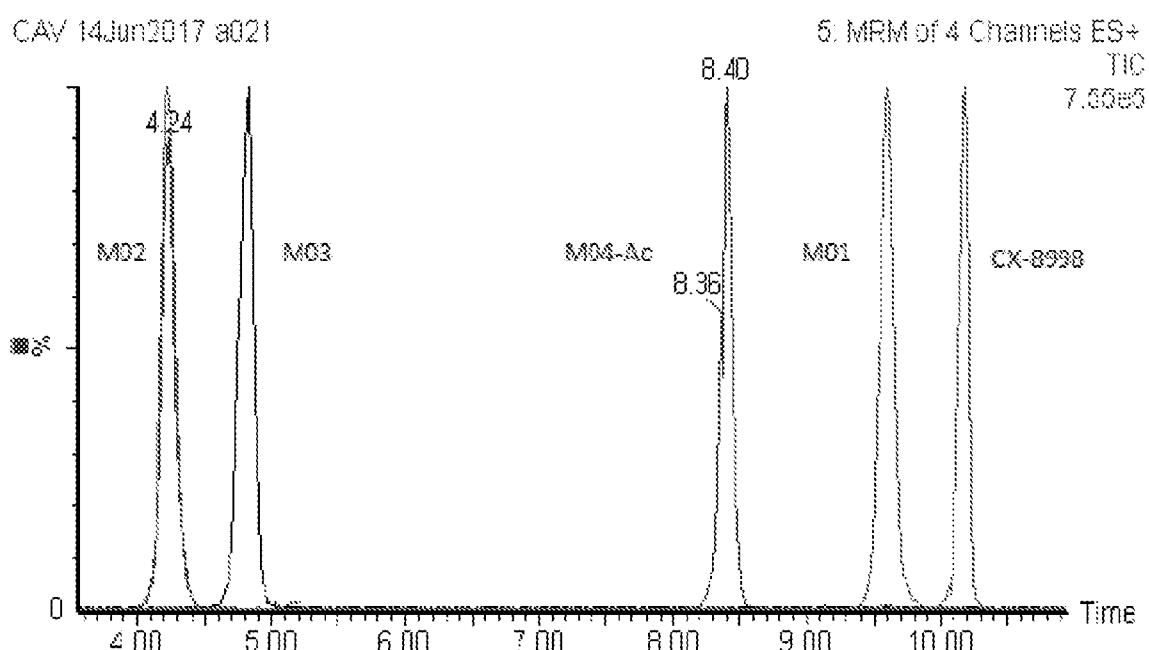


FIG. 26

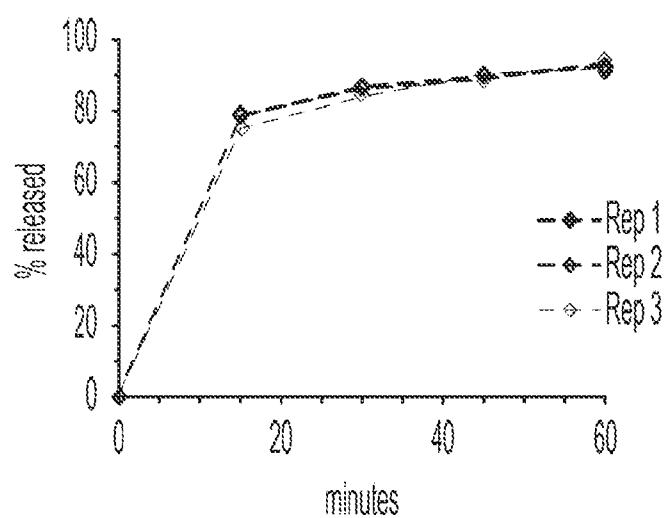


FIG. 27

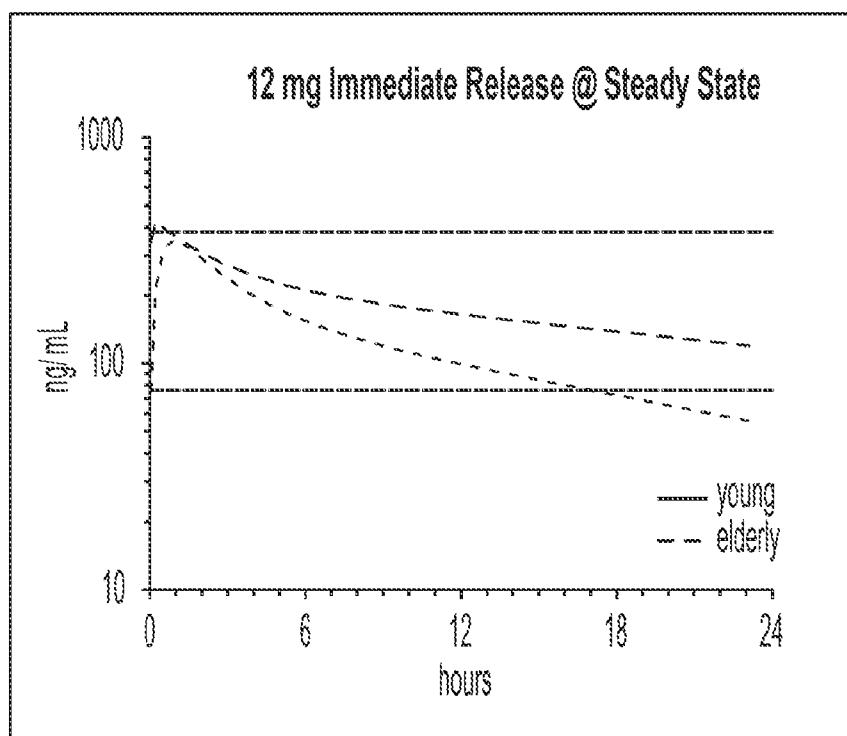
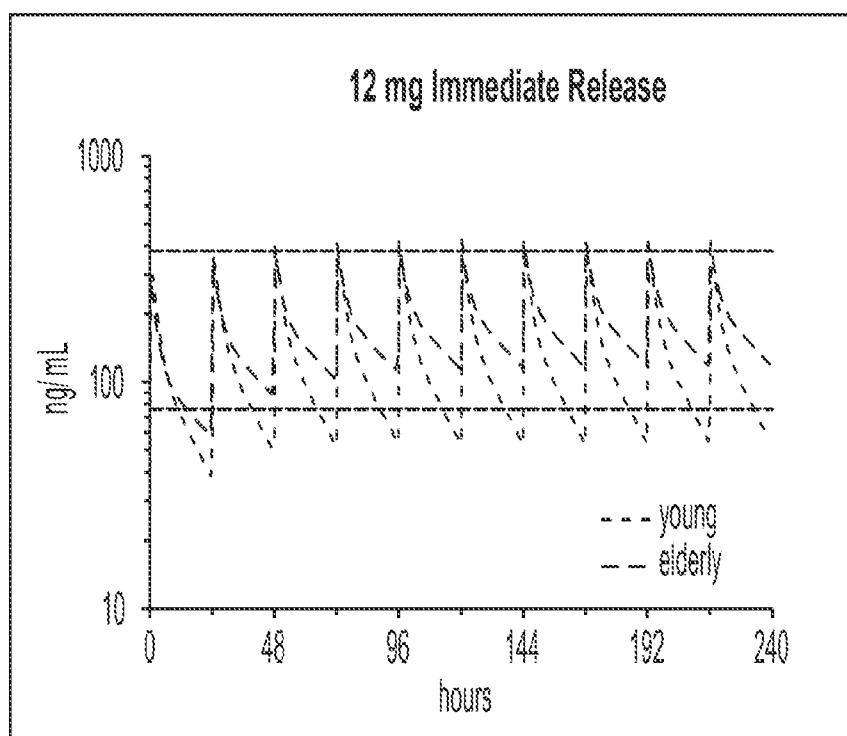


FIG. 28

31/83

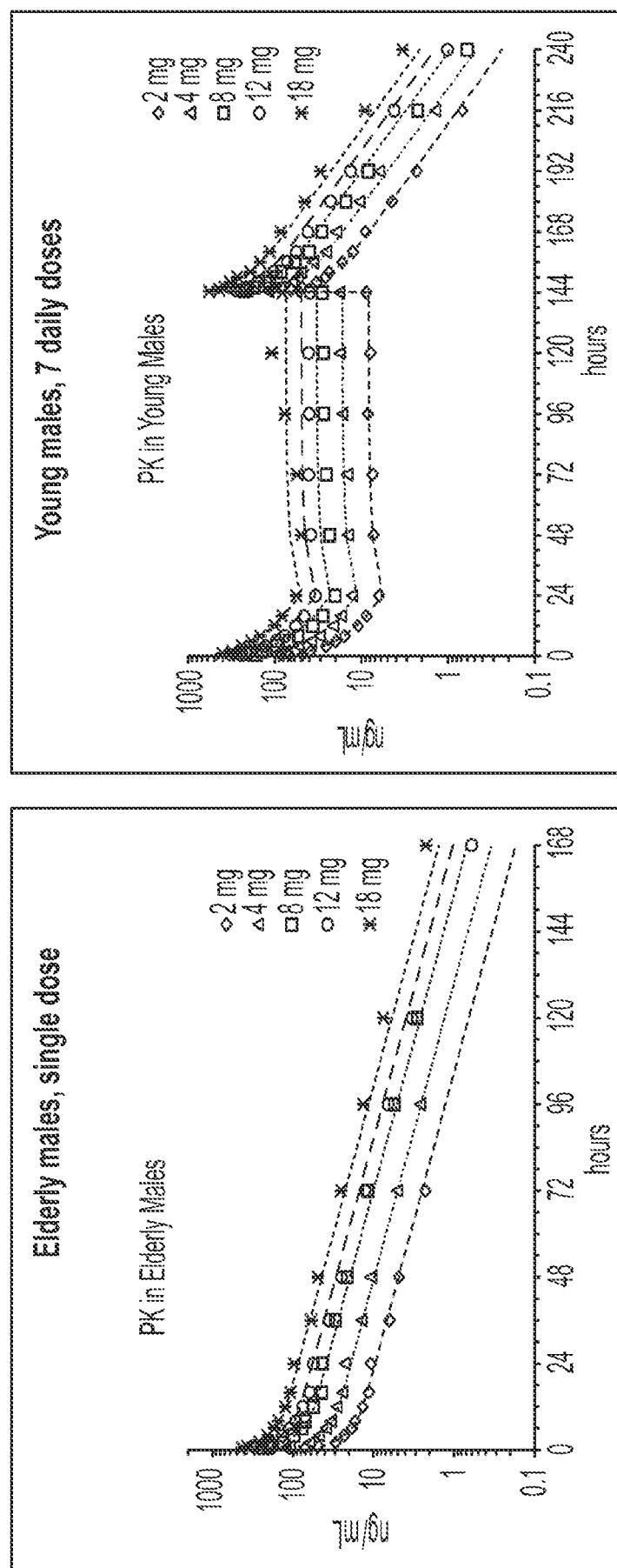


FIG. 29

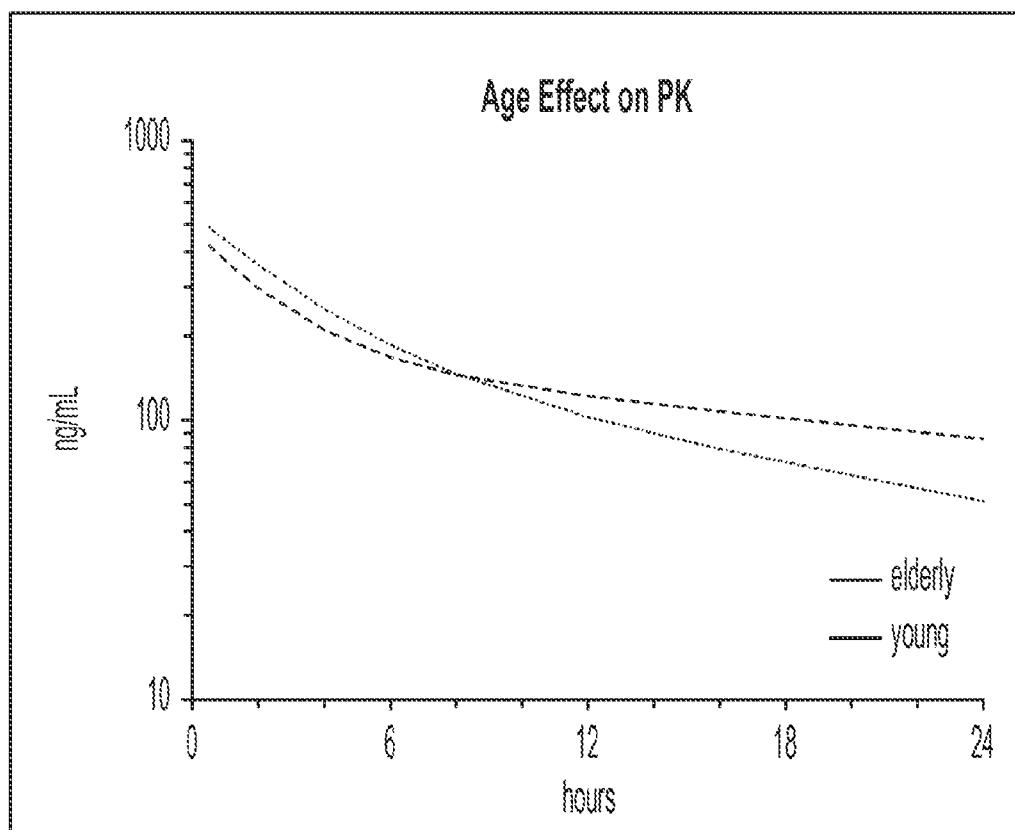


FIG. 30

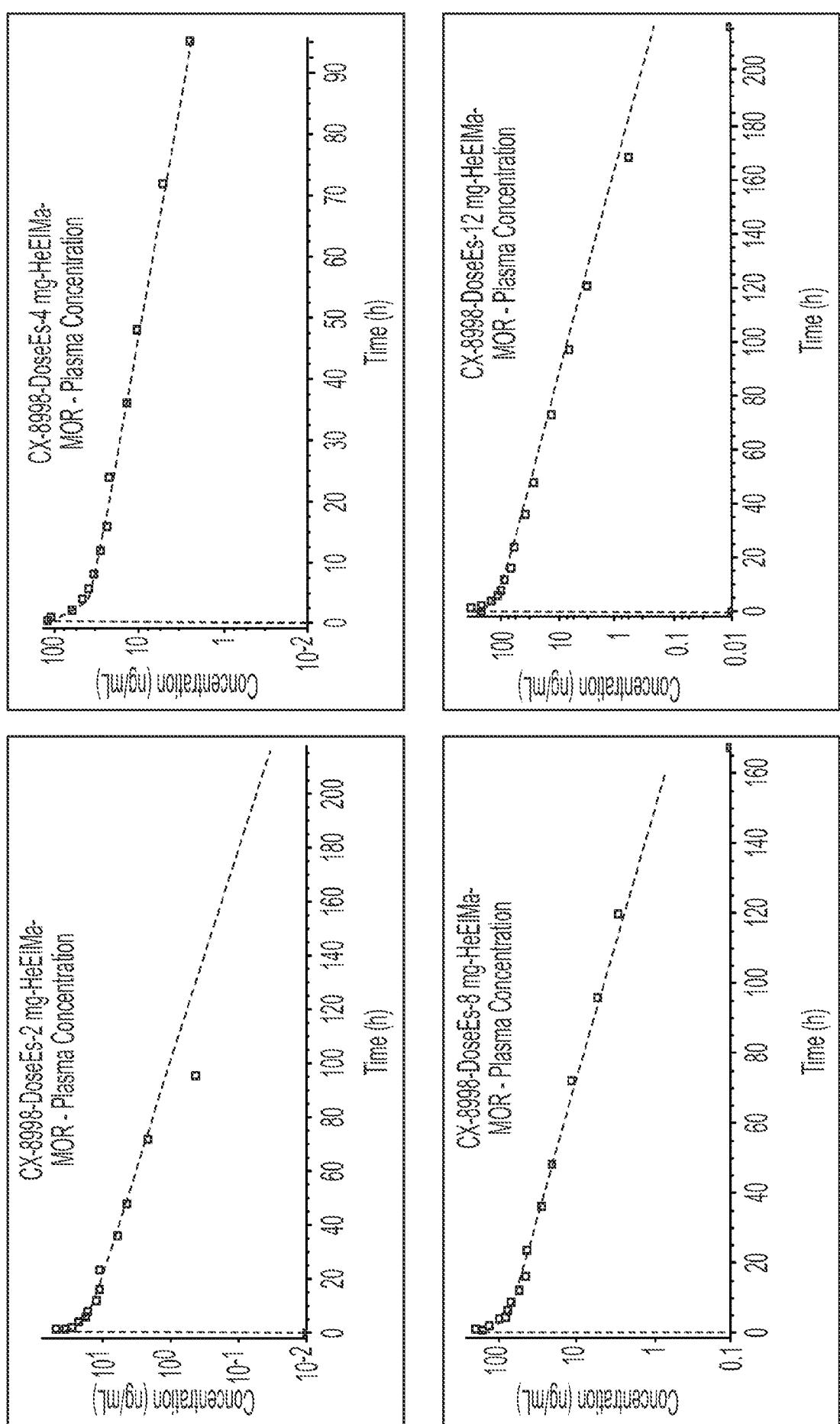


FIG. 31

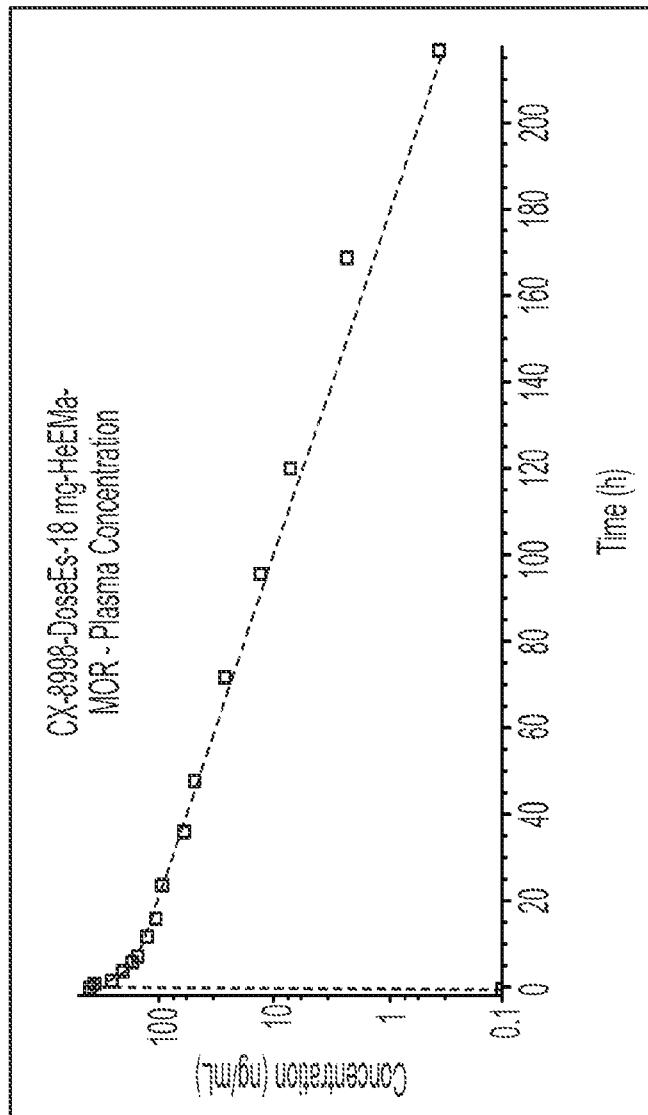


FIG. 31  
CONTINUED

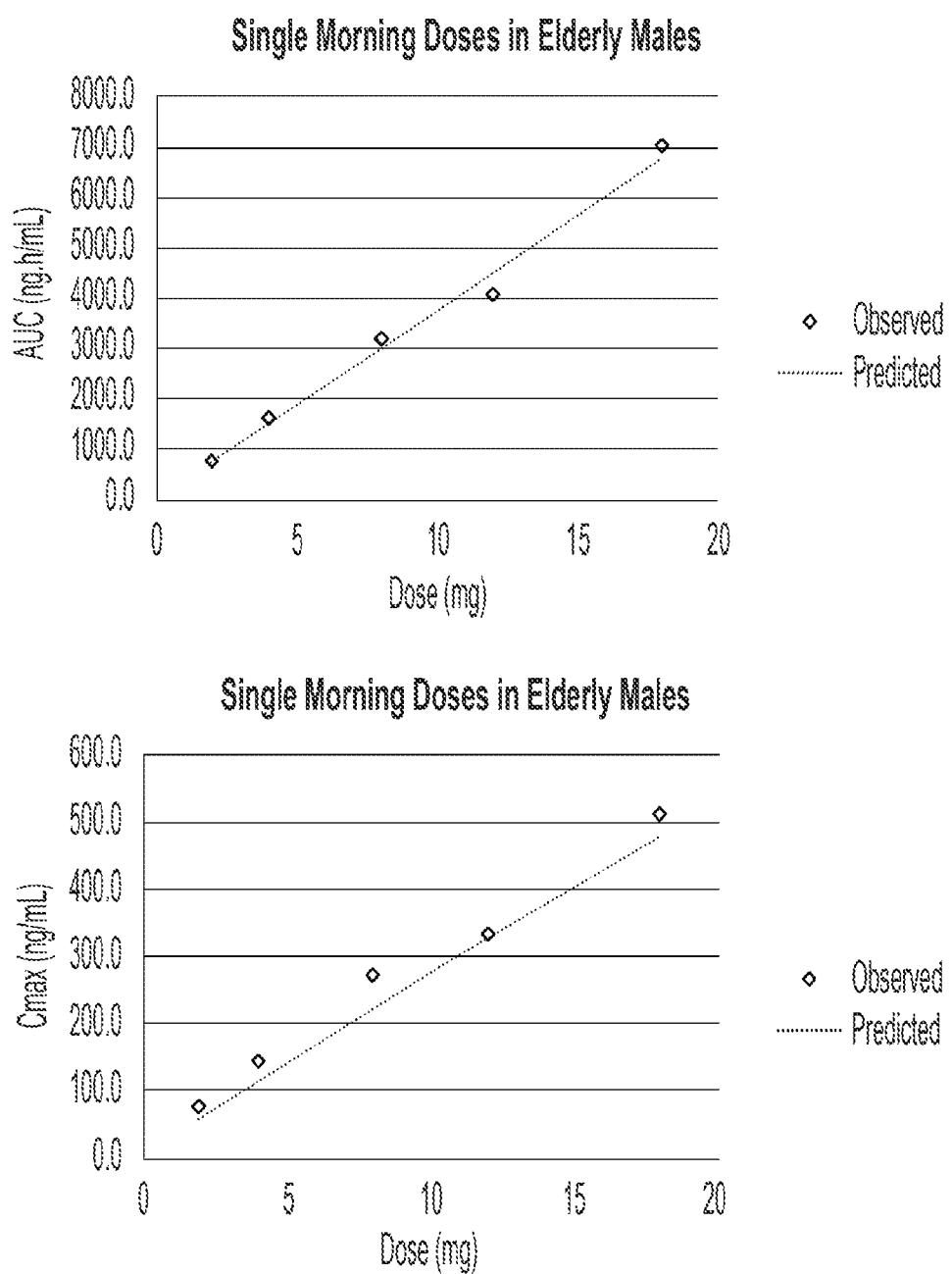


FIG. 32

36/83

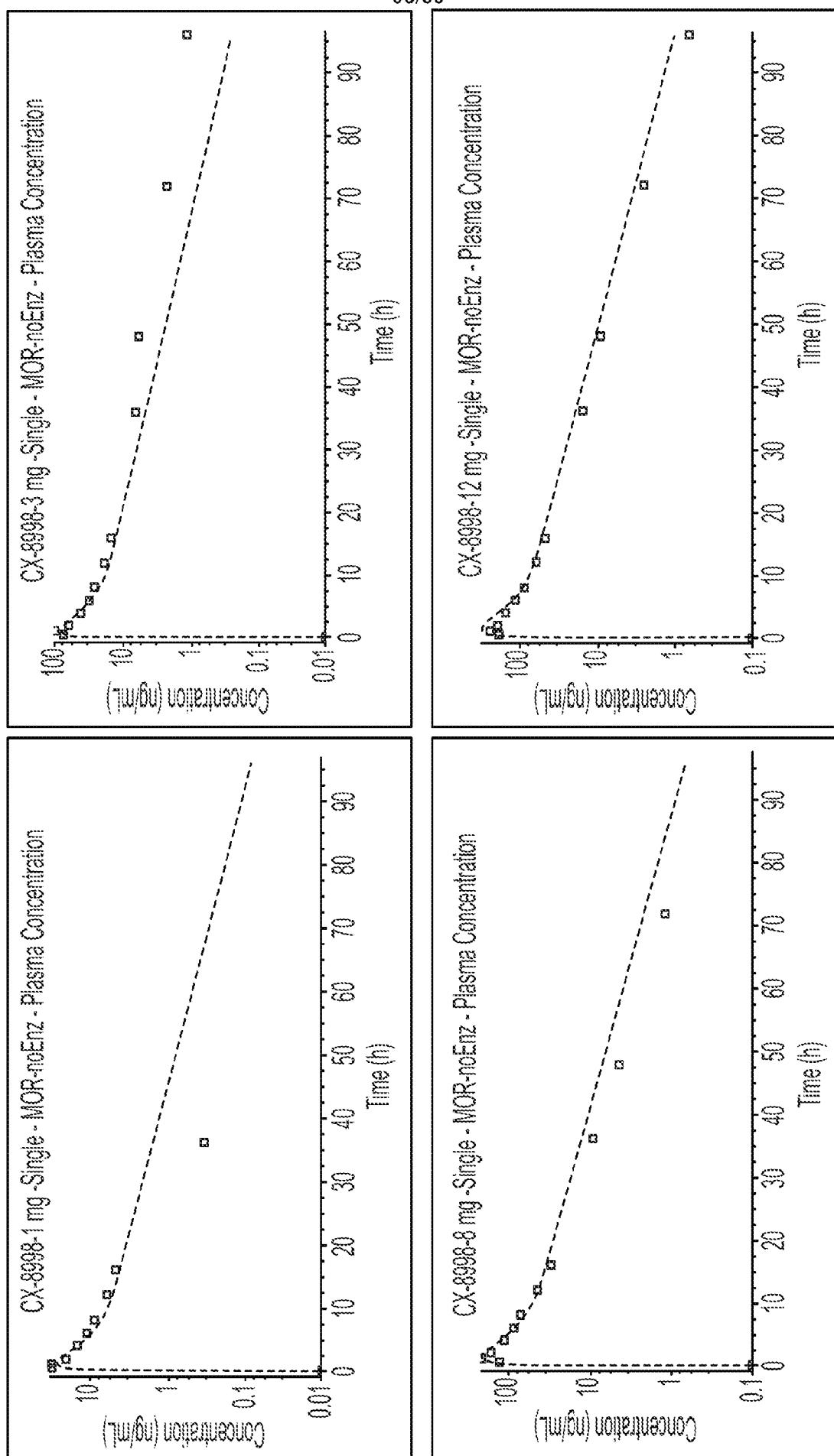


FIG. 33

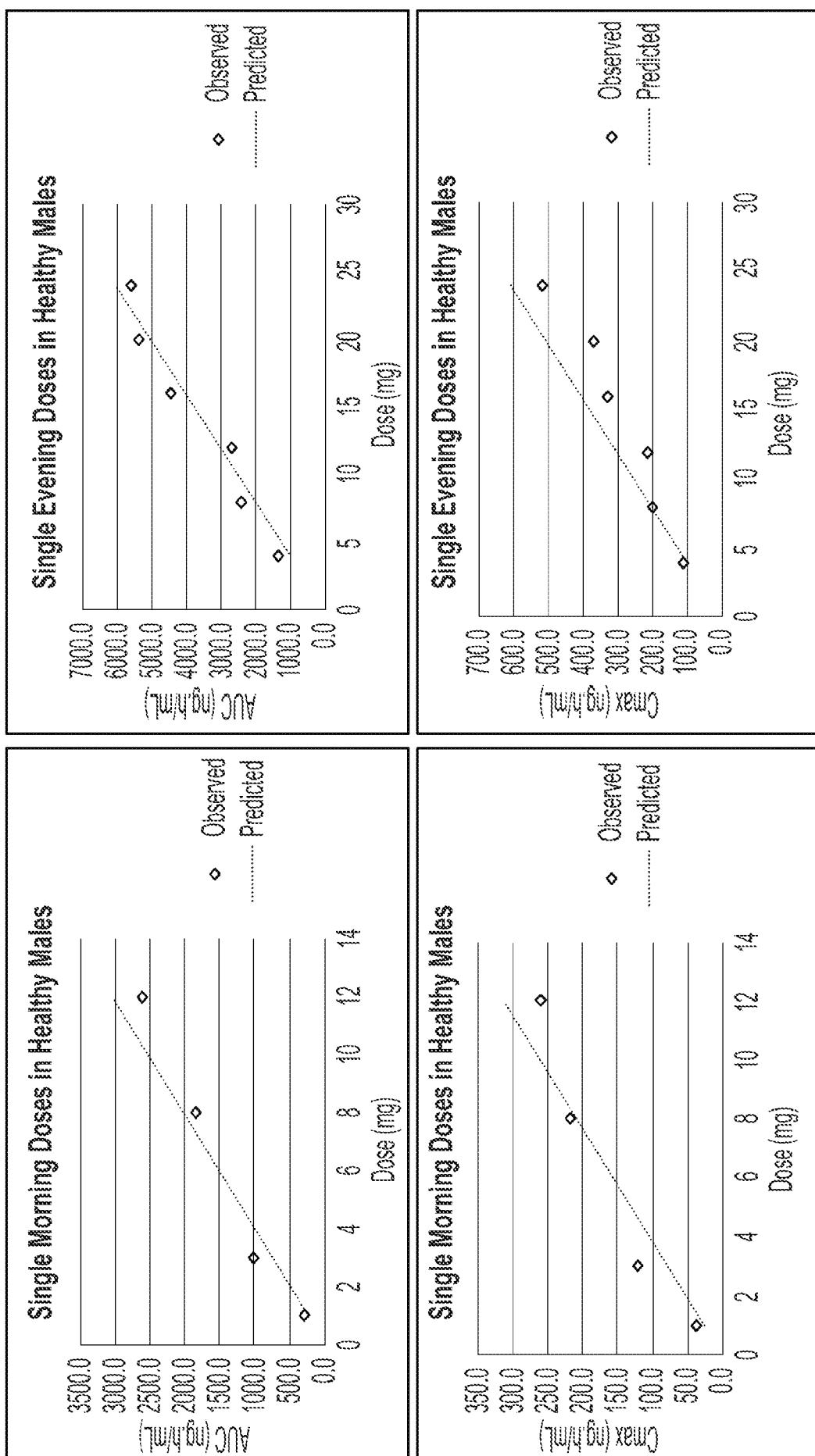


FIG. 34

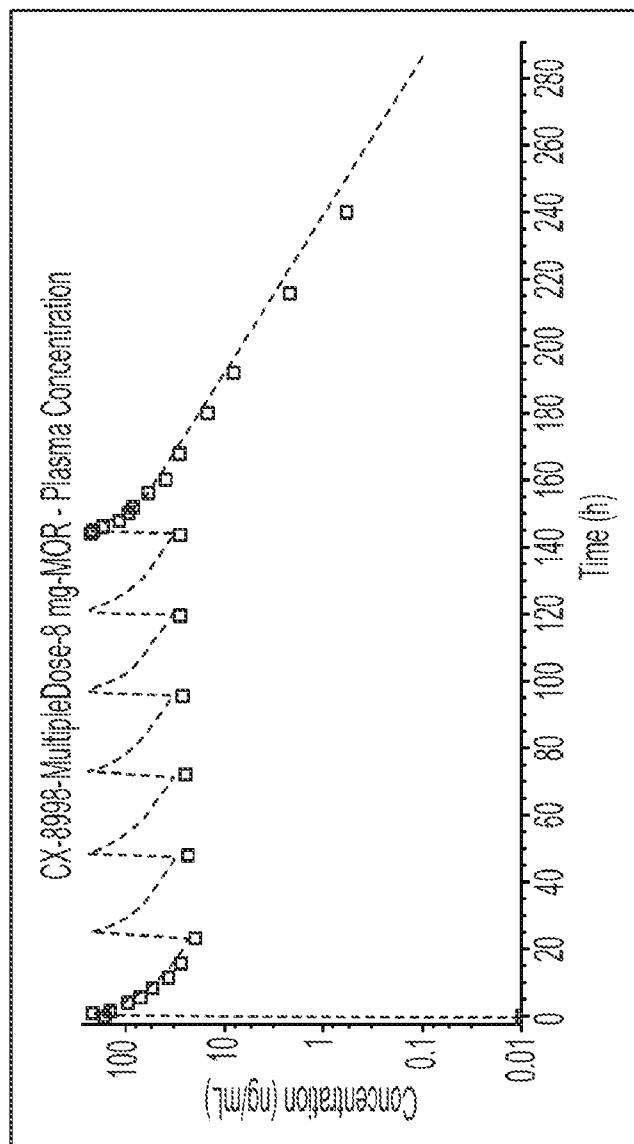


FIG. 35

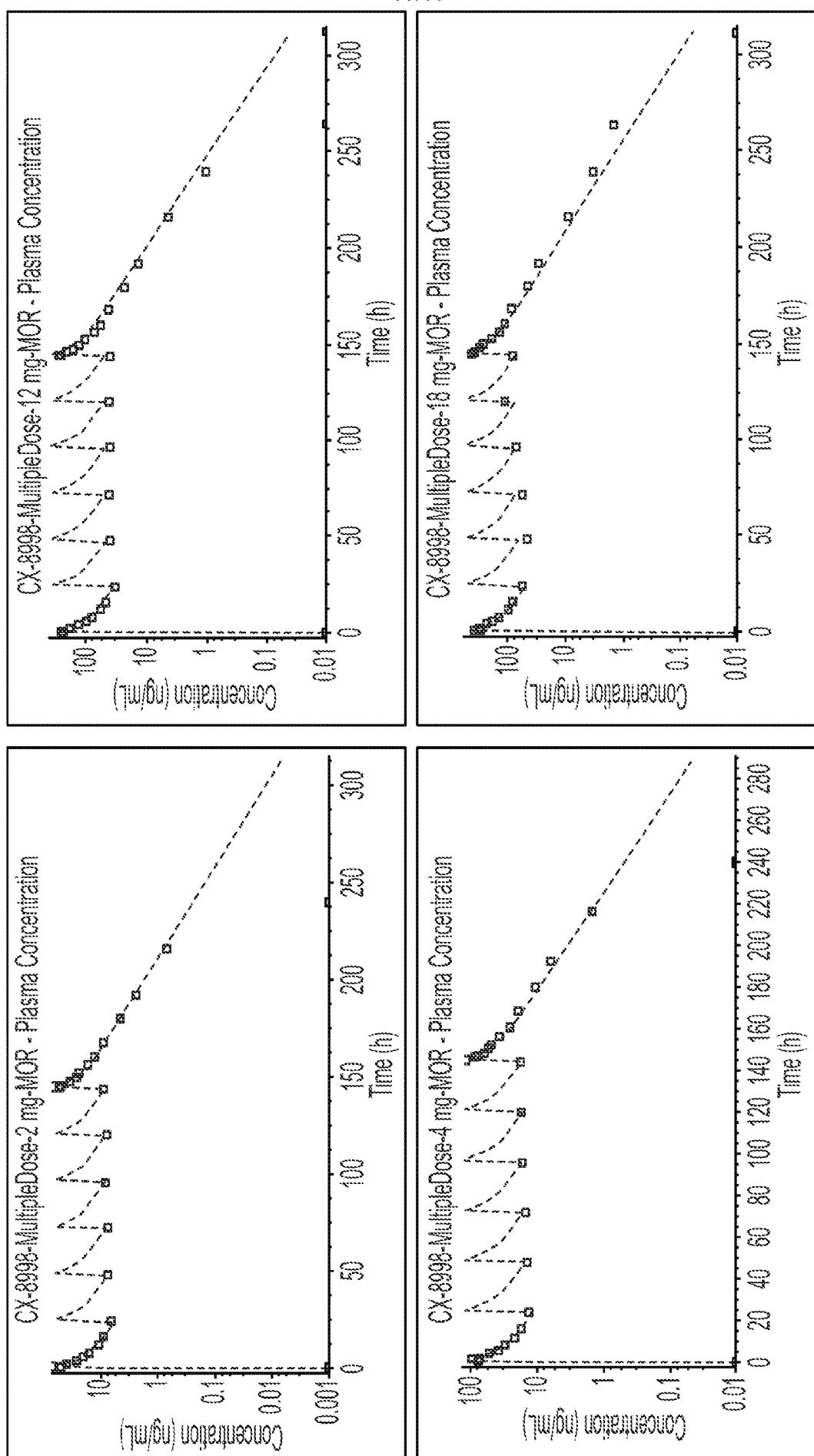


FIG. 35  
CONTINUED

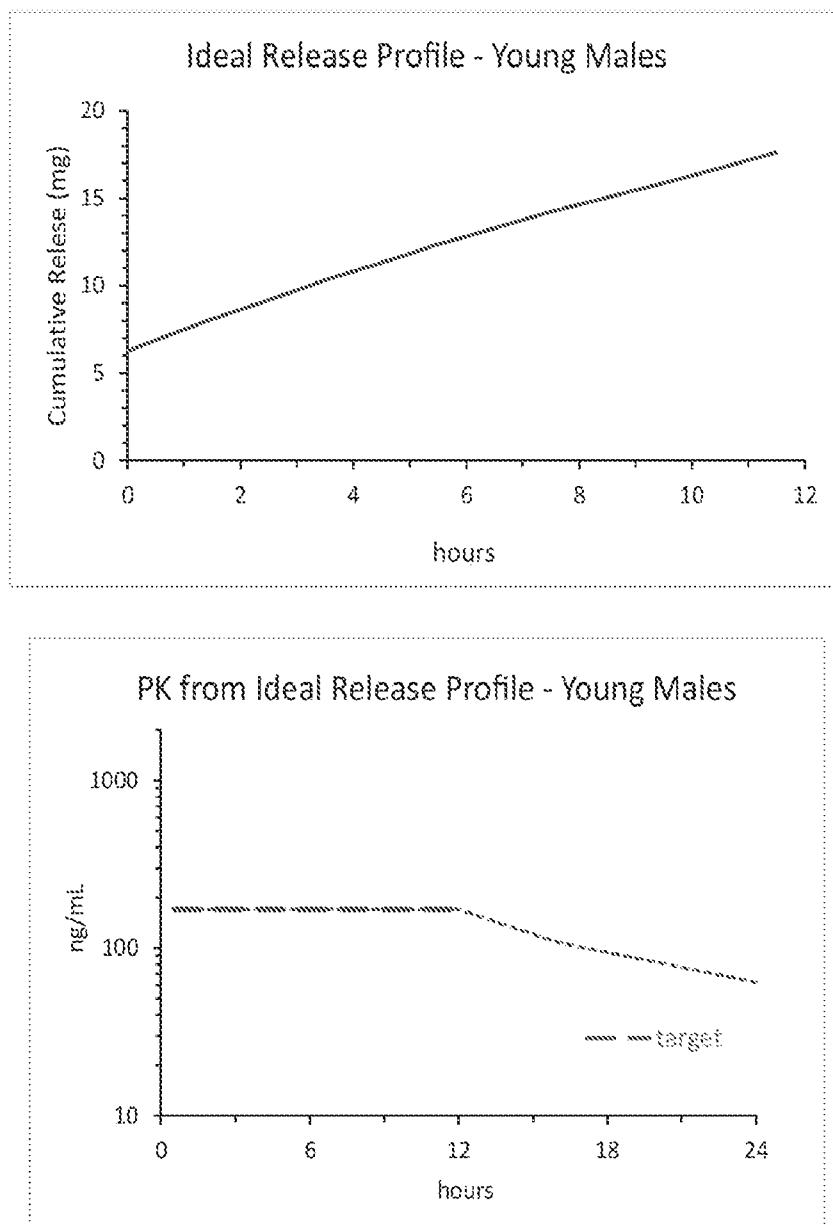


FIG. 36

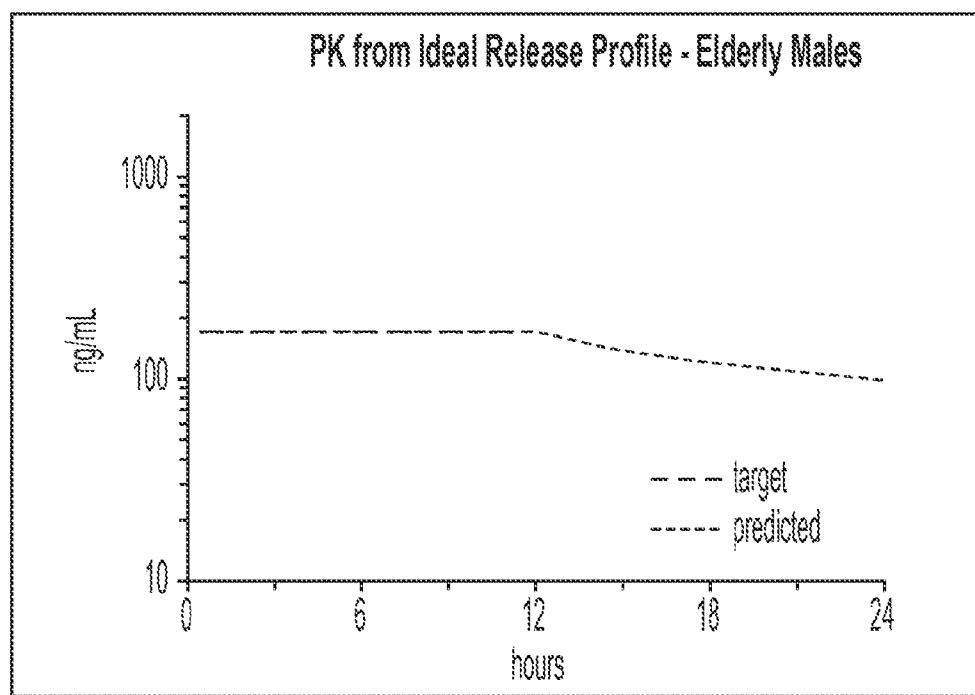
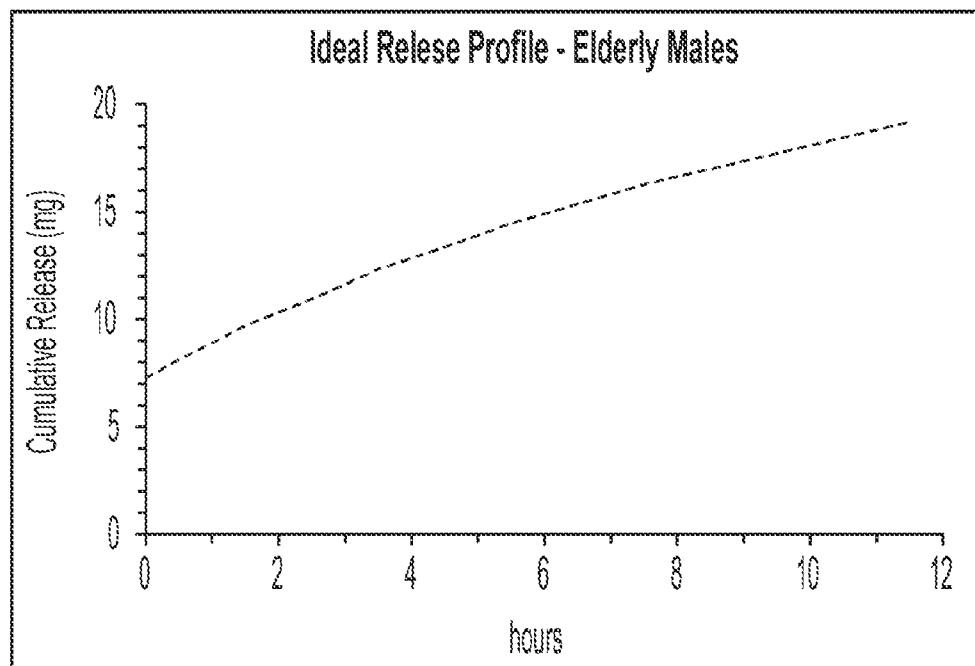


FIG. 37

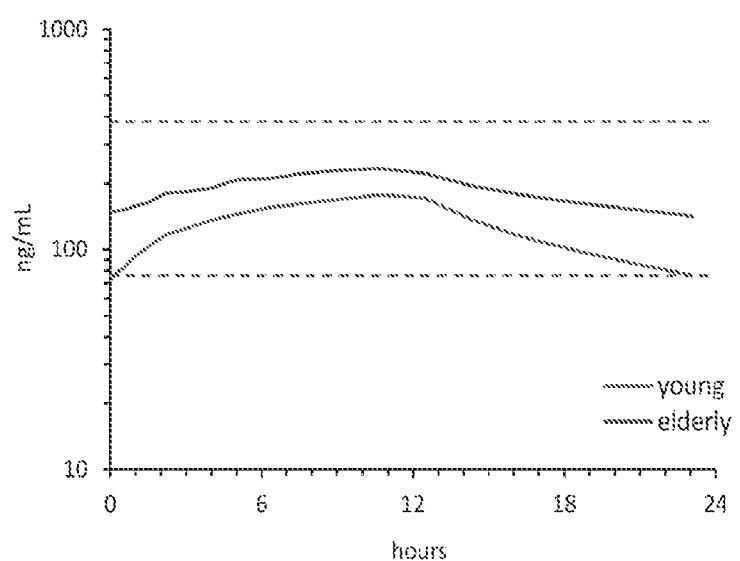
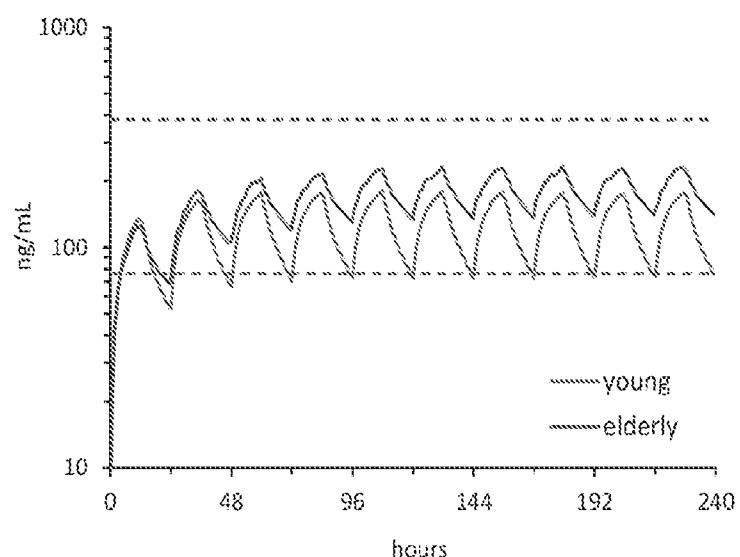


FIG. 38

43/83

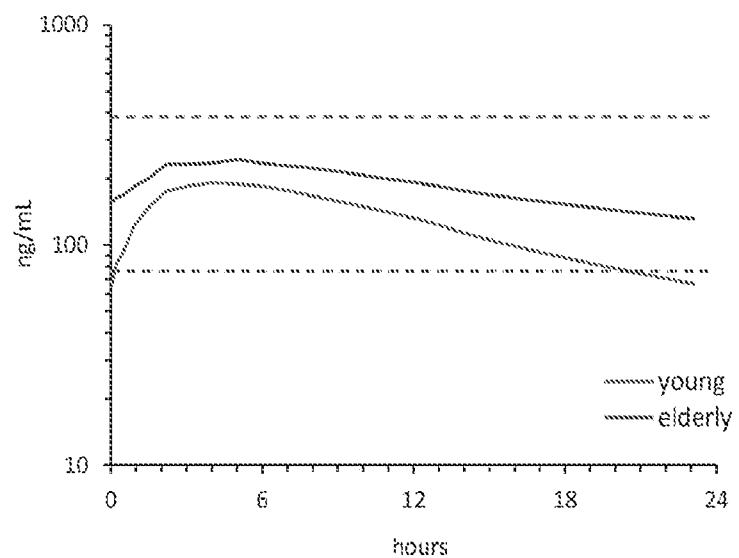
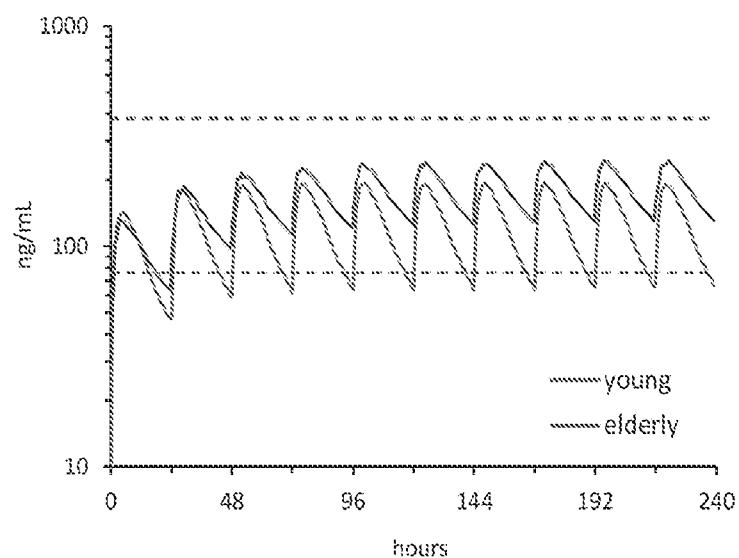


FIG. 39

44/83

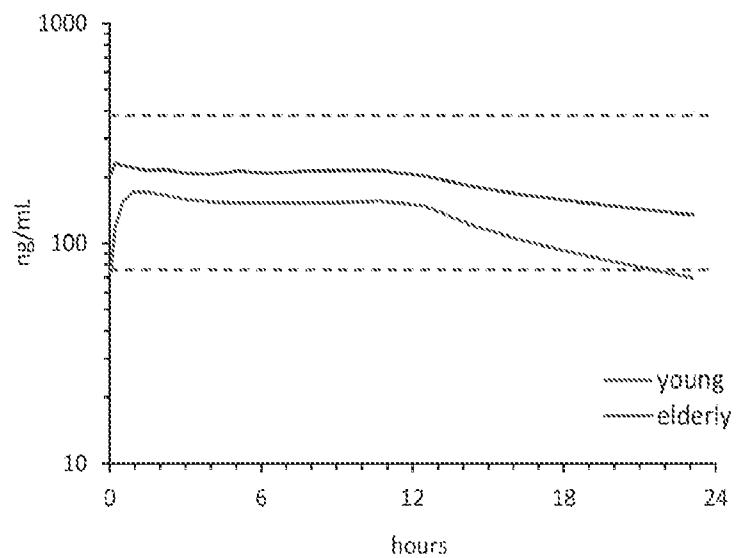
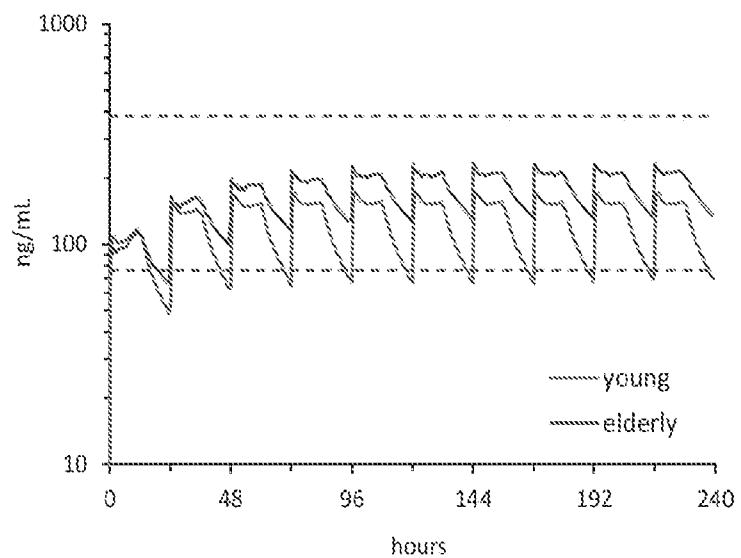


FIG. 40

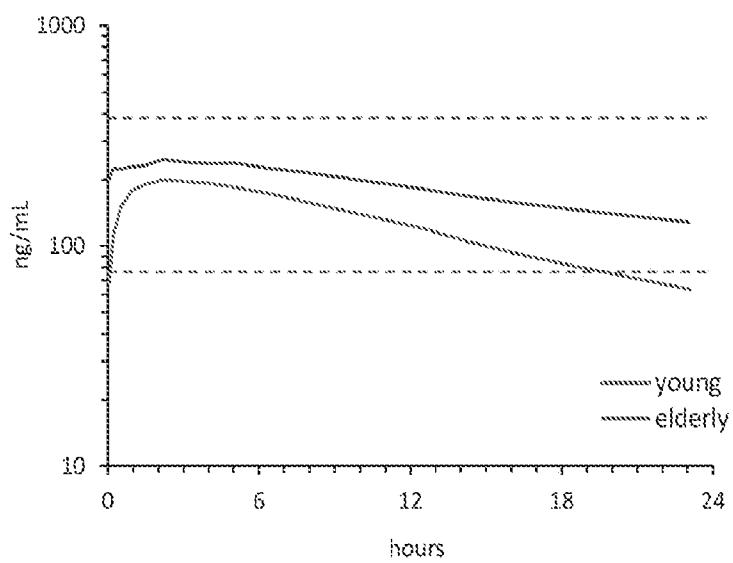
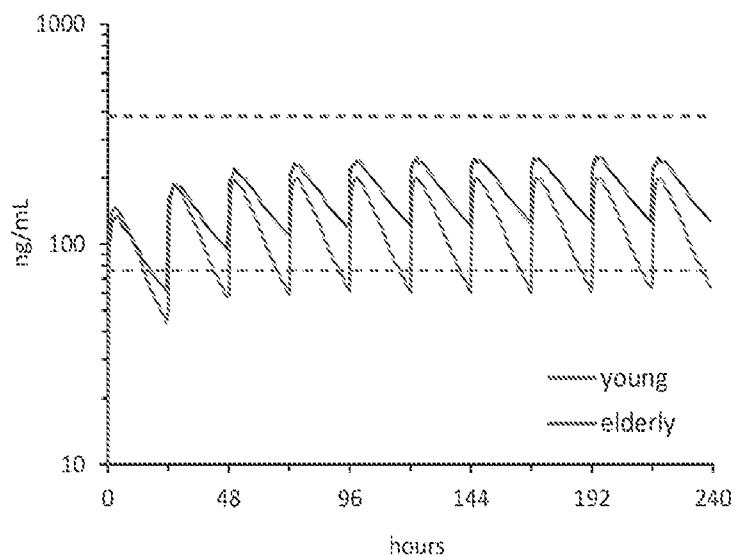


FIG. 41

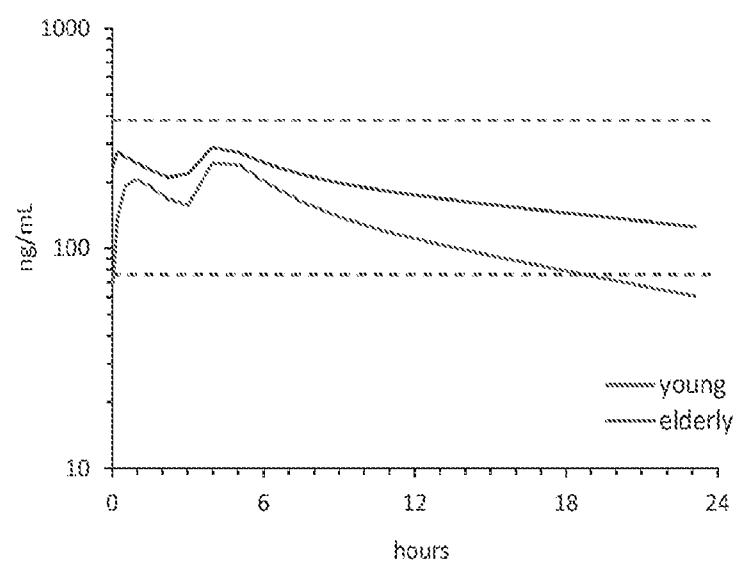
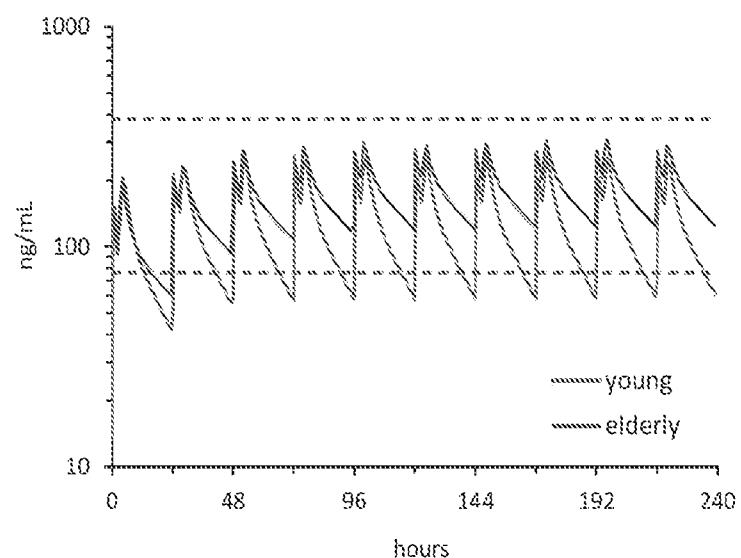


FIG. 42

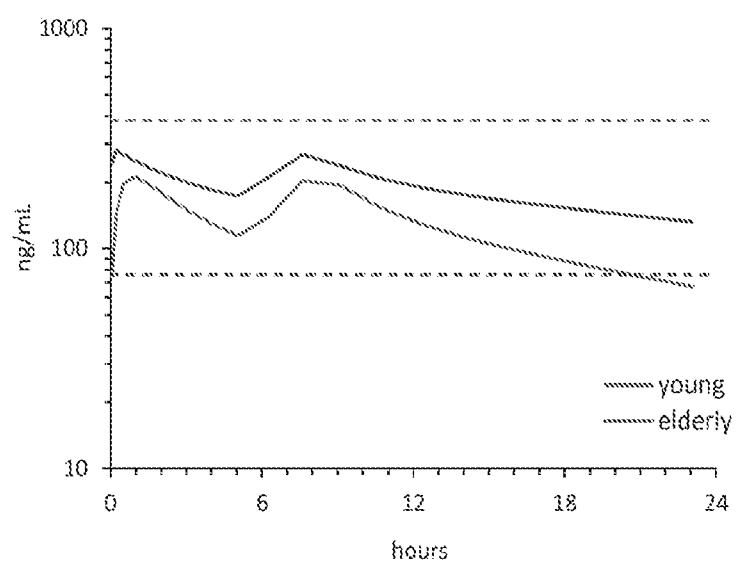
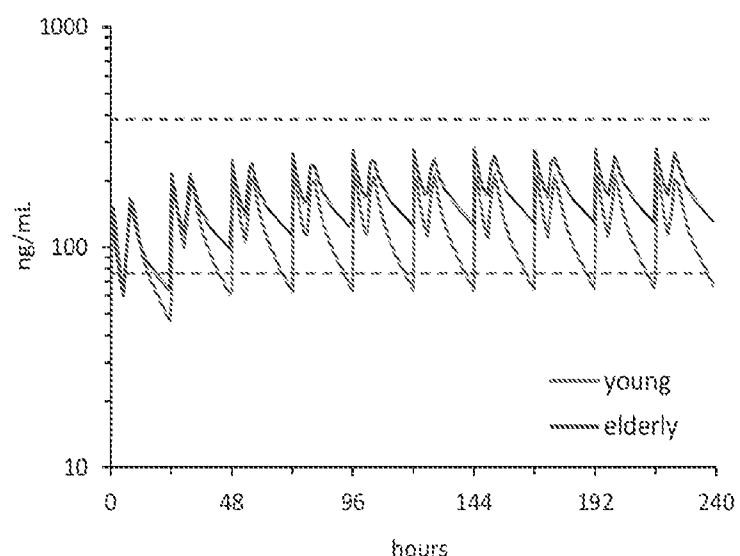


FIG. 43

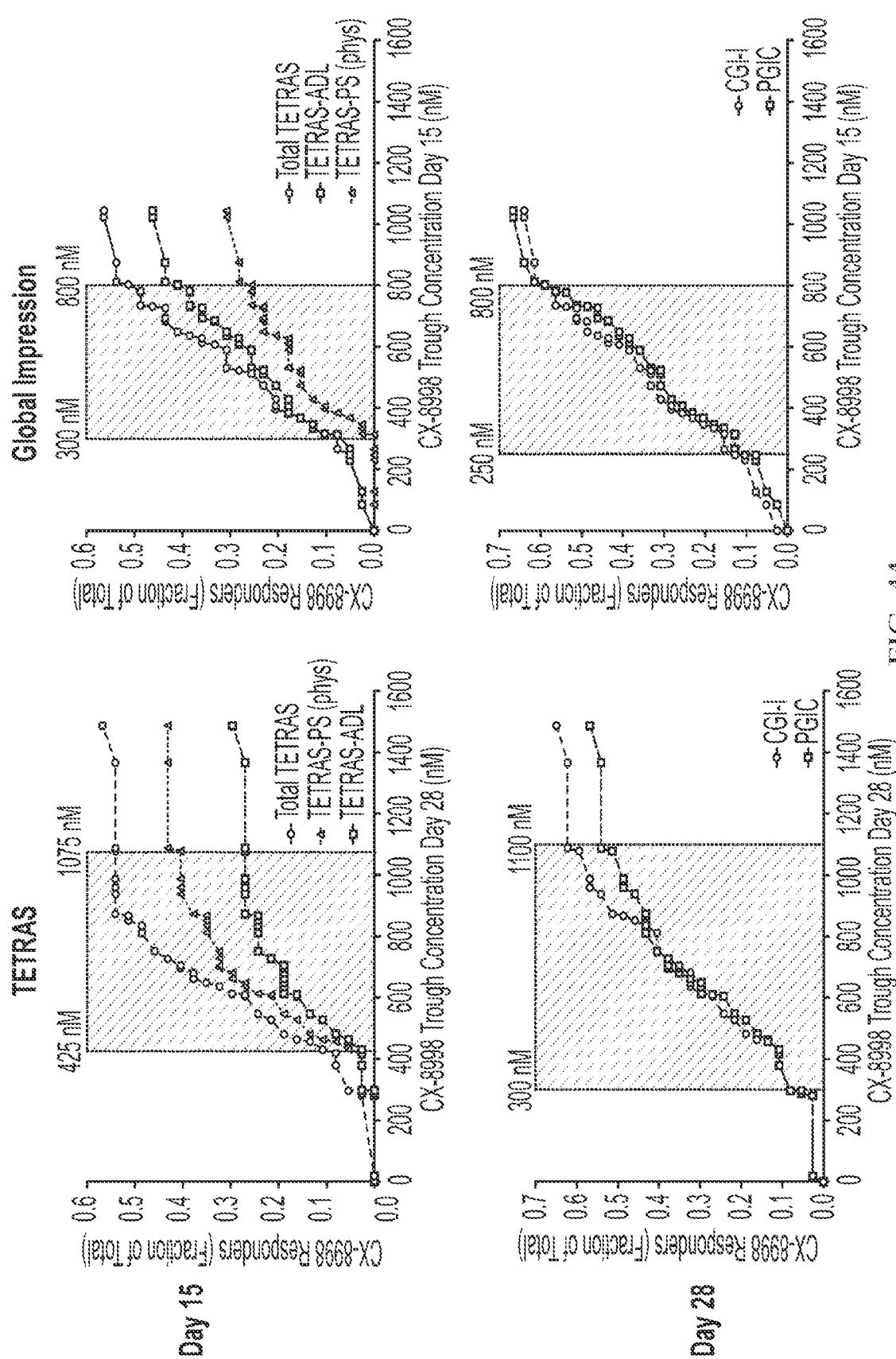


FIG. 44

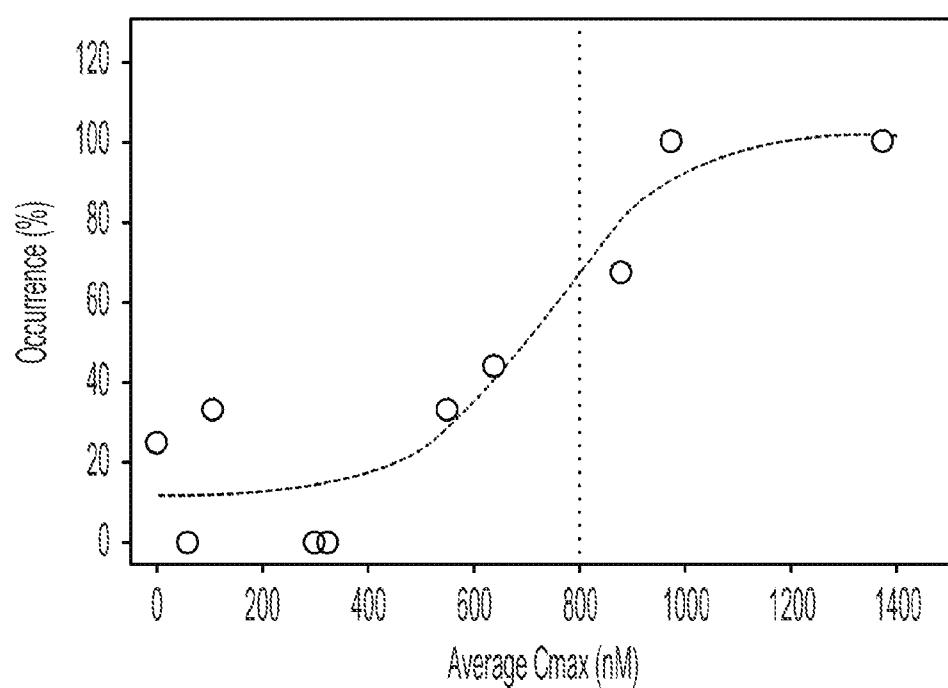


FIG. 45

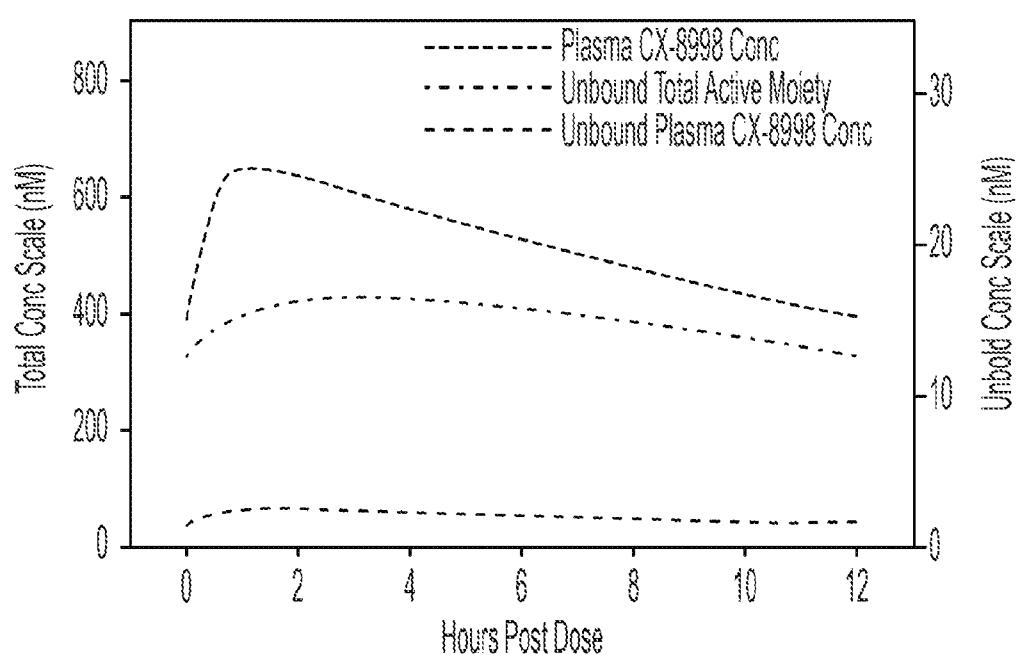


FIG. 46

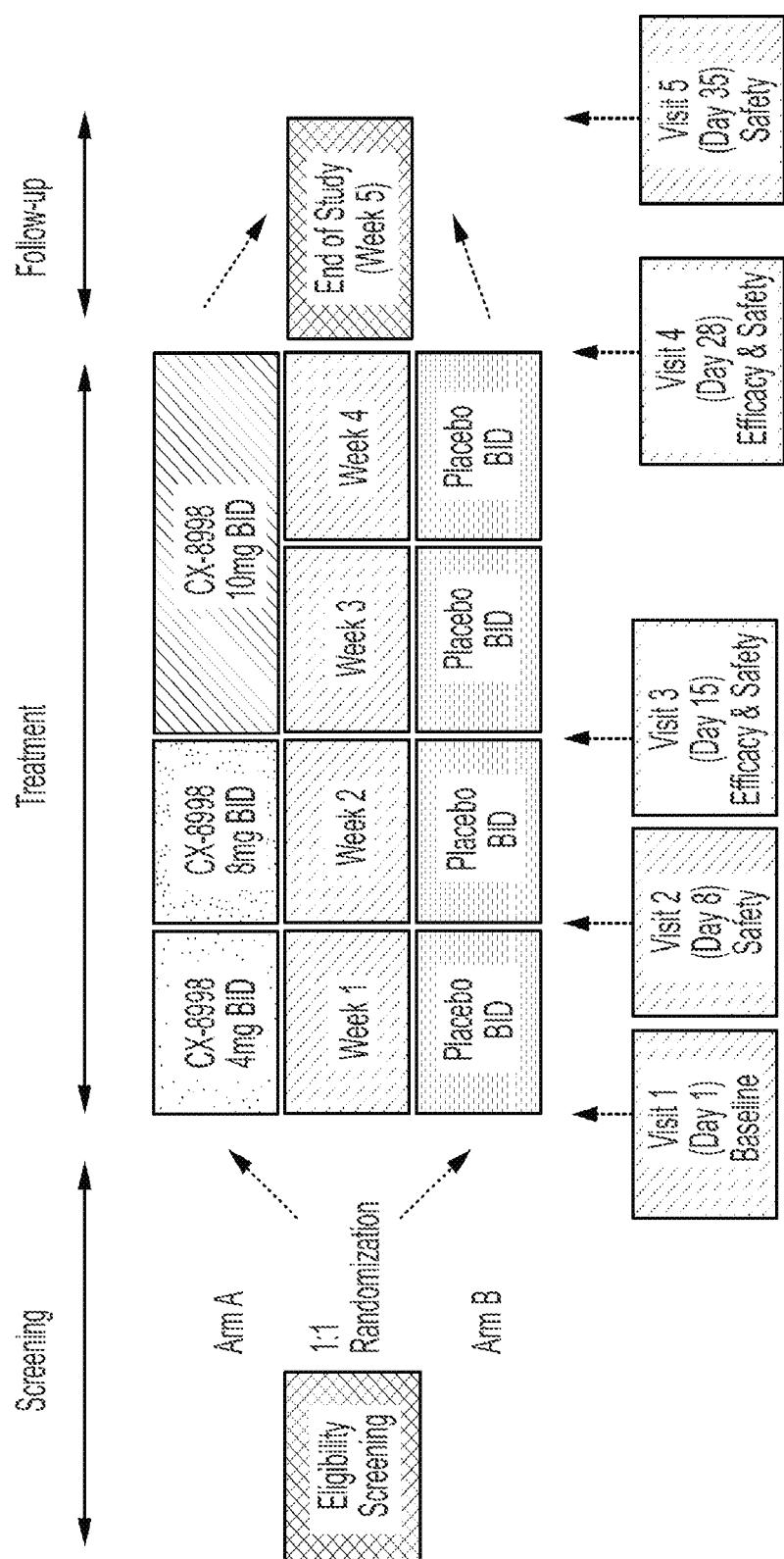


FIG. 47A

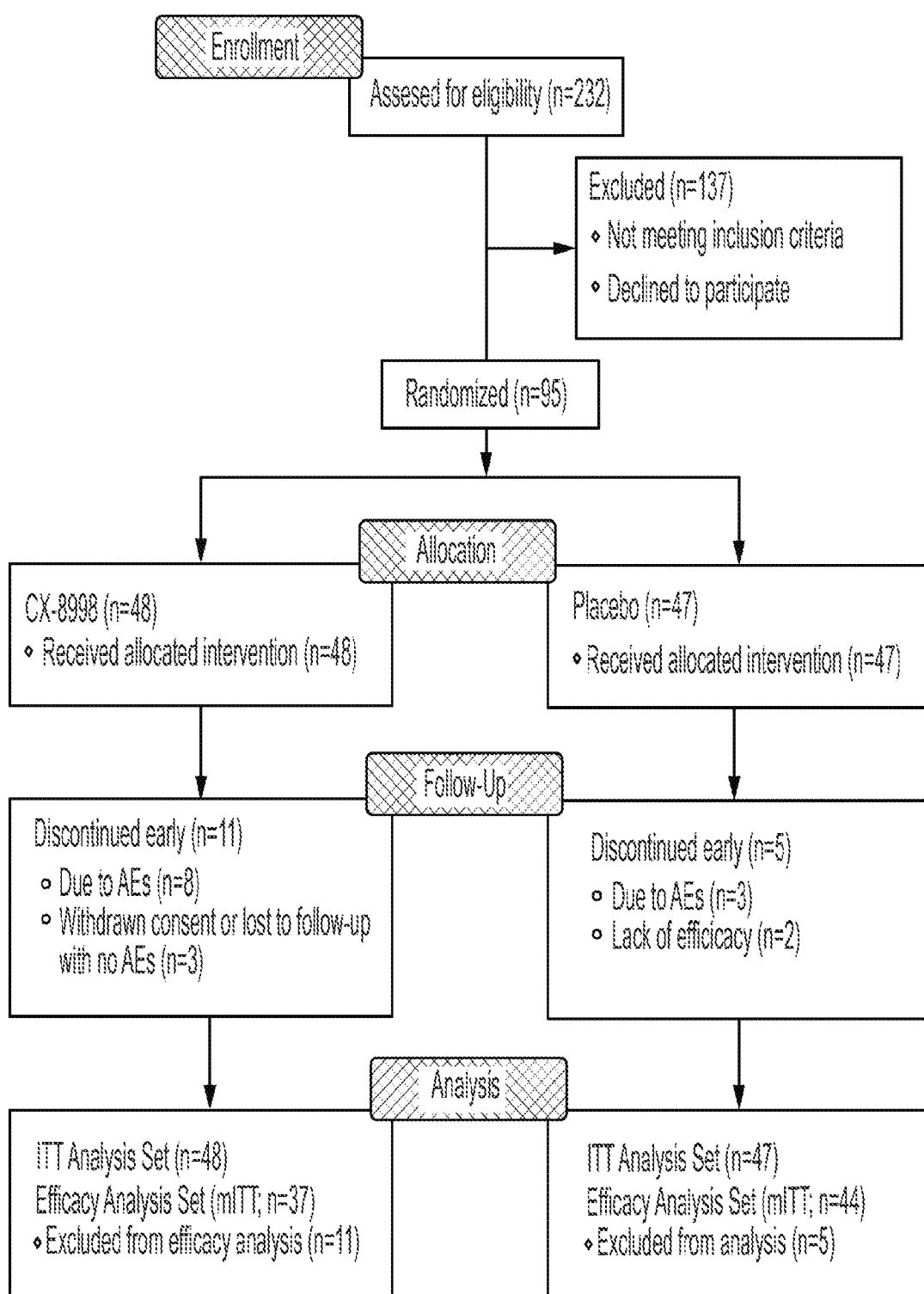


FIG. 47B

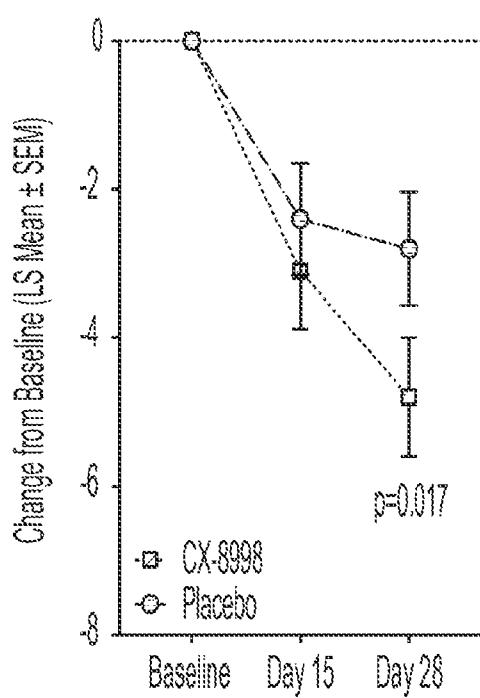


FIG. 48A

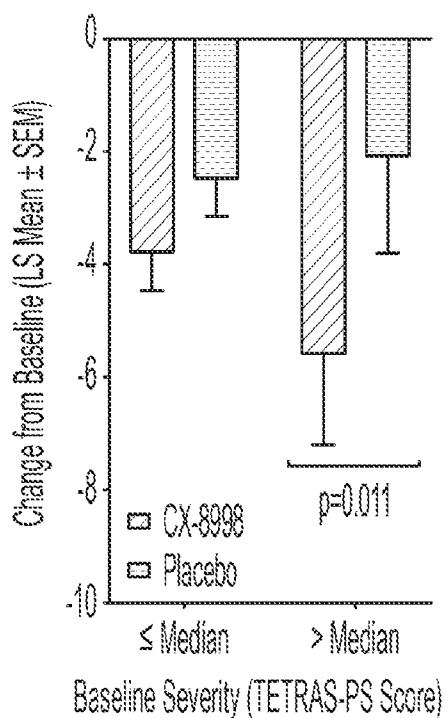


FIG. 48B

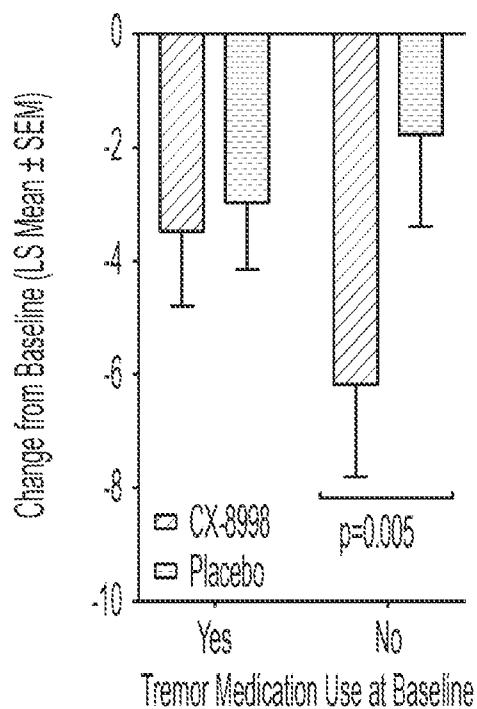


FIG. 48C

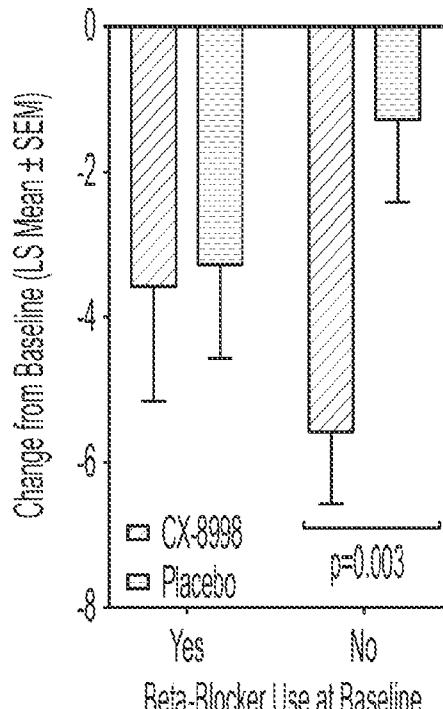


FIG. 48D

54/83

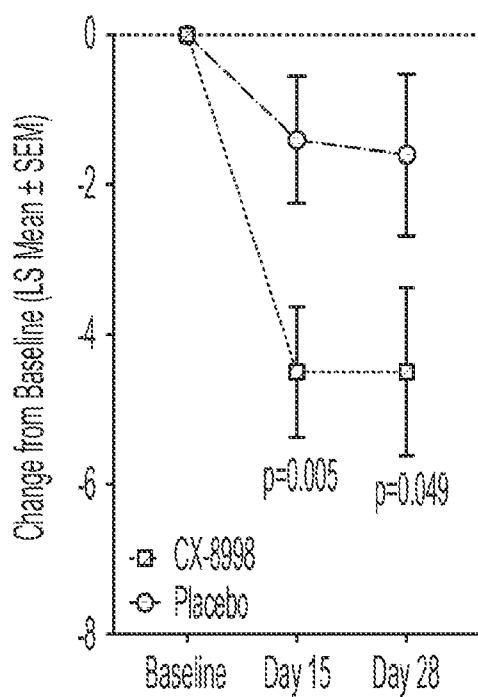


FIG. 49A

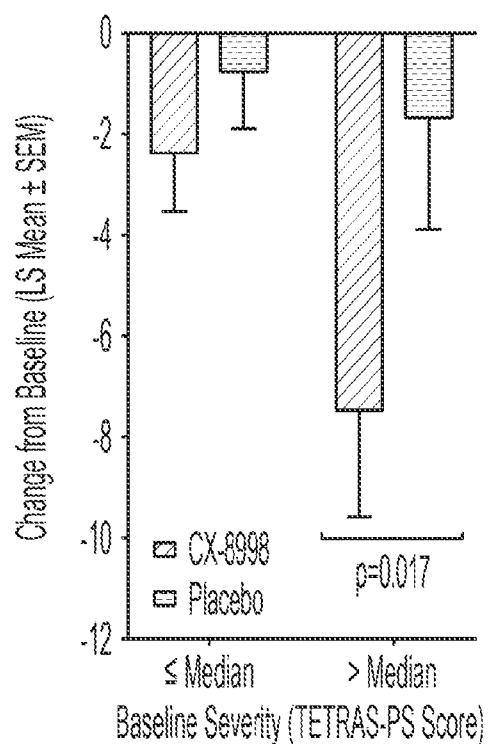


FIG. 49B

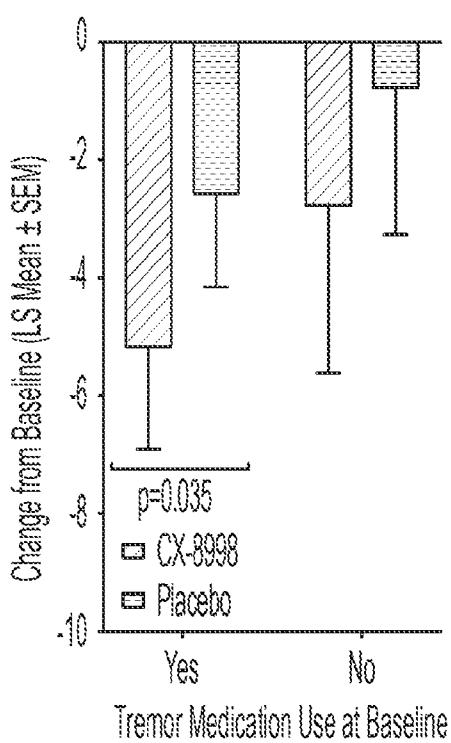


FIG. 49C

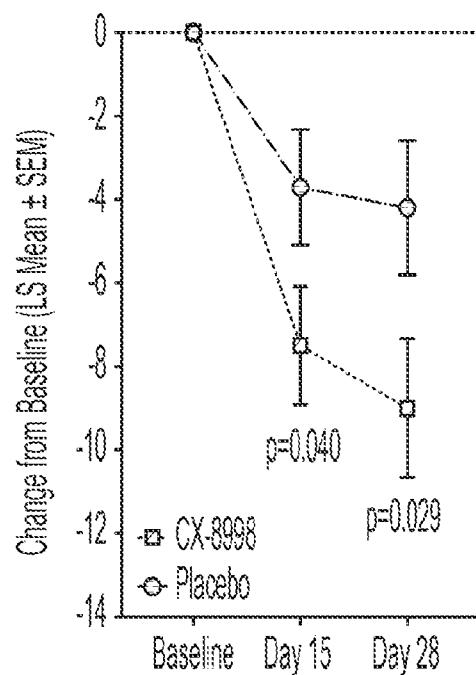


FIG. 49D

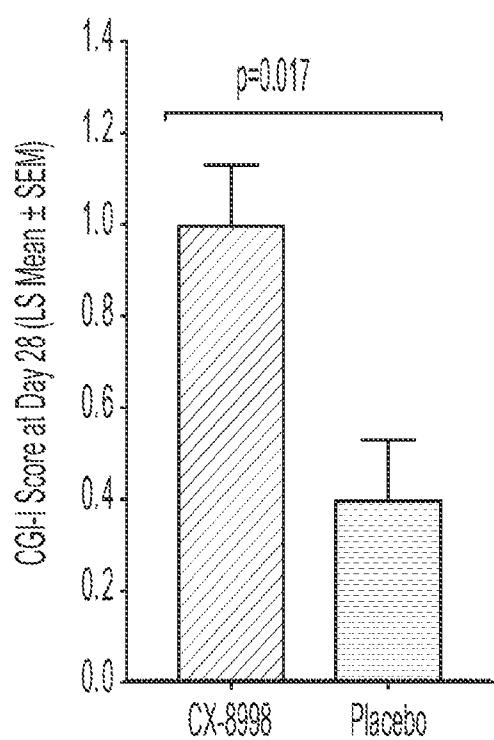


FIG. 50A

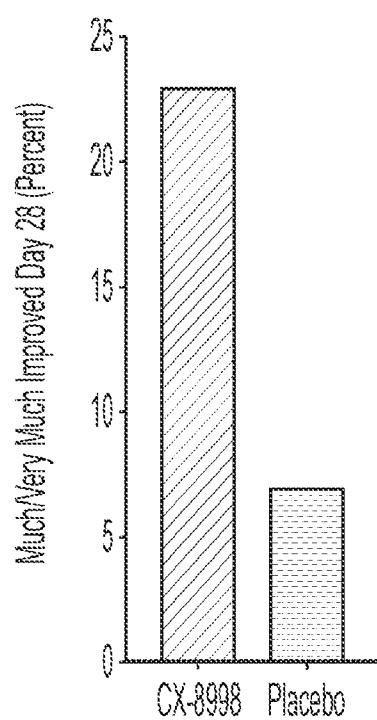


FIG. 50B

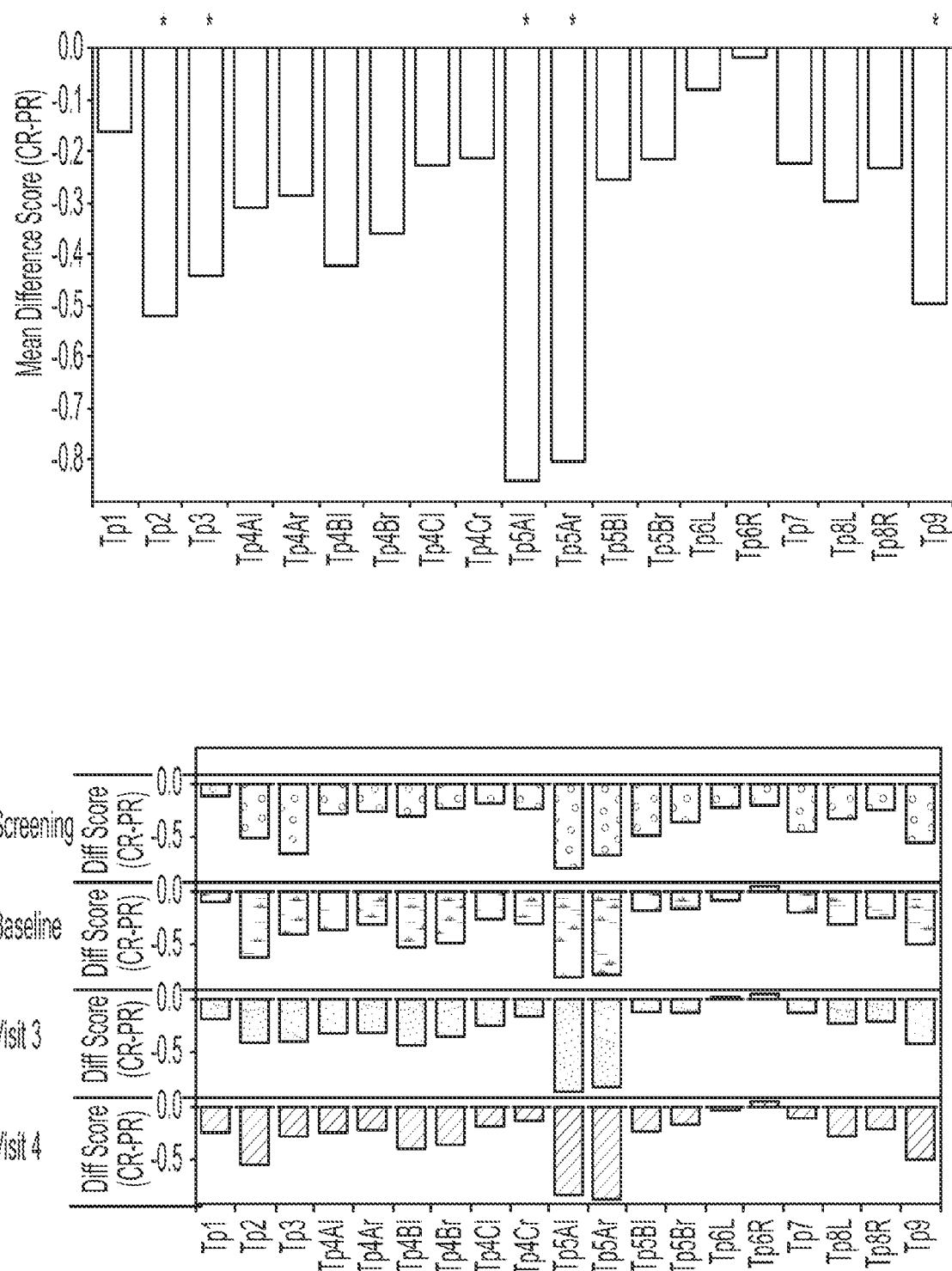


FIG. 51

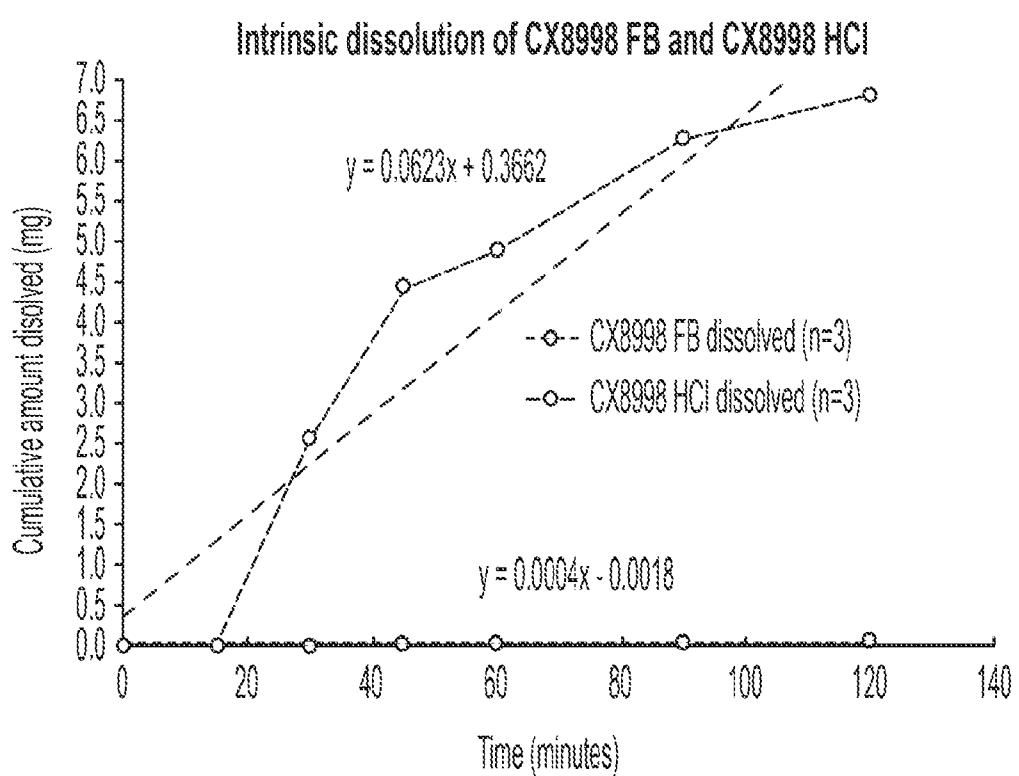


FIG. 52

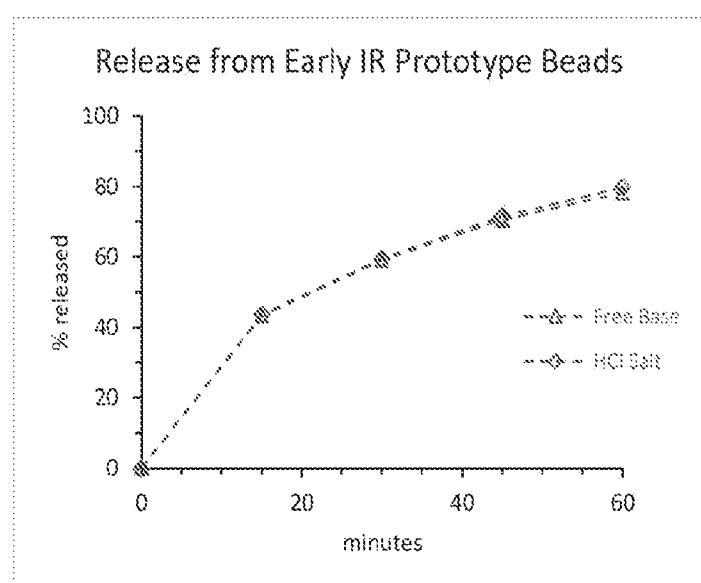


FIG. 53

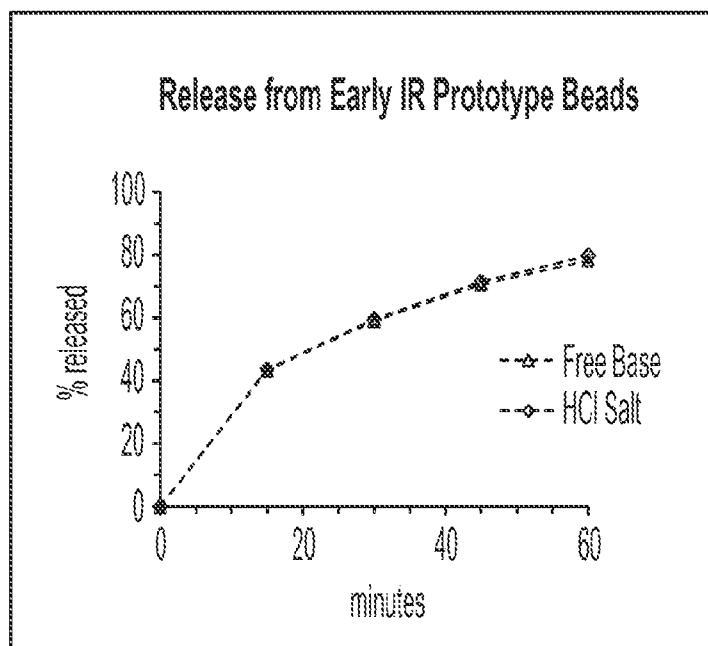


FIG. 54A

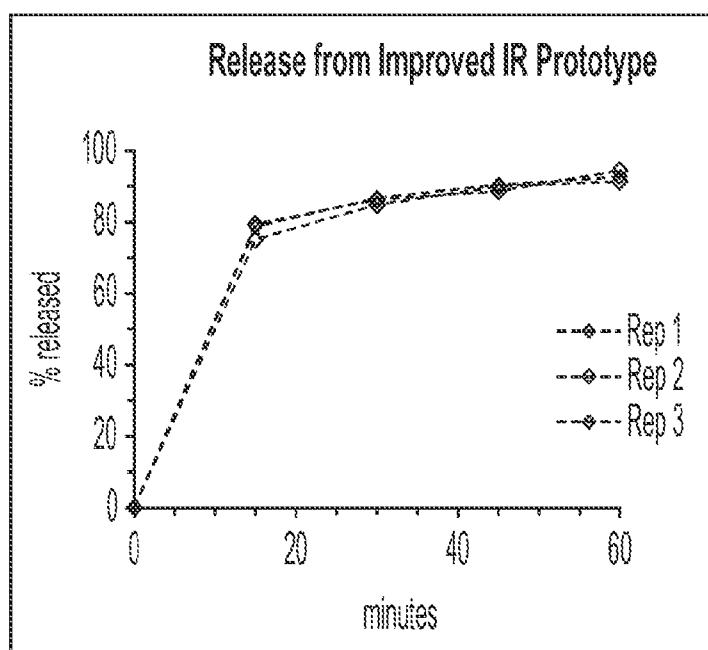


FIG. 54B

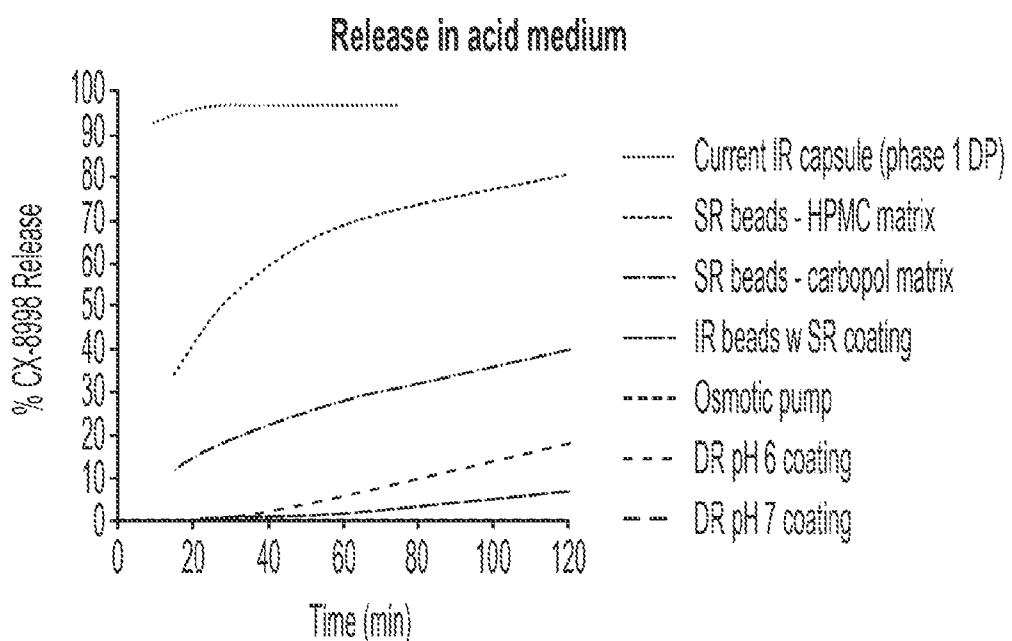


FIG. 55A

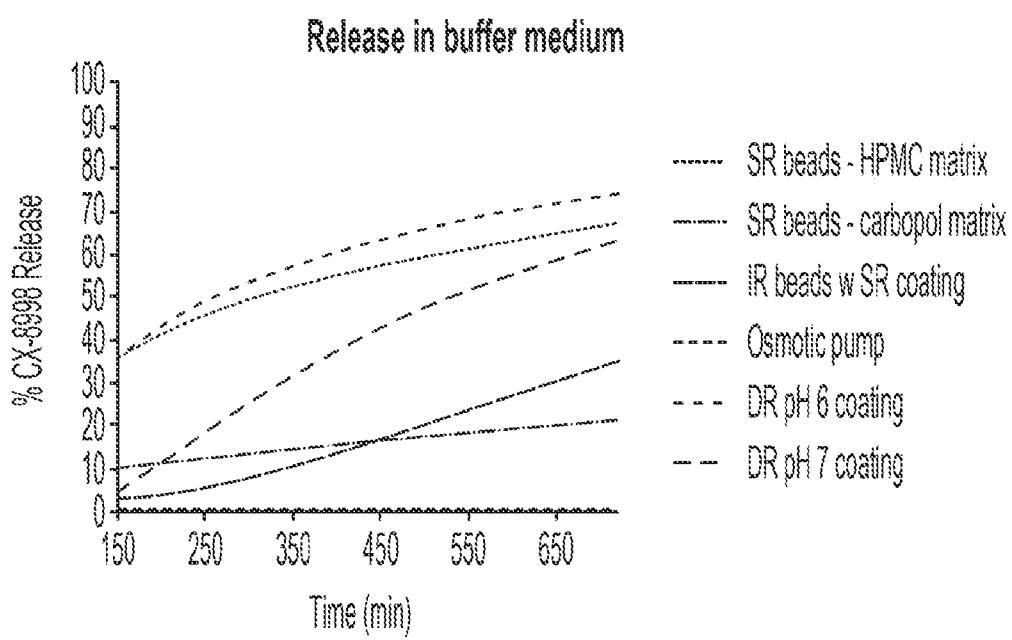


FIG. 55B

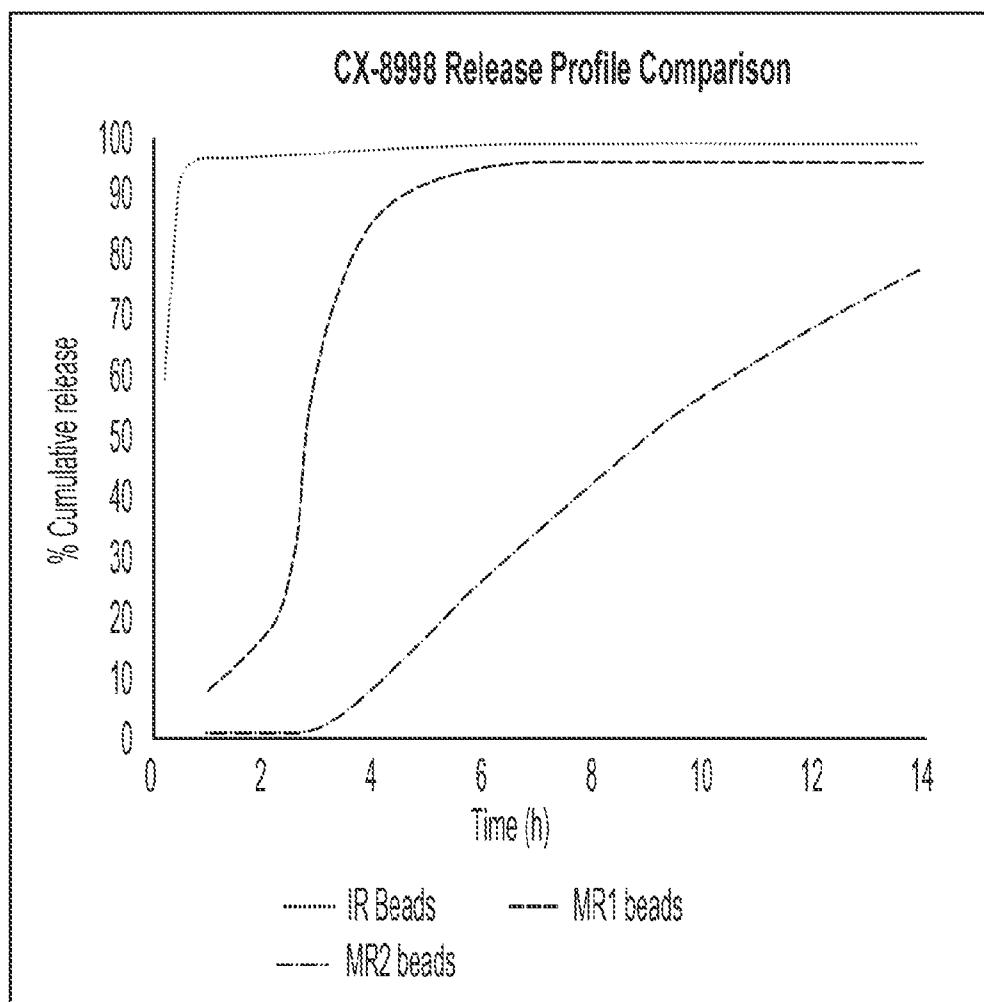


FIG. 56

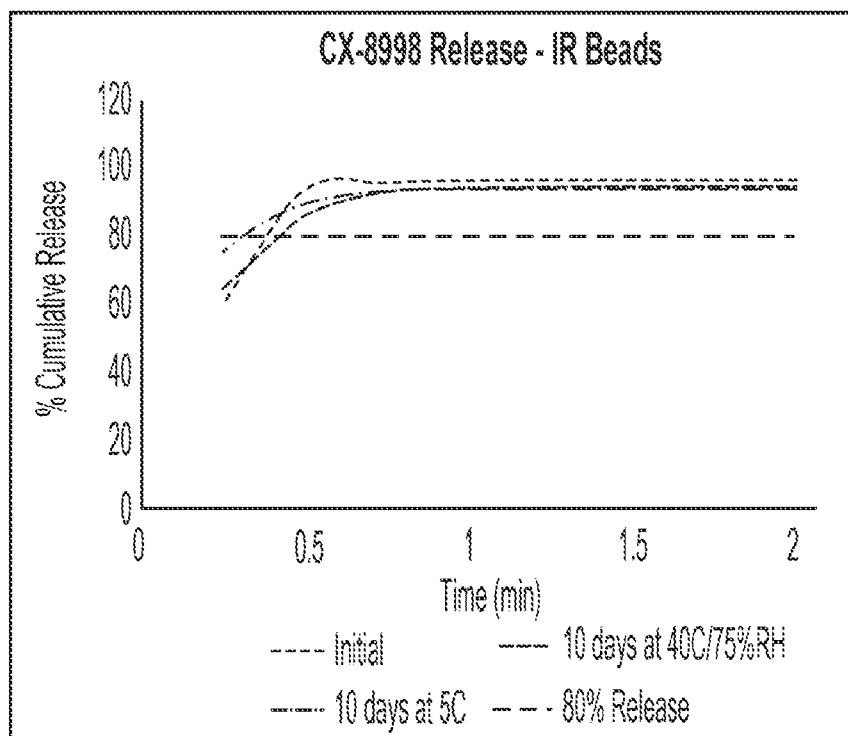


FIG. 57A

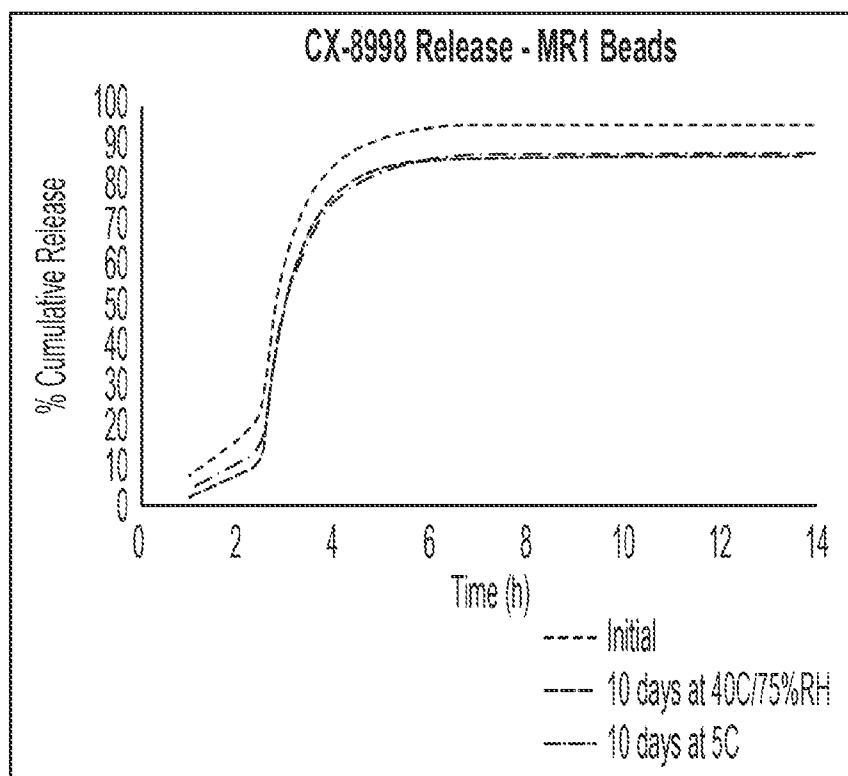


FIG. 57B

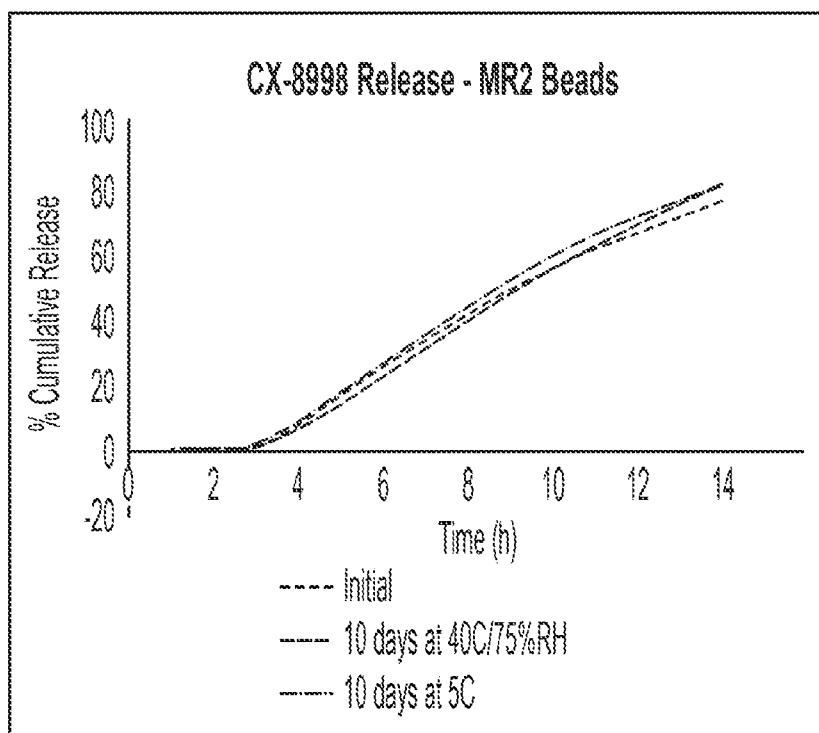
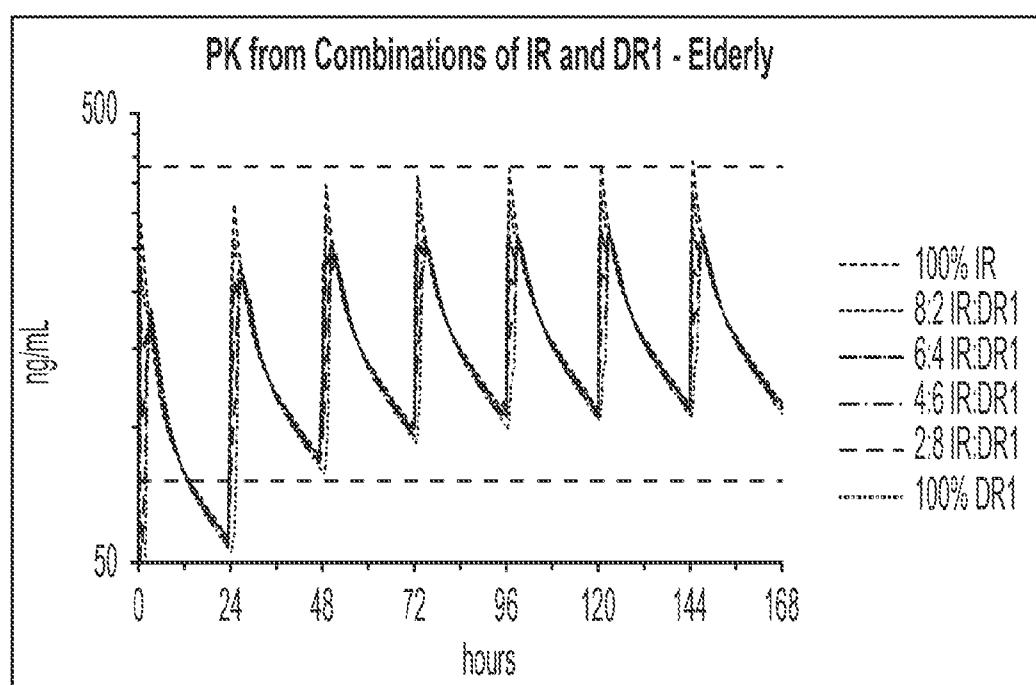


FIG. 57C

## 7-day time course (12 mg QD)



at steady state

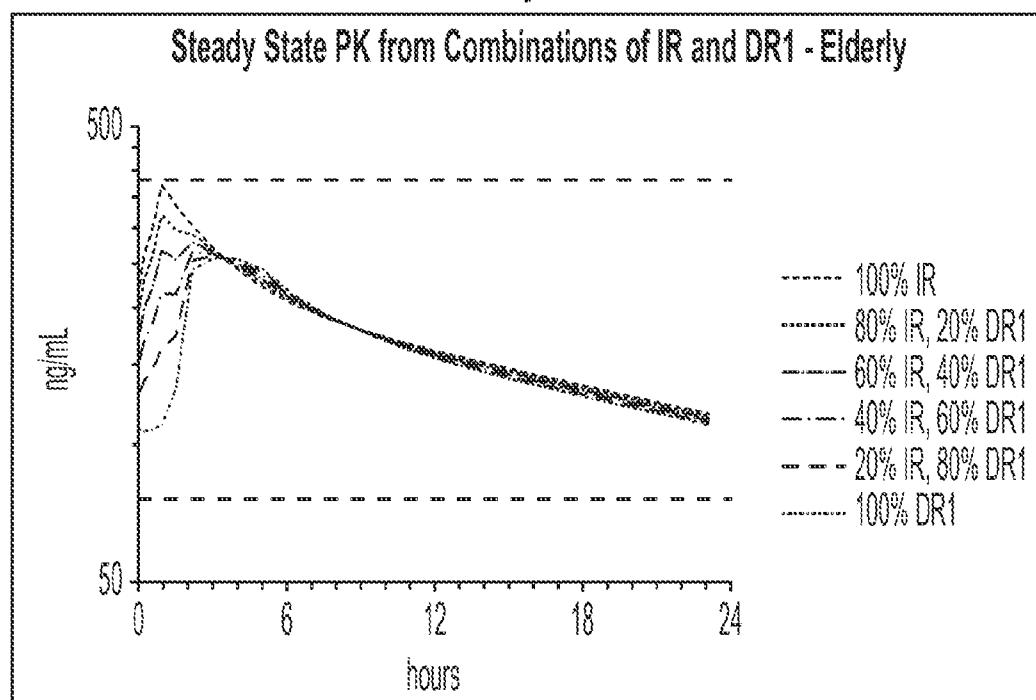
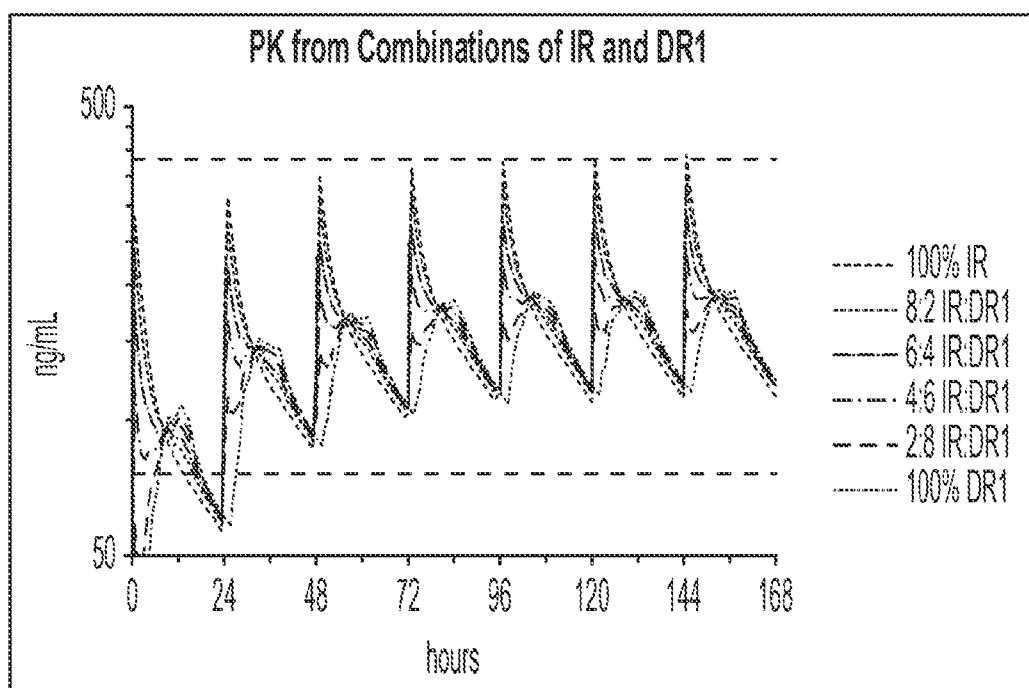


FIG. 58

## 7-day time course (12 mg QD)



at steady state

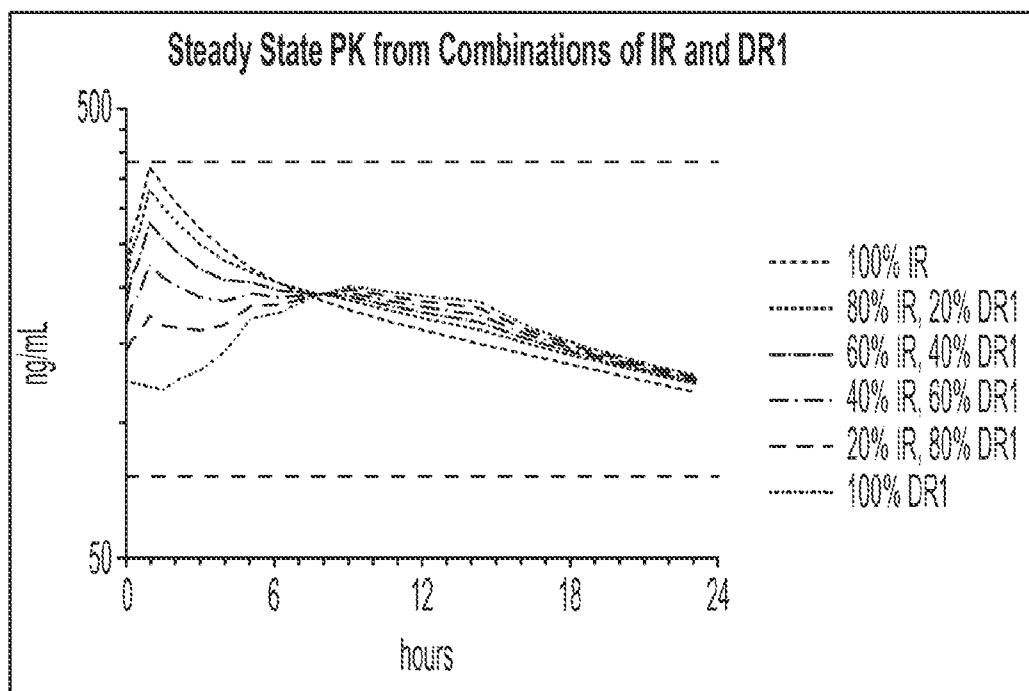
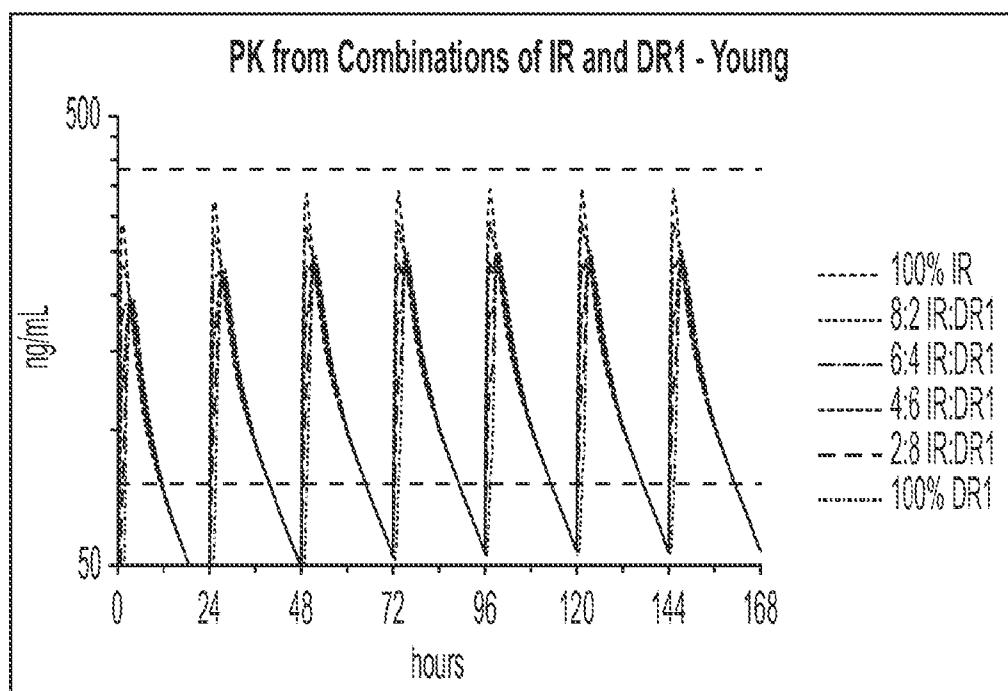


FIG. 59

## 7-day time course (12 mg QD)



at steady state

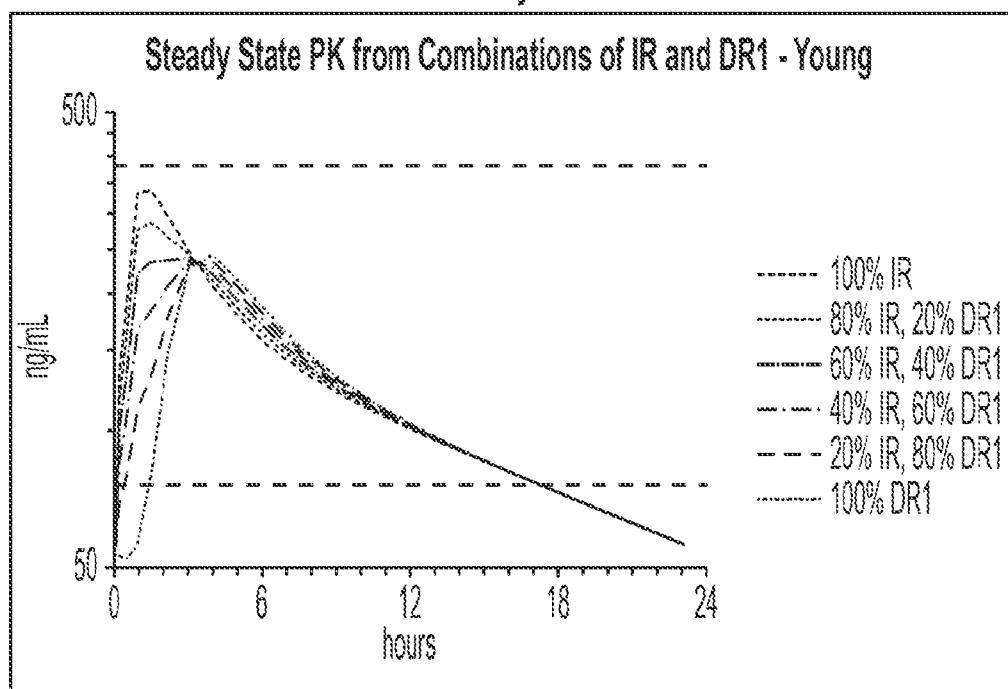
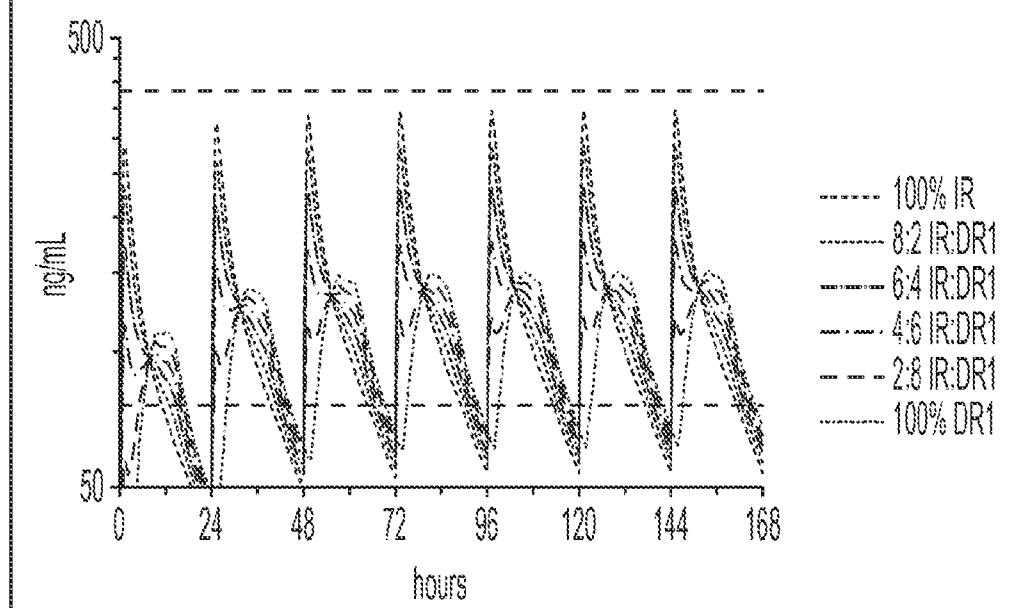


FIG. 60

## 7-day time course (12 mg QD)

## PK from Combinations of IR and DR1



at steady state

## Steady State PK from Combinations of IR and DR2 - Young

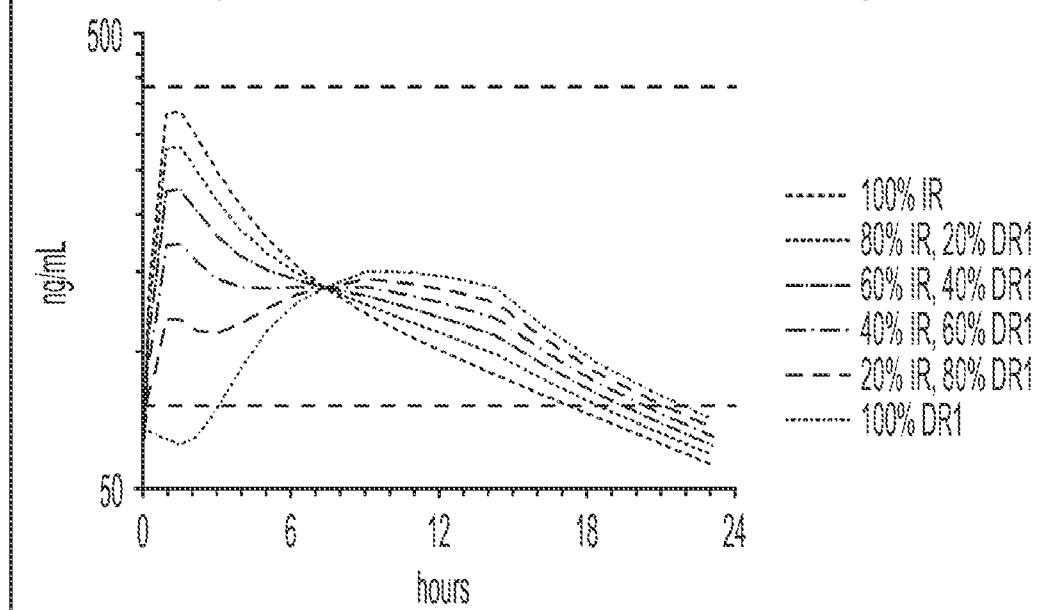


FIG. 61

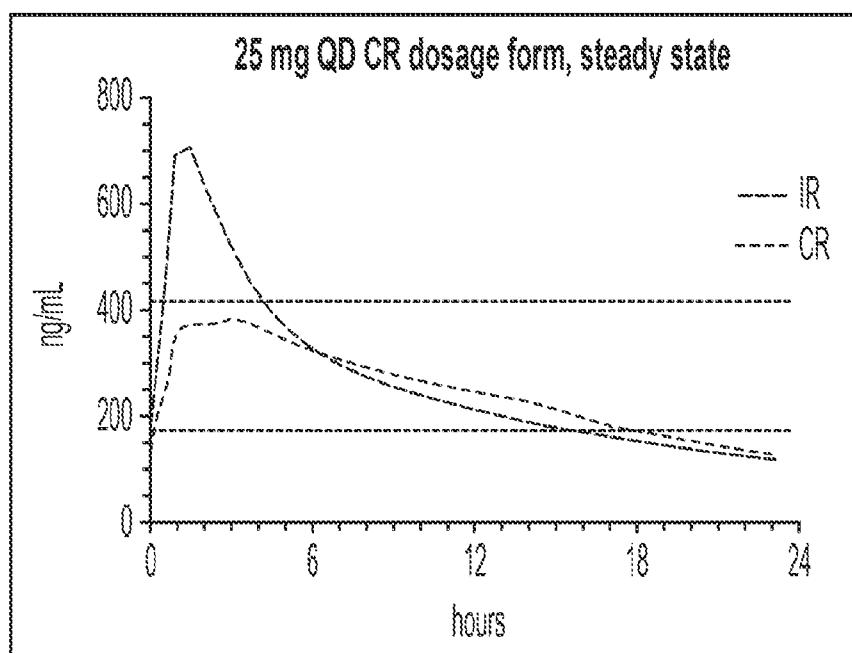
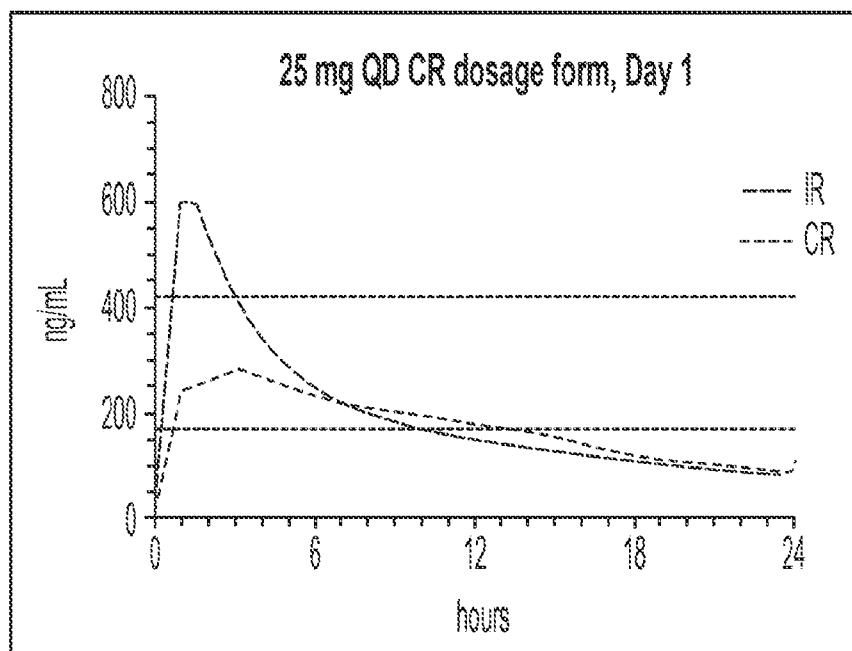


FIG. 62A

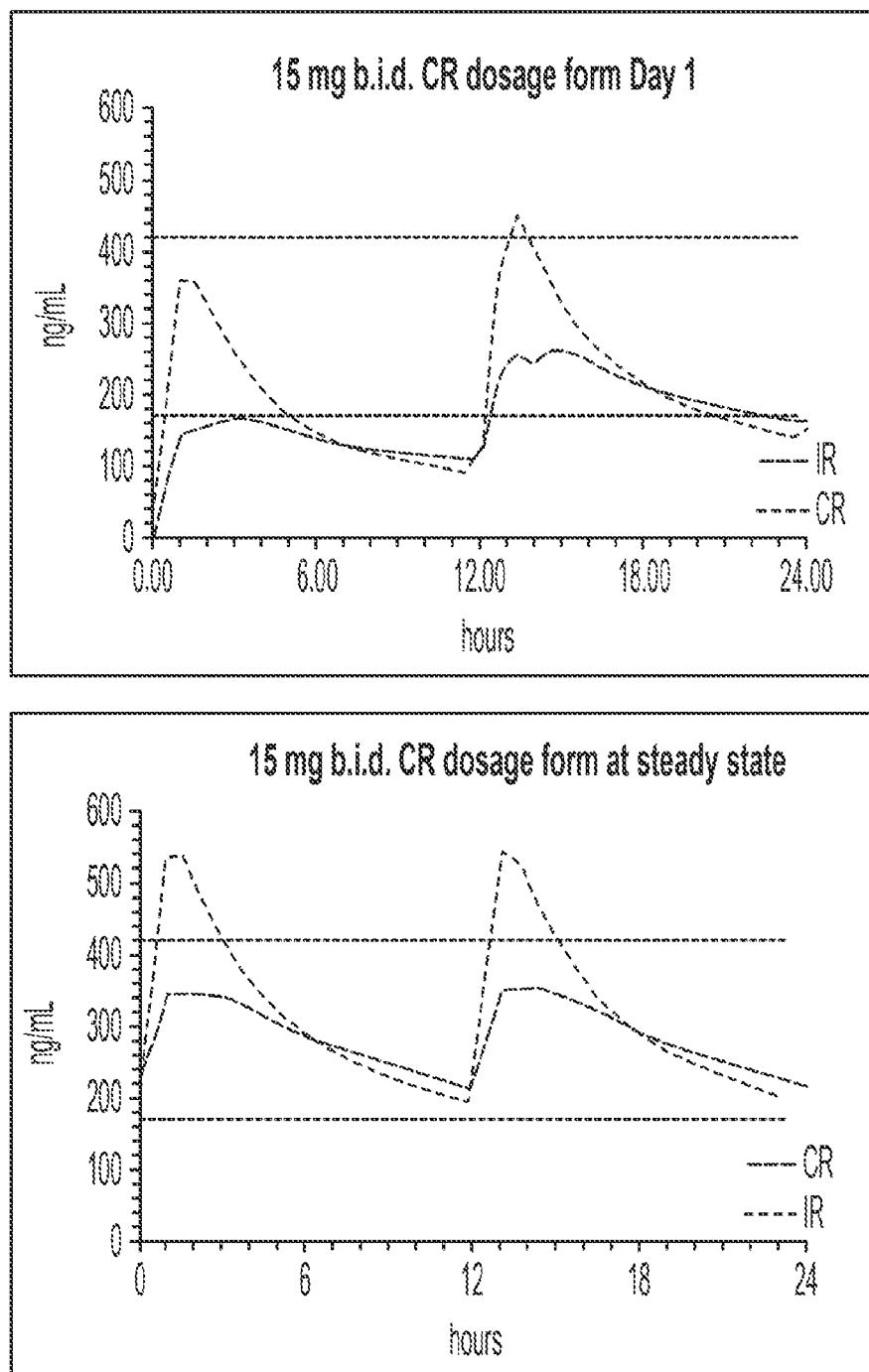


FIG. 62B

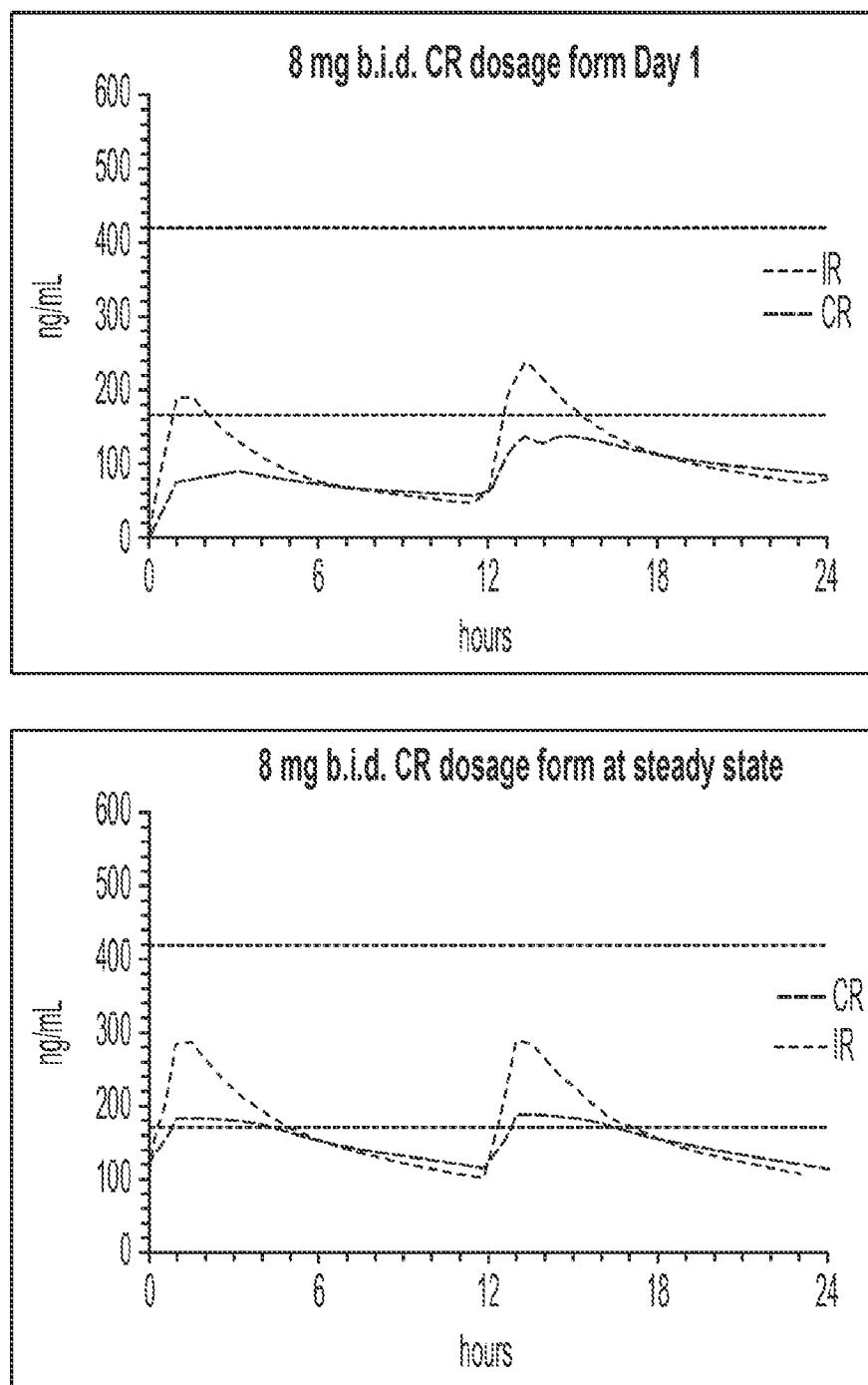


FIG. 62C

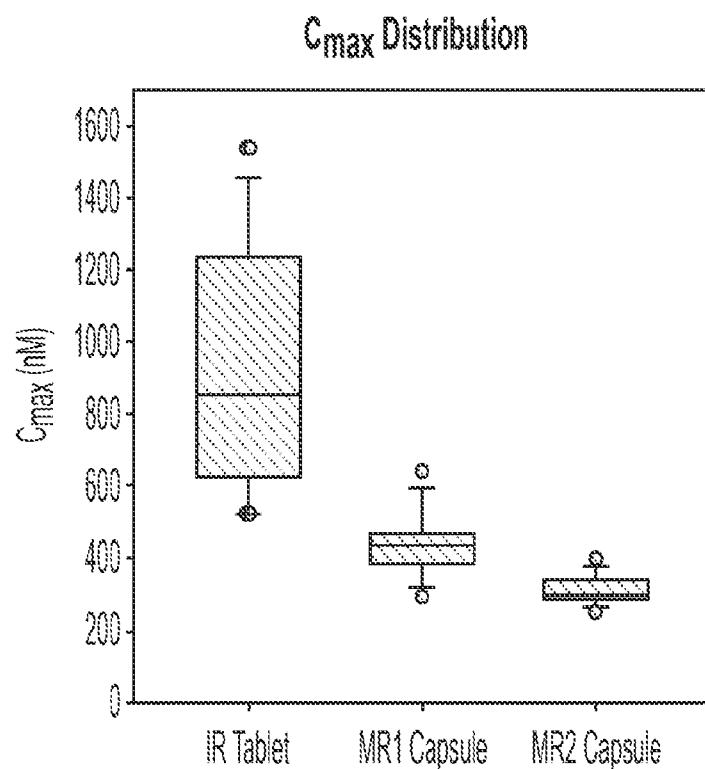


FIG. 63A

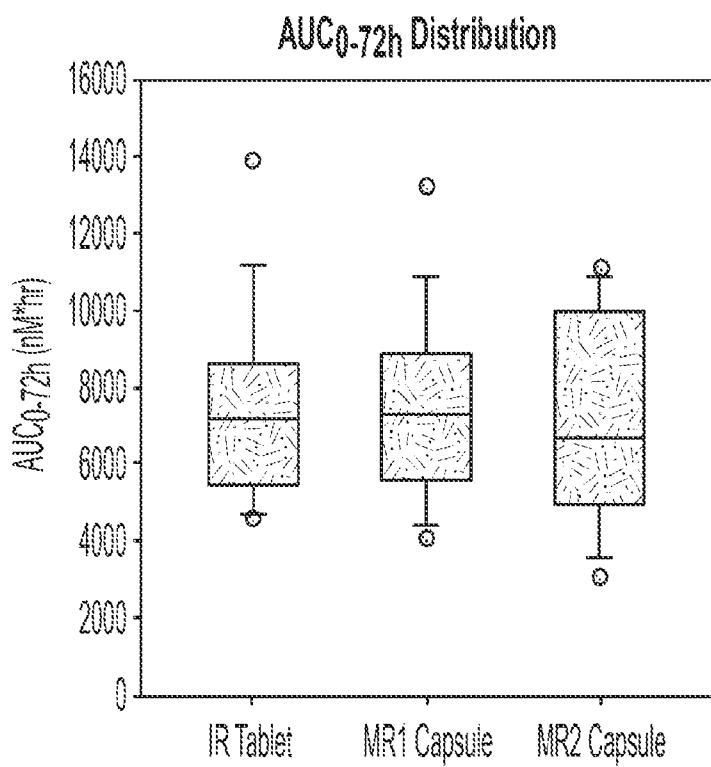


FIG. 63B

72/83

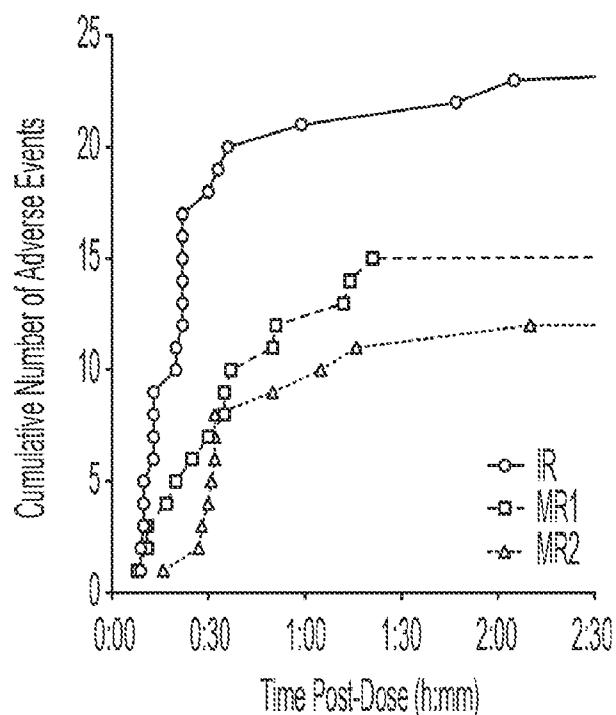


FIG. 64A

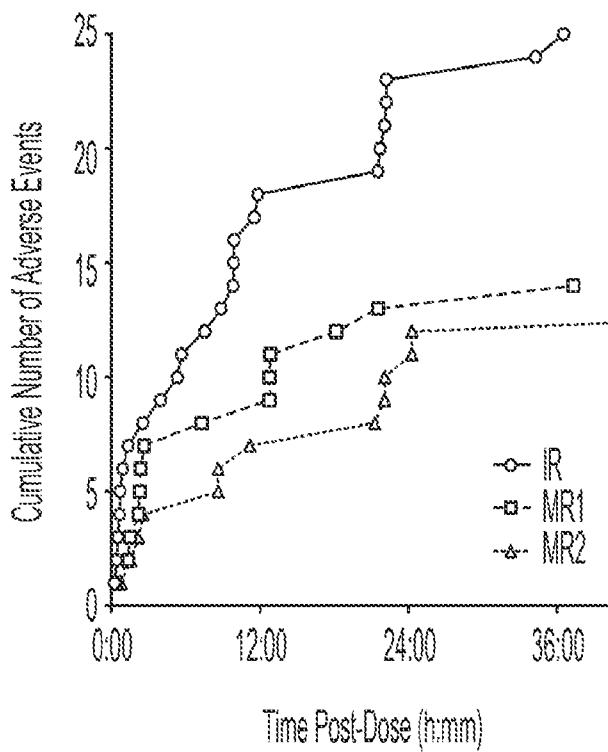


FIG. 64B

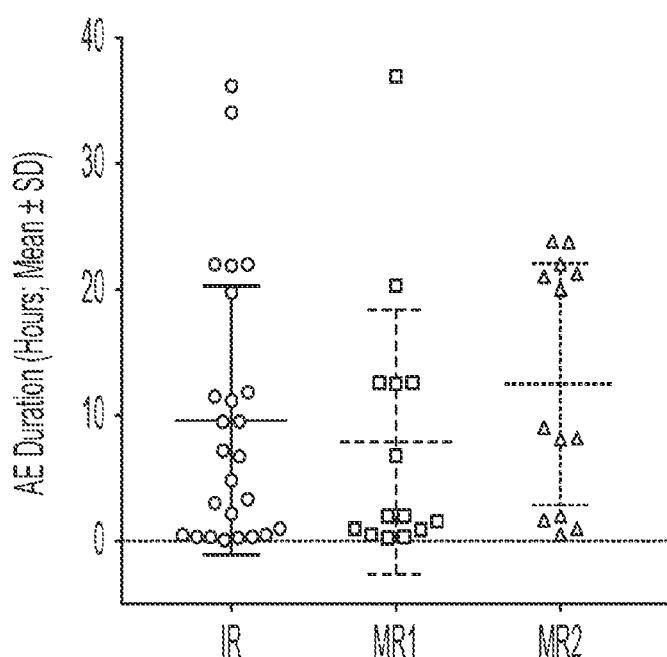


FIG. 64C

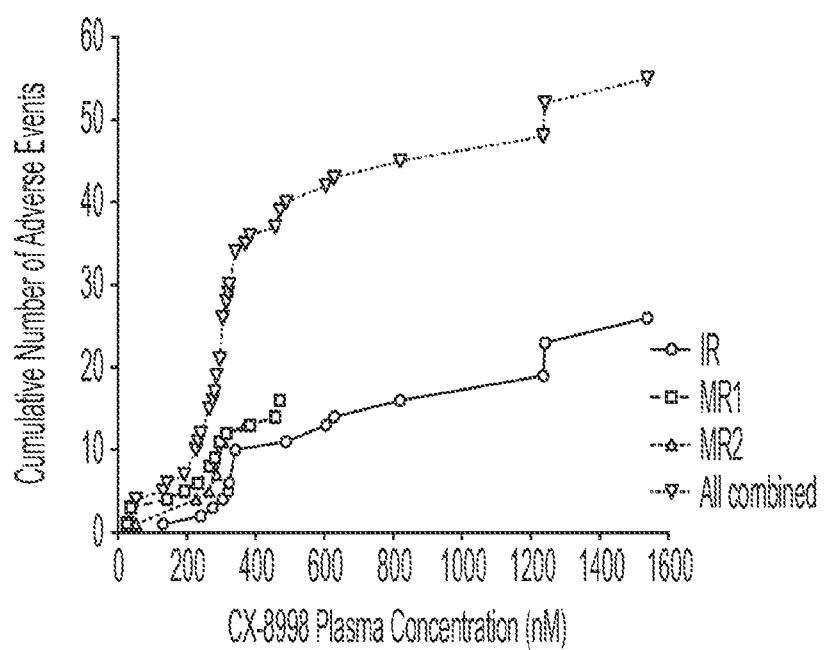


FIG. 64D

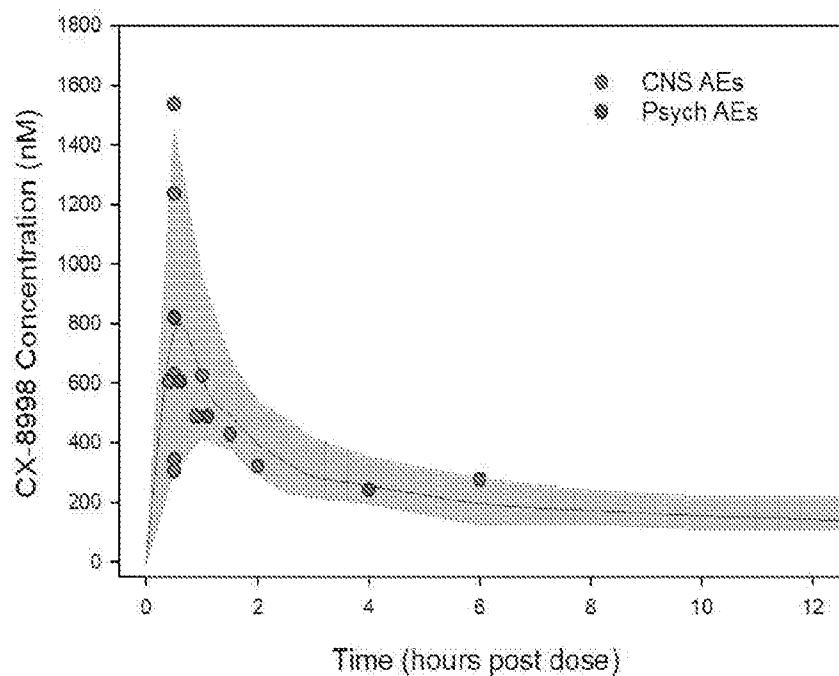


FIG. 65

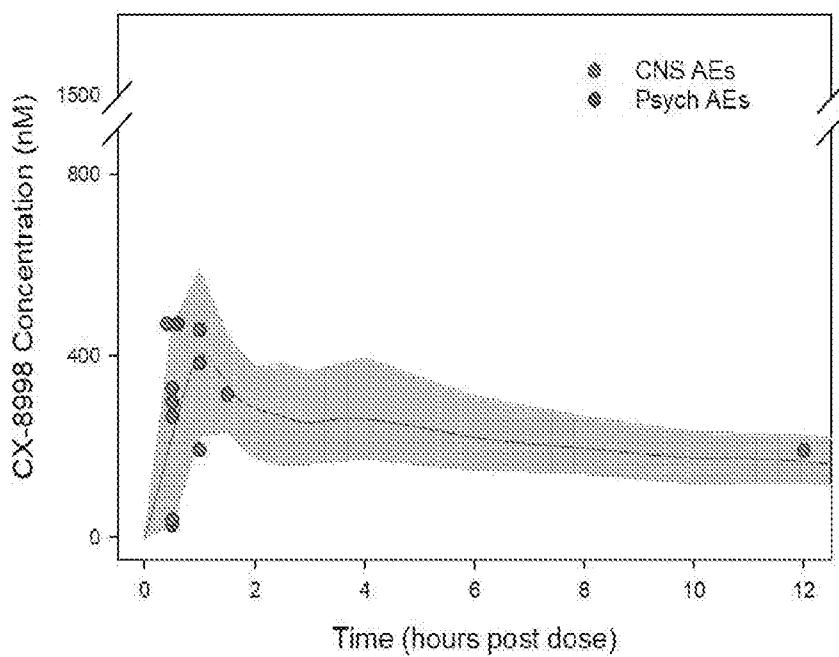


FIG. 66

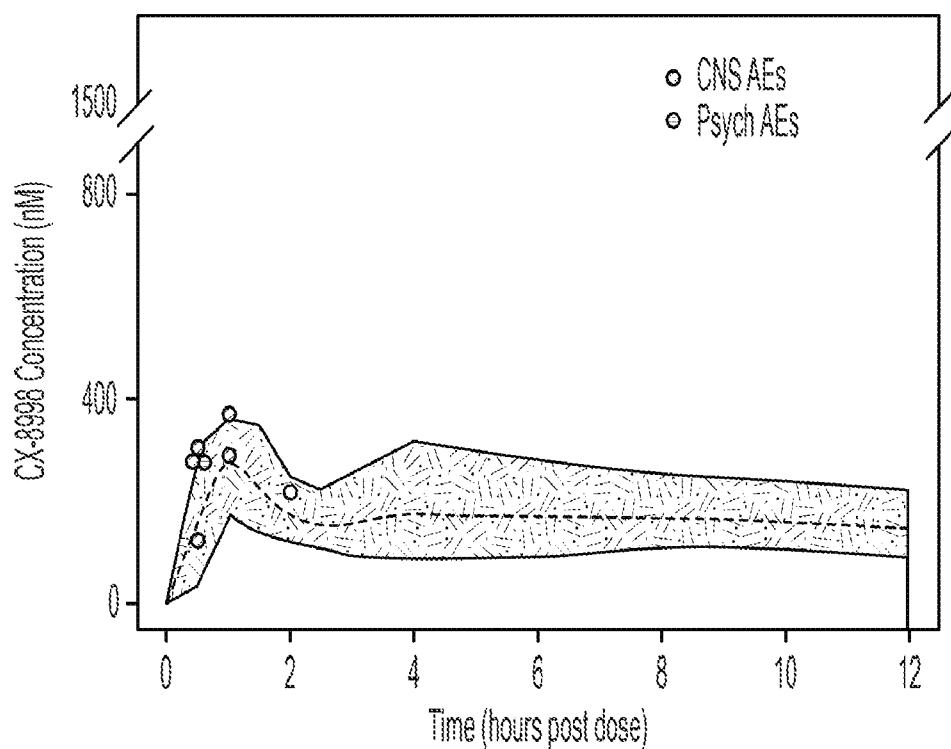


FIG. 67

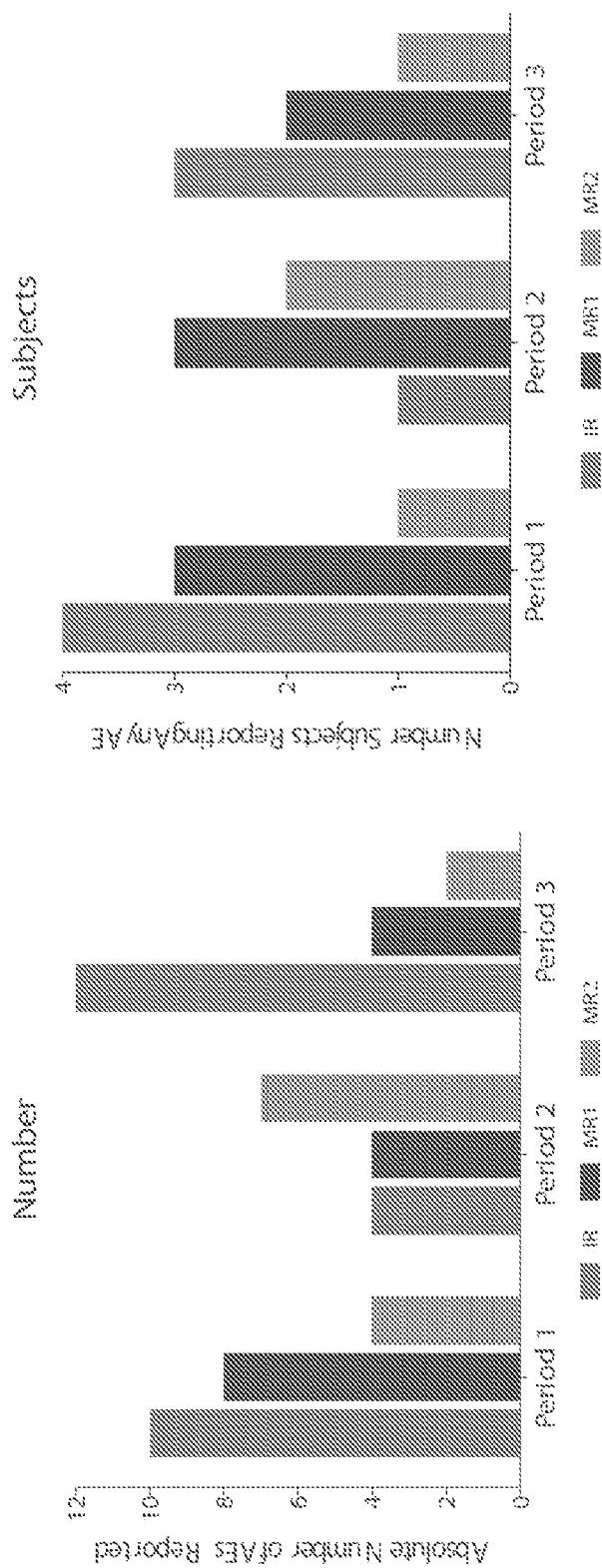


FIG. 68

77/83

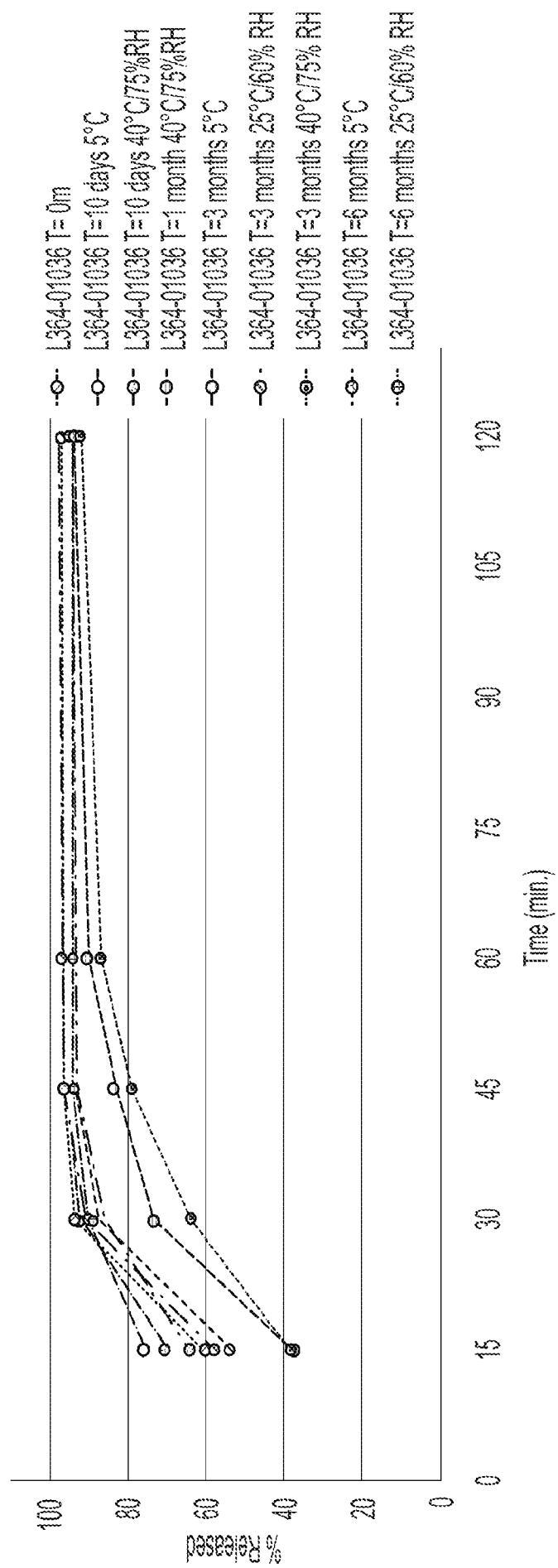


FIG. 69

78/83

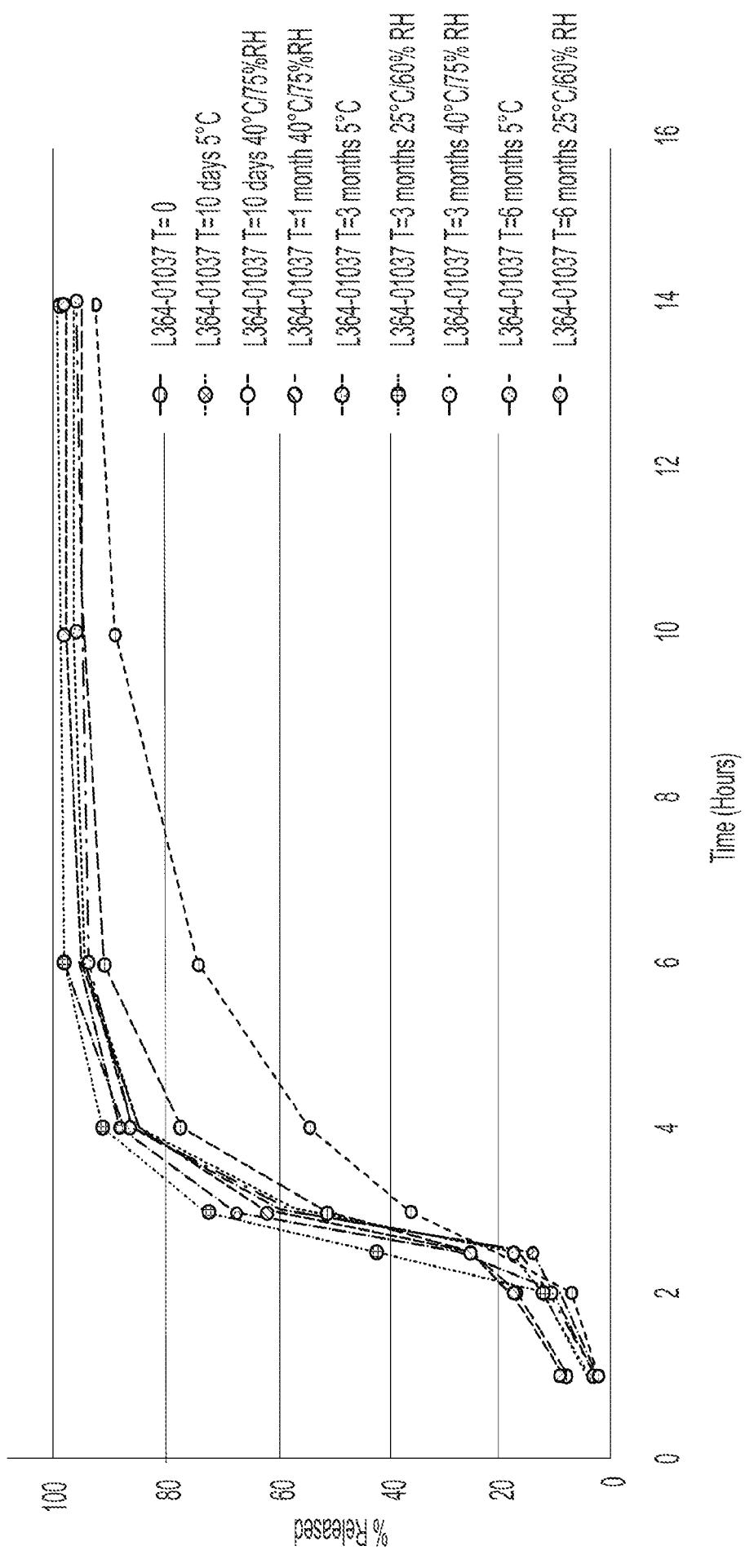
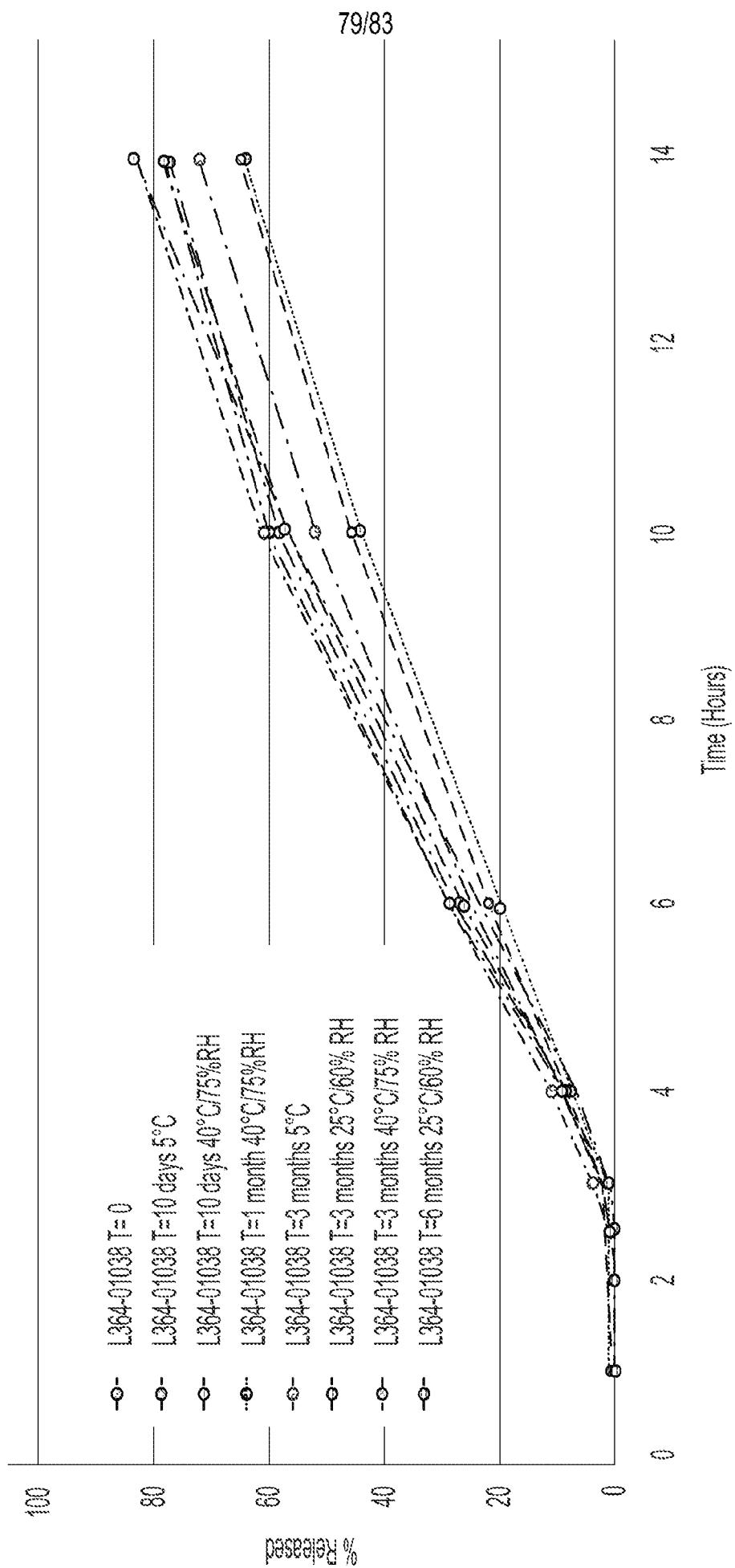


FIG. 70



80/83

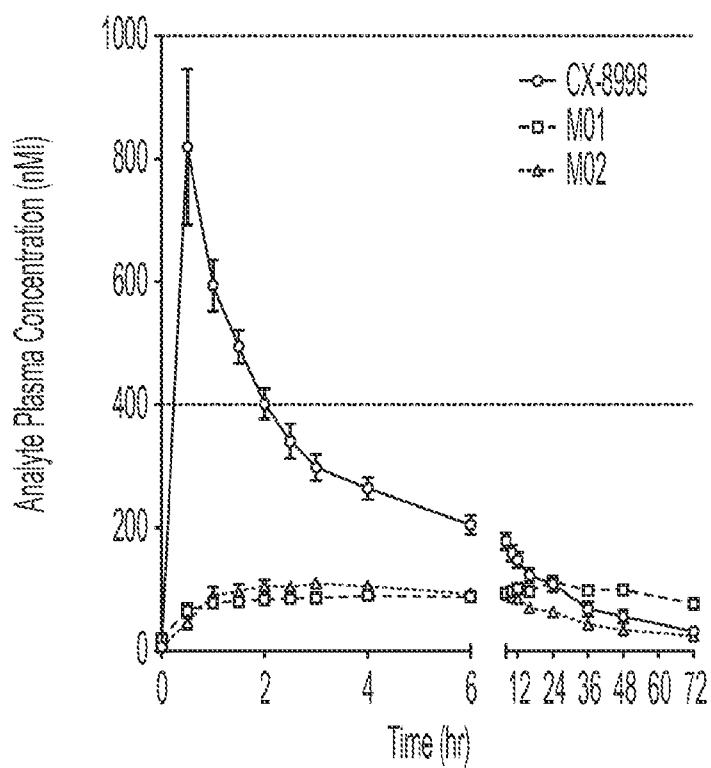


FIG. 72A

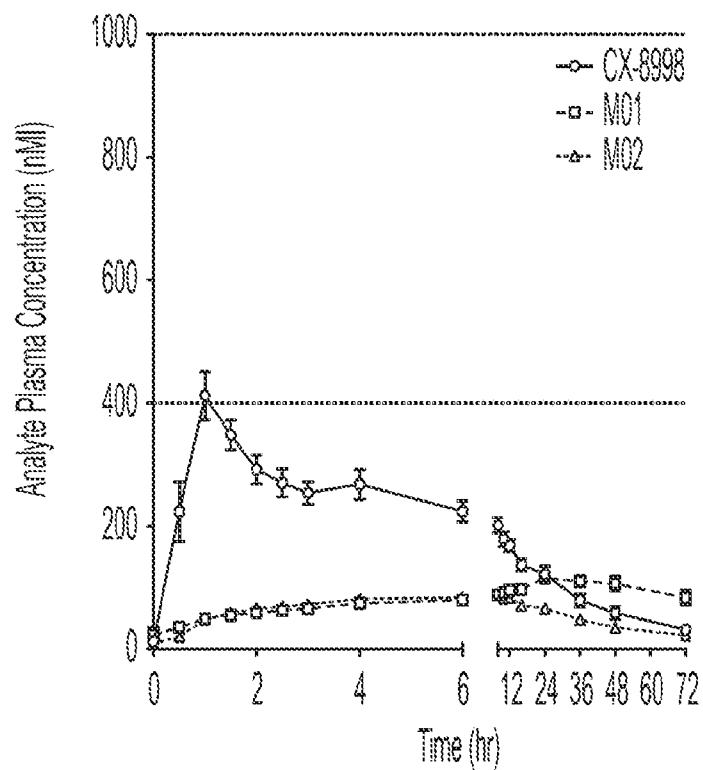


FIG. 72B

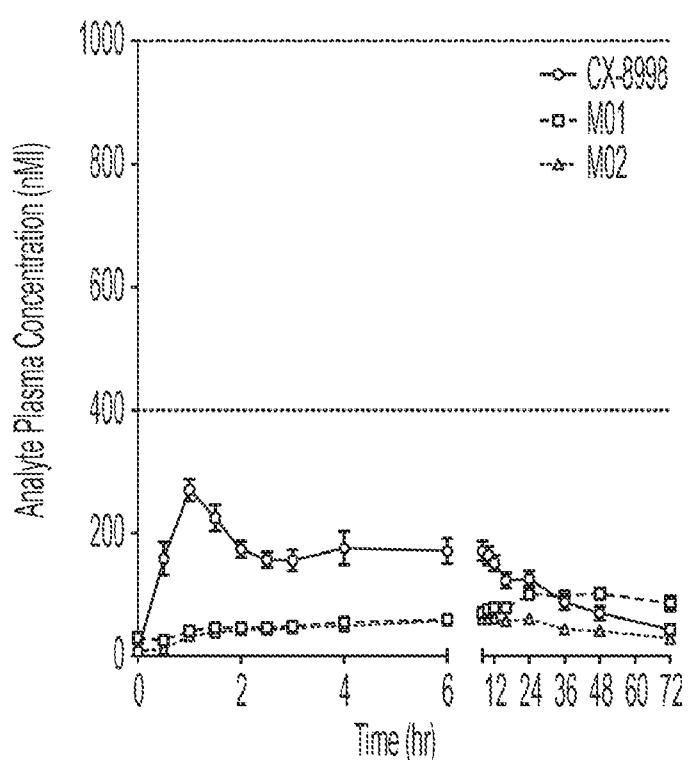


FIG. 72C

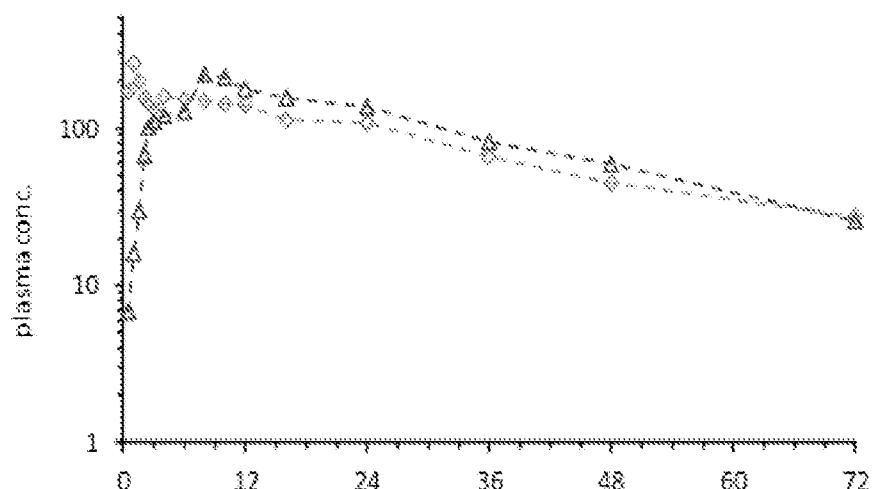


FIG. 73A

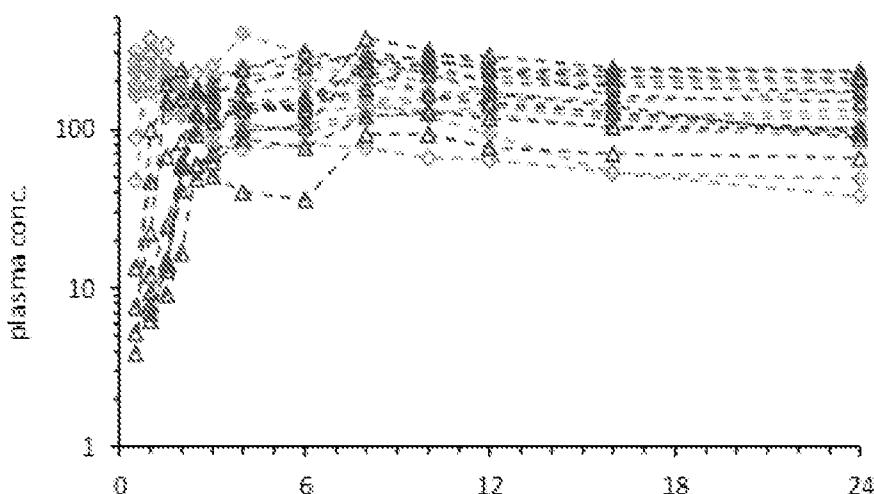


FIG. 73B

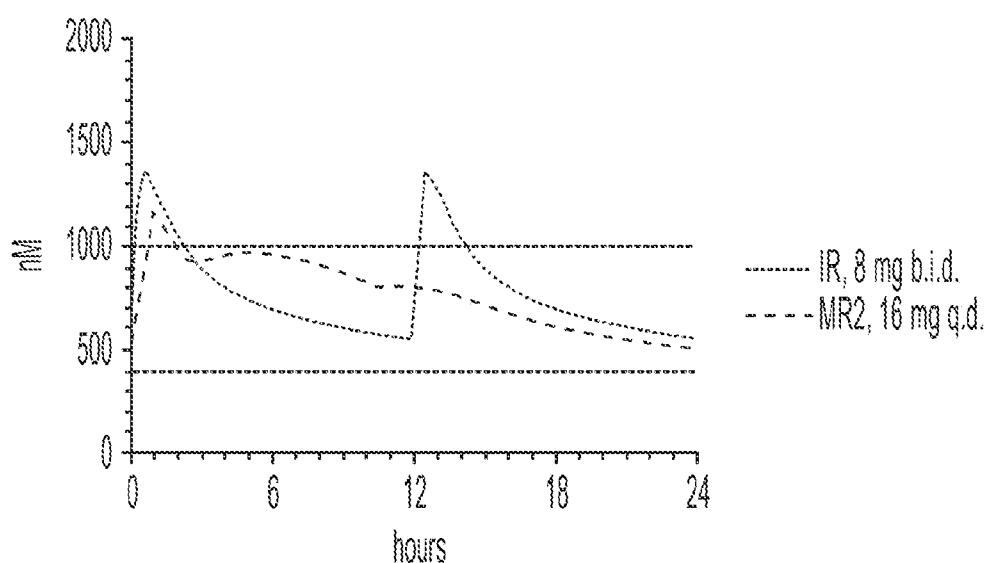


FIG. 74

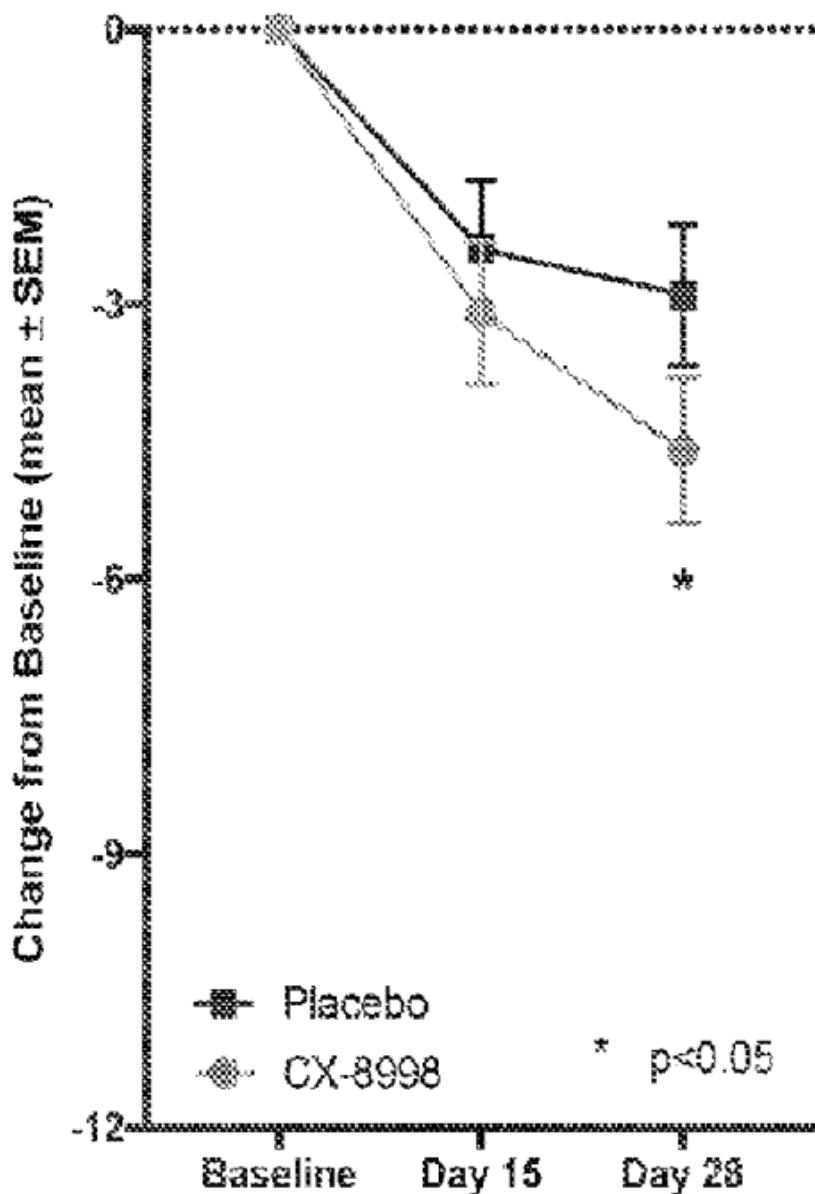


FIG. 1