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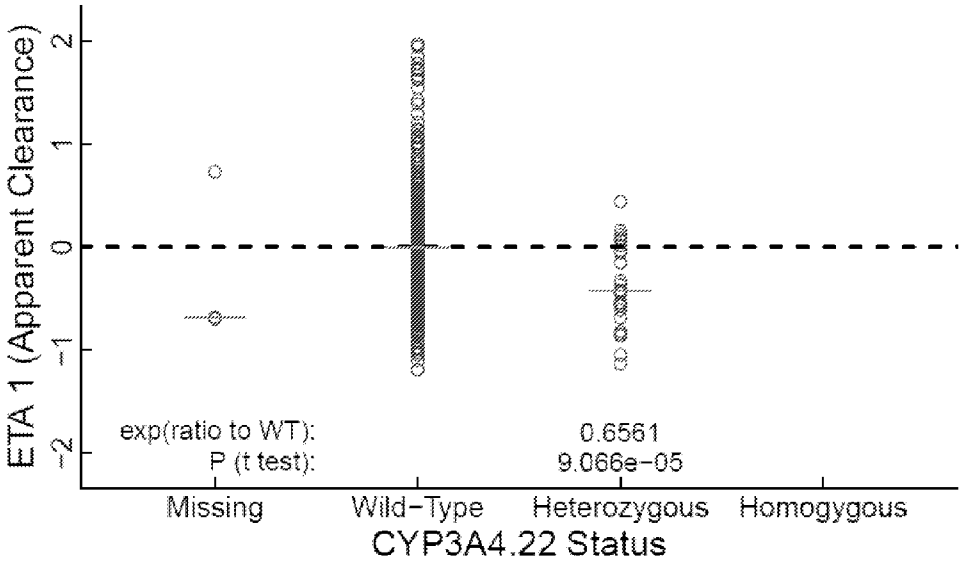
FIG. 3



(57) Abstract: Disclosed herein are methods of administration of tradipitant, and methods for determining an effective amount of tradipitant for use in the treatment of an individual in need thereof. An effective amount of tradipitant is determined for the individual based on one or more of whether the tradipitant is administered without food, and the individual's CYP3A4 metabolism.

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[Continued on next page]

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METHODS OF TREATMENT WITH TRADIPITANT

CROSS REFERENCE TO RELATED APPLICATIONS

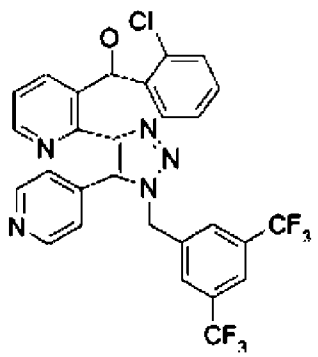
The present patent application claims priority to US provisional patent application nos. 63/476,502 and 63/475,561, both filed December 21, 2022.

BACKGROUND OF THE INVENTION

The invention relates generally to treatment of NK-1 mediated conditions. More particularly, the invention relates to methods of treatment of NK-1 mediated conditions through the administration of the NK-1 antagonist, tradipitant.

The mammalian tachykinins (neurokinin [NK]) are a family of peptide neurotransmitters that share a common C-terminal sequence. This group includes substance P (SP), neurokinin-A (NKA), and neurokinin-B (NKB). SP, the most abundant NK, preferentially binds to the neurokinin type-1 (NK-1) receptor and is involved in the regulation of many physiological processes. NK-1 receptors have been mapped in the central nervous system and were found to have a broad distribution in the brain, including the mid-brain, basal ganglia, hypothalamus, and limbic system. Neurokinin receptors are also widely distributed in the gut, the bronchial tree, and the vascular system.

Tradipitant is a potent and selective neurokinin-1 receptor antagonist, having the chemical names 2-[1-[[3,5-bis(trifluoromethyl)phenyl]methyl]-5-(4-pyridinyl)-1H-1,2,3-triazol-4-yl]-3-pyridinyl](2-chlorophenyl)-methanone and {2-[1-(3,5-Bistrifluoromethylbenzyl)-5-pyridin-4-yl-1H-[1,2,3]triazol-4-yl]-pyridin-3-yl}-(2-chlorophenyl)-methanone, and the following chemical structure:



as disclosed in US Pat. 7,320,994. Tradipitant is also known by the names VLY-686 and LY686017, and may also be referred to herein as "VLY," for example in figures and/or tables.

Tradipitant contains six main structural components: the 3,5-bis-trifluoromethylphenyl moiety, two pyridine rings, the triazol ring, the chlorophenyl ring and the methanone. Crystalline Forms IV and V of tradipitant are disclosed in US Pat. 7,381,826; and a process for synthesizing tradipitant is disclosed in US Pats. 8,772,496; 9,708,291; and 10,035,787.

In preclinical and clinical studies, tradipitant produces a long-lasting blockade of brain NK-1 receptors. Tradipitant is under assessment for efficacy in the treatment of treatment-resistant pruritus associated with atopic dermatitis (see, e.g., WO 2016/141341, WO 2019/055225, and WO 2021/173641), relieving symptoms of gastroparesis (see, e.g., WO 2019/099883 and WO 2020/117811), preventing nausea and vomiting associated with motion sickness during travel (see, e.g., WO 2020/069092), and treating inflammatory lung injury and improving clinical outcomes associated with severe COVID-19 pneumonia and other lower respiratory tract infections (see, e.g., WO 2021/195205 and WO 2023/034718). Each of the foregoing patents and published patent applications is incorporated by reference as though fully set forth herein.

Human metabolism of tradipitant is accomplished in vitro and in vivo through ketone reduction (metabolites M2, M4), N-glucuronidation (metabolite M8), pyridine N-oxidation (metabolites M3, M4), and glucuronidation (metabolite M8). Factors affecting metabolic clearance of tradipitant and its metabolites impact an individual's exposure to the parent compound, as well as any active metabolites.

Cytochrome P450 3A (CYP3A4) is the predominant isoenzyme present in the liver, and is responsible for the metabolism of many clinically prescribed drugs. Known exonic CYP3A4 variants include, without limitation, CYP3A4*2 (rs55785340, 15722T>C; exon 7; results in Ser222Pro alteration); CYP3A4*7 (6003G>A, rs56324128; exon 3; results in a Gly56Asp alteration); CYP3A4*8 (13917G>A, rs72552799; exon 5; results in an Arg130Gln alteration); CYP3A4*9 (14301G>A, rs72552798; exon 6; results in a Val170Ile alteration); CYP3A4*10 (14313G>C, rs4986908; exon 6; results in Asp174His alteration); CYP3A4*11

(21876C>T, rs67784355; exon 11; results in a Thr363Met alteration); CYP3A4*12 (21905C>T, rs12721629; exon 11; results in a Leu373Phe alteration); CYP3A4*13 (22035C>T, rs4986909; exon 11; results in a Pro416Leu alteration); CYP3A4*14 (44T>C, rs12721634; exon 1; results in a Leu15Pro alteration); CYP3A4*15 (14278G>A, rs4986907; exon 6; results in an Arg162Gln alteration); CYP3A4*16 (15612C>G, rs12721627; exon 7; results in a Thr185Ser alteration); CYP3A4*17 (15624T>C, rs4987161; exon 7; results in a Phe189Ser alteration); CYP3A4*18 (20079T>C, rs28371759; exon 10; results in a Leu293Pro alteration); CYP3A4*21 (20148 A>G in exon 10, resulting in substitution of Tyr319 with Cys. Other variants have also been identified, including missense variant CYP3A4*3 (23181T>C, rs4986910 and M445T); CYP3A4*4 (13880A>G, 352A>G, I118V and rs55951658); CYP3A4*5 (rs55901263, 15711C>G and P218R); CYP3A4*6 (17670_17671insA, 277Frameshift and rs4646438); CYP3A4*19 (23246C>T, rs4986913); and CYP3A4*20 (insertion of single base 25898_25899insA, 488Frameshift, rs67666821 results in a premature stop codon leading to a truncated protein with no function). Additionally, CYP3A4*22 is a SNP variant in intron 6 (rs35599367C > T) that is associated with decreased CYP3A4 activity relative to wildtype (CYP3A4*1/*1). The *22 variant has a minor allele frequency (MAF) of 8% in Caucasians and 4% in Asian and African populations. A number of clinical studies associate CYP3A4*22 with reduced tacrolimus and cyclosporin A clearance in renal transplant patients, lower clearance of immunosuppressants such as everolimus in renal transplant patients, and lower sirolimus metabolic rates in human liver microsomes in vitro. Endoxifen blood concentrations are also increased in breast cancer patients carrying CYP3A4*22 compared to *1/*1 carriers (wt) (n=16 carrying *22, n=116 wt).

Methods of treatment with tradipitant which account for inter-individual variability, genetic and otherwise, in tradipitant clearance are therefore desirable.

BRIEF DESCRIPTION OF THE INVENTION

A first aspect of the invention provides a method of administering tradipitant to an individual in need thereof, comprising: determining a CYP3A4 genotype of the individual; and if the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, then administering tradipitant to the individual in a first amount. However, if the individual has a CYP3A4 genotype that is associated with

decreased metabolism of tradipitant relative to wildtype, then the method comprises administering tradipitant in a second amount, wherein the second amount is smaller than the first amount.

In certain embodiments, the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes at least one *22 allele, or more particularly, two *22 alleles.

In certain embodiments, the second, smaller amount is about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount.

In certain embodiments, the second amount is about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount.

In certain embodiments, the first amount is about 100-400 mg/day, 100-300 mg/day, 100-200 mg/day, 150-400 mg/day, 150-300 mg/day, 150-200 mg/day, about 170 mg/day, or about 85 mg/day.

A second aspect of the invention provides a method of determining an effective amount of tradipitant for administration to an individual in need thereof, comprising: determining a CYP3A4 genotype of the individual from a biological sample collected from the individual. If the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, then the method includes determining that the effective amount of tradipitant is a first amount. If the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, then the method includes determining that the effective amount of tradipitant is a second amount, that is smaller than the first amount.

In certain embodiments, the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes at least one *22 allele, or more particularly two *22 alleles.

In certain embodiments, the second, smaller amount is about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount.

In certain embodiments, the second, smaller amount is about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount.

In certain embodiments, the first amount is about 100-400 mg/day, 100-300 mg/day, 100-200 mg/day, 150-400 mg/day, 150-300 mg/day, 150-200 mg/day, about 170 mg/day, or about 85 mg/day.

A third aspect of the invention provides a method of administering tradipitant to an individual in need thereof, comprising: orally administering to the individual a solid dosage form comprising tradipitant and one or more pharmaceutically acceptable excipients without food, i.e., in the absence of food.

In certain embodiments, the method further comprises instructing the individual to fast for at least thirty (30) minutes, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, or at least ten (10) hours prior to the administering. Likewise, the method further comprises the individual fasting for such period prior to the administering.

In certain embodiments, the method further comprises instructing the individual to fast for a period of at least one half (0.5) hour to about 1.5 hour prior to the administering. Likewise, the method further comprises the individual fasting for such period prior to the administering.

In certain embodiments, the method further comprises instructing the individual to fast for at least thirty (30) minutes, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, or at least ten (10) hours following the administering. Likewise, the method further comprises the individual fasting for such period following the administering.

In certain embodiments, the method further comprises instructing the individual to fast for a period of about two (2) hours to about 2.5 hours following the administering. Likewise, the method further comprises the individual fasting for such period following the administering.

In certain embodiments, tradipitant is given at a dose of about 100-400 mg/day, 100-300 mg/day, 100-200 mg/day, 150-400 mg/day, 150-300 mg/day, 150-

200 mg/day, about 170 mg/day, or about 85 mg/day.

In certain embodiments, the solid dosage form comprises a capsule or a tablet.

A fourth aspect of the invention provides a method of administering tradipitant to an individual in need thereof, comprising: determining a CYP3A4 genotype of the individual. If the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, then the method further comprises orally administering to the individual a solid dosage form comprising tradipitant in a first amount and one or more pharmaceutically acceptable excipients without food, i.e., in the absence of food. However, if the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, then the method further comprises orally administering to the individual a solid dosage form comprising tradipitant in a second amount and one or more pharmaceutically acceptable excipients without food, i.e., in the absence of food, wherein the second amount is smaller than the first amount.

In certain embodiments, the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes at least one *22 allele, or more particularly two *22 alleles.

In certain embodiments, the second, smaller amount is about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount.

In certain embodiments, the second, smaller amount is about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount.

In certain embodiments, the first amount is about 100-400 mg/day, 100-300 mg/day, 100-200 mg/day, 150-400 mg/day, 150-300 mg/day, 150-200 mg/day, about 170 mg/day, or about 85 mg/day.

In certain embodiments, the solid dosage form comprises a capsule or a tablet.

In certain embodiments, the method further comprises instructing the individual to fast for at least thirty (30) minutes, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, or at least ten (10) hours prior to

the administering. Likewise, the method further comprises the individual fasting for such period prior to the administering.

In certain embodiments, the method further comprises instructing the individual to fast for a period of at least one half (0.5) hour to about 1.5 hour prior to the administering. Likewise, the method further comprises the individual fasting for such period prior to the administering.

In certain embodiments, the method further comprises instructing the individual to fast for at least thirty (30) minutes, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, or at least ten (10) hours following the administering. Likewise, the method further comprises the individual fasting for such period following the administering.

In certain embodiments, the method further comprises instructing the individual to fast for a period of about two (2) hours to about 2.5 hours following the administering. Likewise, the method further comprises the individual fasting for such period following the administering.

A fifth aspect of the invention provides a method of administering tradipitant to an individual in need thereof, comprising: determining an effective amount of tradipitant for administration to the individual, wherein the effective amount is determined based on whether or not the individual has fasted prior to administration; and administering tradipitant in a solid immediate release form comprising the effective amount of tradipitant and one or more pharmaceutically acceptable excipients.

In certain embodiments, the effective amount of tradipitant is a first effective amount if the individual is in a fasted condition at a time of administration, and the effective amount is a second effective amount if the individual is in a fed condition at a time of administration.

In certain embodiments, the first effective amount is larger than the second effective amount.

In certain embodiments, the individual is experiencing an acute manifestation of a tradipitant-responsive disease or disorder.

In certain embodiments, the individual is experiencing a chronic manifestation of a tradipitant-responsive disease or disorder.

A sixth aspect of the invention provides a method for determining an effective amount of tradipitant for administration to an individual in need thereof, comprising: determining the effective amount based on whether the individual is in a fasted or fed condition at the time of administration.

A seventh aspect provides tradipitant for use in any of the foregoing methods.

An eighth aspect provides a use of tradipitant in accordance with any of the foregoing methods.

These and other aspects, advantages and salient features of the invention will become apparent from the following detailed description, which, when taken in conjunction with the annexed drawings, disclose embodiments of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A shows a graph plotting the ratio of tradipitant metabolite concentrations ((M2 + M3 + M4) / M8) against CYP3A4 genotype.

FIG. 1B shows a graph plotting the ratio of (tradipitant concentration / metabolite M3 concentration) against CYP3A4 genotype.

FIG. 2A shows the concentration of tradipitant in plasma (in ng/mL) in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 2B shows the concentration of tradipitant metabolite M2 in plasma (in ng/mL) in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 2C shows the concentration of tradipitant metabolite M3 in plasma (in ng/mL) in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 2D shows the concentration of tradipitant metabolite M4 in plasma (in ng/mL) in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 2E shows the concentration of tradipitant metabolite M8 in plasma (in ng/mL) in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 2F shows the ratio of concentrations of tradipitant to M8 in plasma in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 2G shows the ratio of concentrations of all metabolites to M8 in plasma in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 2H shows the ratio of concentrations of tradipitant to M3 in plasma in individuals having CYP3A4*22 heterozygous genotypes (*22 het) vs. wild type genotype (*1/*1).

FIG. 3 shows a graph relating apparent clearance of tradipitant with CYP3A4*22 status (missing, wild type, heterozygous, or homozygous).

FIG. 4 provides a schematic illustration of the design of the study described in Example 2.

FIG. 5 shows a schematic illustration of the study design described in Example 2, relative to periods 1 and 2.

FIG. 6 shows a schematic illustration of the study design described in Example 2, relative to periods 3 and 4.

FIGS. 7A and **7B** show the geometric mean plasma concentrations of tradipitant after oral administration of 170 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 7A**) and semi-logarithmic (**FIG. 7B**) axes.

FIGS. 8A and **8B** show the geometric mean plasma concentrations of tradipitant after oral administration of 85 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 8A**) and semi-logarithmic (**FIG. 8B**) axes.

FIGS. 9A and **9B** show the geometric mean plasma concentrations of metabolite M2 after oral administration of 170 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear **(FIG. 9A)** and semi-logarithmic (**FIG. 9B**) axes.

FIGS. 10A and **10B** show the geometric mean plasma concentrations of metabolite M2 after oral administration of 85 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (FIG. 10A) and semi-logarithmic (**FIG. 10B**) axes.

FIGS. 11A and **11B** show the geometric mean plasma concentrations of metabolite M3 after oral administration of 170 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 11A**) and semi-logarithmic (**FIG. 11B**) axes.

FIGS. 12A and **12B** show the geometric mean plasma concentrations of metabolite M3 after oral administration of 85 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 12A**) and semi-logarithmic (**FIG. 12B**) axes.

FIGS. 13A and **13B** show the geometric mean plasma concentrations of metabolite M4 after oral administration of 170 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 13A**) and semi-logarithmic (**FIG. 13B**) axes.

FIGS. 14A and **14B** show the geometric mean plasma concentrations of metabolite M4 after oral administration of 85 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 14A**) and semi-logarithmic (**FIG. 14B**) axes.

FIGS. 15A and **15B** show the geometric mean plasma concentrations of metabolite M8 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 15A**) and semi-logarithmic (**FIG. 15B**) axes.

FIGS. 16A and **16B** show the geometric mean plasma concentrations of

metabolite M8 after oral administration of 85 mg of tradipitant to healthy volunteers under fed and fasted conditions, with linear (**FIG. 16A**) and semi-logarithmic (**FIG. 16B**) axes.

The drawings are intended to depict only typical aspects of the disclosure, and therefore should not be considered as limiting the scope of the disclosure.

DETAILED DESCRIPTION OF THE INVENTION

Various embodiments of the present invention are described herein in reference to uses of tradipitant for the treatment of one or more tradipitant-responsive diseases or disorders. As used herein, the term "tradipitant-responsive diseases or disorders" is understood to refer to diseases and disorders understood in the art to be treatable with tradipitant, and may include, for example, pruritus, atopic dermatitis, gastroparesis, motion sickness, craving, lower respiratory infections, and other diseases and disorders as described in US Patent Nos. 7,320,994; 8,772,496; 7,381,826; 10,463,655; 10,772,880; 11,324,735; and 10,821,099; and US and WO Patent Application Publication Nos. US 2020/0030307; US 2021/0228555; US 2022/0096449; WO 2021/195025, WO 2021/173641, and WO 2023/034718. Each of the foregoing patent publications is incorporated by reference herein as though fully set forth herein. The term "tradipitant-responsive disease or disorder" is also understood to refer to symptoms of any of the foregoing, whether the underlying disease is diagnosed, undiagnosed, suspected, or simply consistent with symptoms reported by or exhibited by the individual, e.g., individuals in whom the "tradipitant-responsive disease or disorder" cannot be, or has not been ruled out. An individual experiencing a tradipitant-responsive disease or disorder may be considered an individual "in need of treatment" with tradipitant.

As used herein, the terms "patient," "subject," and "individual" refer to human beings, as well as companion animals (e.g., dogs and cats) and other domesticated animals (e.g., horses, cattle, and sheep). It will be understood that the most preferred patient is a human being.

The invention further relates to the treatment of a tradipitant-responsive disease or disorder either prophylactically or therapeutically. The terms "treatment"

and "treating" are intended to refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the disorders described herein, and is intended to include prophylactic treatment of such disorders. The term may refer to, but does not necessarily indicate a total elimination of all disorder symptoms.

Individuals suffering from a tradipitant-responsive disease or disorder can be treated by orally administering tradipitant in an effective amount, or at an effective dose. As used herein, the terms "effective amount" or "effective dose" of tradipitant refer to an amount or dose, respectively, that is effective in treating the disorders described herein. These terms may refer to an amount in conjunction with a dosing frequency required to achieve plasma concentrations of at least about 100 ng/mL, e.g., 125 ng/mL or greater, 150 ng/mL or greater, 175 ng/mL or greater, 200 ng/mL or greater, or 225 ng/mL or greater of tradipitant. Such plasma concentration levels can be achieved, e.g., by orally administering to the individual tradipitant in a solid immediate release form comprising one or more pharmaceutically acceptable excipients and tradipitant in an amount of, e.g., 100-400 mg/day, 100-300 mg/day, or 100-200 mg/day, which may be given as 50-200 mg bid, 50-150 mg bid, or 50-100 mg bid; 150-400 mg/day, 150-300 mg/day, or 150-200 mg/day, which may be given as 75-200 mg bid, 75-150 mg bid, or 75-100 mg bid; or 85-170 mg/day, which may be given as, e.g., 85 mg qd, 85 mg bid, or 170 mg qd. With regard to dosing, "qd" refers to dosing once per day; "bid" dosing typically means dosing once in the morning and once in the evening, generally no less than about 8 hours or more than about 16 hours apart, e.g., every 10 to 14 hours or 12 hours (Q12H), e.g., at 9:00 and 21:00. The solid immediate release form may be, e.g., a capsule or a tablet, and may include tradipitant in crystalline form IV or V and one or more pharmaceutically acceptable excipients.

According to one aspect of the invention, a method is provided for treating an individual as described herein, by administering tradipitant to such individual. According to the method, the individual may be selected for treatment with tradipitant based upon an initial determination that the individual is suffering from or experiencing symptoms of a tradipitant-responsive disease or disorder. Following such identification of an individual in need of treatment with tradipitant, the method includes orally administering to the individual a solid dosage form comprising tradipitant and one or more pharmaceutically acceptable excipients as described

herein, where the tradipitant is administered without food, i.e., when the individual is in a fasted state or condition, and the tradipitant is administered in the absence of food.

In particular, the method may include instructing the individual to take tradipitant without food. In various embodiments, instructing the individual to take tradipitant without food may include instructing the individual to fast for a specified period of time prior to oral administration of the tradipitant. The period of time may be, for example, at least thirty (30) minutes, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, at least ten (10) hours, or a period of about one half (0.5) hour to about 1.5 hour prior to administering the tradipitant. Instructing the individual to take tradipitant without food may further include instructing the individual to fast for a period of time following the administration of the tradipitant. The period of time may be, for example, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, at least ten (10) hours, or a period of about two (2) to about 2.5 hours after administering the tradipitant. In still further embodiments, the individual may be instructed to take tradipitant without food, for example, to fast for a first period of time before administration of tradipitant and also to fast for a second period of time after administration of tradipitant. The first and second periods of time may be of the same duration or different durations, and may be independently selected from the durations described above, or other durations as would be understood by the skilled clinician. Such method also includes the actual fasting by the individual as described herein, i.e., compliance with the instructions described above.

According to another aspect of the invention, a method is provided for administering tradipitant to an individual in need thereof. According to the method, the individual may be selected for treatment with tradipitant based upon an initial determination that the individual is suffering from or experiencing symptoms of a tradipitant-responsive disease or disorder. Following such identification of an individual in need of treatment with tradipitant, the method includes determining the CYP3A4 genotype of the individual. The determining step may particularly be performed prior to administering the tradipitant. In certain embodiments, such a determination may be made by obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the individual has a CYP3A4 gene variant genotype. In this

context, "obtaining" may refer to collecting or acquiring a biological sample from the patient, while "having obtained" may refer to referring, instructing, or otherwise causing another individual, e.g., a medical or healthcare professional, to perform the obtaining. "Having obtained" may also refer to having previously caused the obtaining to have been performed, e.g., where an assay that identifies the individual's CYP3A4 genotype has been performed in the past, and the result may be reviewed in the individual's medical records. Similarly, in this context, "performing the genotyping assay" may refer to physically performing the steps to examine the individual's DNA using a genotyping assay, while "having performed" may refer to referring, instructing, or otherwise causing another individual, e.g., a medical or healthcare professional, to carry out the performing. The expression, "having performed" may also refer to having previously caused the performance of the assay. Performing (or having performed) the assay may include the steps of extracting or having extracted genomic DNA or mRNA from the biological sample, and sequencing or having sequenced CYP3A4 DNA derived from the extracted genomic DNA or from the extracted mRNA. The sequencing (or having sequenced) step may further comprise amplifying or having amplified a CYP3A4 region in the extracted genomic DNA or mRNA to prepare a DNA sample enriched in DNA from the CYP3A4 gene region; and sequencing (or having sequenced) the DNA sample by hybridizing the DNA sample to nucleic acid probes to determine if the patient has a CYP3A4 variant genotype.

In certain embodiments, the CYP3A4 variant detected in a selected individual may be an intron 6 single nucleotide polymorphism (SNP) (rs35599367 C>T, CYP3A4*22). Individuals who are carriers of the CYP3A4*22 allele may be either heterozygous (one copy of the *22 allele, referred to herein as *22 het) or homozygous (two copies of the *22 allele). Other variants may also be known and understood by one of skill in the art, as discussed above.

The method may further include administering tradipitant to the individual at a dose that is determined based upon the individual's CYP3A4 genotype. In a case in which the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, the method includes administering tradipitant to the individual in a first amount. However, in a case in which the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, then the method instead includes administering tradipitant in a second amount, where the

second amount is smaller than the first amount. Examples of CYP3A4 genotypes that are associated with decreased metabolism of tradipitant relative to wildtype include CYP3A4 genotypes that include at least one *22 allele (i.e., *22 het), or CYP3A4 genotypes that include two *22 alleles (i.e., homozygous for *22 allele).

In certain embodiments, the second, smaller amount of tradipitant may be about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount. The first amount is considered to be 100% of the amount that would be administered to an individual who has a CYP3A4 genotype associated with normal metabolism of tradipitant, or who does not have a CYP3A4 genotype that is associated with decreased tradipitant metabolism relative to wildtype. Such an individual may actually have a wildtype (*1/*1) genotype, or may carry one or more variants that simply do not significantly affect metabolism of tradipitant. Where the second, smaller amount of tradipitant is about 66-68% of the first amount, this represents about a 32-34% reduction relative to the normal effective amount. Such dosage reductions may be suitable for an individual whose CYP3A4 genotype includes at least one, or exactly one *22 allele.

In other embodiments, the first amount may be defined the same way, and the second, smaller amount of tradipitant may be about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount. Such dosage reductions may be suitable for an individual whose CYP3A4 genotype includes at least one, or exactly two *22 alleles.

Because CYP3A4*22 status has been shown, as described herein in Example 1, to significantly impact metabolic clearance of tradipitant, the determination of the CYP3A4 genotype of an individual who is in need of treatment with tradipitant, enables dosing with tradipitant in a manner that facilitates the desired exposure level of the patient to the parent compound and any active metabolites thereof. In particular, individuals receiving tradipitant in the first amount, also referred to as the "normal amount" or "normal effective amount," may be administered an effective dose that is, e.g., 150-400 mg/day, 100-400 mg/day, 150 to 300 mg/day, 100-300 mg/day, 150 to 200 mg/day, 100-200 mg/day, about 170 mg/day, or about 85 mg/day,

administered as, e.g., 75 to 200 mg bid, 50-200 mg bid, 75 to 150 mg bid, 50-150 mg bid, 75 to 100 mg bid, 50-100 mg bid, about 85 mg bid, or about 85 mg qd, while individuals receiving the second, smaller amount of tradipitant may receive a dose reduced proportionally as discussed above. Regardless of whether a given individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, and receives the first amount, or a CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype, and receives the second, smaller amount, the dose administered in both cases may be sufficient to achieve and maintain a plasma concentration level of tradipitant in the individual of at least about 100 ng/mL, e.g., 125 ng/mL or greater, 150 ng/mL or greater, 175 ng/mL or greater, 200 ng/mL or greater, or 225 ng/mL or greater over the course of the treatment period.

In another embodiment, an individual in need of treatment with tradipitant may be selected for treatment with tradipitant based upon an initial determination that the individual is suffering from or experiencing symptoms of a tradipitant-responsive disease or disorder. Following such identification of an individual in need of treatment with tradipitant, the method includes determining whether the individual is being treated with, or has consumed a compound that is a CYP3A4 inhibitor. The determining step may particularly be performed prior to administering the tradipitant.

The method may further include administering tradipitant to the individual at a dose that is determined based upon whether or not a CYP3A4 inhibitor is co-administered with the tradipitant. In a case in which a CYP3A4 inhibitor is not being co-administered to the individual, the method includes administering tradipitant to the individual in a first amount, in a manner similar to the above-described case in which the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant. However, in a case in which a CYP3A4 inhibitor is co-administered with tradipitant to the individual, then the method may include administering tradipitant to the individual in a second ament, where the second amount is smaller than the first amount, in a manner similar to the above-described case in which the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype. In certain embodiments, the CYP3A4 inhibitor may be selected from amiodarone, aprepitant, cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, posaconazole, voriconazole, and verapamil. In particular embodiments, the CYP3A4 inhibitor may be considered a strong CYP3A4 inhibitor, and may be selected from: clarithromycin,

itraconazole, ketoconazole, and posaconazole, or from ketoconazole and grapefruit juice.

As described above, in certain embodiments, the second, smaller amount of tradipitant may be about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount. The first amount is considered to be 100% of the amount that would be administered to an individual who is co-administered a CYP3A4 inhibitor with the tradipitant. In certain embodiments, co-administration of tradipitant with a CYP3A4 inhibitor is associated with a decrease of about 26.3% in apparent clearance, an increase of about 26% in Cmax, and an increase of about 36% in AUC.

Where the second, smaller amount of tradipitant is about 66-68% of the first amount, this represents about a 32-34% reduction relative to the normal effective amount. Such dosage reductions may be suitable for an individual who is co-administered tradipitant and a CYP3A4 inhibitor. Administration of the smaller, second amount to such patients facilitates use of tradipitant while avoiding exposure to higher levels of tradipitant due to variations in CYP3A4 metabolism.

In other embodiments, the first amount may be defined the same way, and the second, smaller amount of tradipitant may be about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount. Such dosage reductions may be suitable for an individual who is co-administered tradipitant and a CYP3A4 inhibitor.

Co-administration of tradipitant with CYP3A4 inhibitors, and particularly with strong CYP3A4 inhibitors leads to increased exposure to tradipitant. Therefore, the identification of an individual in need of treatment with tradipitant, who is or would be co-administered tradipitant and the CYP3A4 inhibitor, enables dosing with tradipitant in a manner that facilitates the desired exposure level of the patient to the parent compound and any active metabolites thereof. In particular, individuals receiving tradipitant in the first amount, also referred to as the “normal amount” or “normal effective amount,” may be administered an effective dose that is, e.g., 150-400 mg/day, 100-400 mg/day, 150 to 300 mg/day, 100-300 mg/day, 150 to 200

mg/day, 100-200 mg/day, about 170 mg/day, or about 85 mg/day, administered as, e.g., 75 to 200 mg bid, 50-200 mg bid, 75 to 150 mg bid, 50-150 mg bid, 75 to 100 mg bid, 50-100 mg bid, about 85 mg bid, or about 85 mg qd, while individuals receiving the second, smaller amount of tradipitant may receive a dose reduced proportionally as discussed herein. Regardless of whether a given individual is administered tradipitant in the absence of a CYP3A4 inhibitor, and receives the first amount, or is co-administered tradipitant and a CYP3A4 inhibitor, and receives the second, smaller amount, the dose administered in both cases may be sufficient to achieve and maintain a plasma concentration level of tradipitant in the individual of at least about 100 ng/mL, e.g., 125 ng/mL or greater, 150 ng/mL or greater, 175 ng/mL or greater, 200 ng/mL or greater, or 225 ng/mL or greater over the course of the treatment period.

According to another aspect of the invention, methods are provided for determining an effective amount of tradipitant for administration to an individual in need thereof. In one embodiment, the method includes determining a CYP3A4 genotype of the individual from a biological sample, as described above. If the individual is found to have a CYP3A4 genotype that is associated with normal metabolism of tradipitant, e.g., wildtype, the method includes determining that the effective amount of tradipitant is a first amount, while if the individual is found to have a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, then the method includes determining that the effective amount of tradipitant is a second amount that is smaller than the first amount. CYP3A4 genotypes associated with decreased metabolism of tradipitant may include at least one, and in some cases two CYP3A4*22 alleles.

In another embodiment, the method includes determining whether the individual is being treated with, or has consumed a compound known to be a CYP3A4 inhibitor, such that the CYP3A4 inhibitor may be co-administered with tradipitant. If a CYP3A4 inhibitor will not be co-administered, the method includes determining that the effective amount of tradipitant is a first amount, while if co-administration of tradipitant with a CYP3A4 inhibitor will occur, then the method includes determining that the effective amount of tradipitant is a second amount that is smaller than the first amount. In certain embodiments, the CYP3A4 inhibitor may be selected from amiodarone, aprepitant, cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole,

posaconazole, voriconazole, and verapamil. In particular embodiments, the CYP3A4 inhibitor may be considered a strong CYP3A4 inhibitor, and may be selected from: clarithromycin, itraconazole, ketoconazole, and posaconazole, or from ketoconazole and grapefruit juiceIn certain embodiments, the first amount of tradipitant may be a dose of, e.g., 150-400 mg/day, 100-400 mg/day, 150 to 300 mg/day, 100-300 mg/day, 150 to 200 mg/day, 100-200 mg/day, about 170 mg/day, or about 85 mg/day administered as, e.g., 75 to 200 mg bid, 50-200 mg bid, 75 to 150 mg bid, 50-150 mg bid, 75 to 100 mg bid, 50-100 mg bid, about 85 mg bid, or about 85 mg qd, and the second, smaller amount of tradipitant may be a dose that is reduced proportionally as discussed herein. For example, in certain embodiments, the second, smaller amount of tradipitant may be about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount. Such dosage reductions may be suitable for an individual whose CYP3A4 genotype includes at least one, or exactly one *22 allele, or an individual who is being or will be co-administered tradipitant and a CYP3A4 inhibitor.

In other embodiments, the second, smaller amount of tradipitant may be about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount. Such dosage reductions may be suitable for an individual whose CYP3A4 genotype includes at least one, or exactly two *22 alleles, or an individual who is being or will be co-administered tradipitant and a CYP3A4 inhibitor.

In the method described herein for determining an effective amount of tradipitant, regardless of which dose is determined to be effective for a particular individual, the dose administered may be sufficient to achieve and maintain a plasma concentration level of tradipitant in the individual to whom the dose was administered. The plasma concentration level may be at least about 100 ng/mL, e.g., 125 ng/mL or greater, 150 ng/mL or greater, 175 ng/mL or greater, 200 ng/mL or greater, or 225 ng/mL or greater over the course of the treatment period.

According to another aspect of the invention, a method is provided for administering tradipitant to an individual in need thereof. The method includes

determining a CYP3A4 genotype of the individual as described herein, or whether the individual is being administered a CYP3A4 inhibitor. If the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, and/or is not being administered a CYP3A4 inhibitor, the method includes orally administering to the individual a solid dosage form comprising tradipitant in a first amount and one or more pharmaceutically acceptable excipients without food, e.g., in the absence of food. If the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, or the individual is being administered a CYP3A4 inhibitor, the method includes orally administering to the individual a solid dosage form comprising tradipitant in a second amount that is smaller than the first amount, and one or more pharmaceutically acceptable excipients without food, e.g., in the absence of food. In certain embodiments, the solid immediate release form may be a capsule or a tablet.

Examples of CYP3A4 genotypes that are associated with decreased metabolism of tradipitant relative to wildtype include CYP3A4 genotypes that include at least one *22 allele (i.e., heterozygous for *22 allele), or CYP3A4 genotypes that include *22 alleles (i.e., homozygous for *22 allele). In certain embodiments, the CYP3A4 inhibitor may be selected from amiodarone, aprepitant, cimetidine, ciprofloxacin, clarithromycin, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, posaconazole, voriconazole, and verapamil. In particular embodiments, the CYP3A4 inhibitor may be considered a strong CYP3A4 inhibitor, and may be selected from: clarithromycin, itraconazole, ketoconazole, and posaconazole, or from ketoconazole and grapefruit juice.

Because CYP3A4*22 status has been shown, as described herein in Example 1, to significantly impact metabolic clearance of tradipitant, the determination of the CYP3A4 genotype of an individual who is in need of treatment with tradipitant, facilitates dosing with tradipitant to achieve the desired exposure level of the parent compound and any active metabolites thereof. In particular, individuals receiving tradipitant in the first amount may be administered an effective dose that is, e.g., 150-400 mg/day, 100-400 mg/day, 150 to 300 mg/day, 100-300 mg/day, 150 to 200 mg/day, 100-200 mg/day, about 170 mg/day, or about 85 mg/day, administered as, e.g., 75 to 200 mg bid, 50-200 mg bid, 75 to 150 mg bid, 50-150 mg bid, 75 to 100 mg bid, 50-100 mg bid, about 85 mg bid, or about 85 mg qd, while individuals receiving the second, smaller amount of tradipitant may receive a dose that is

proportionally reduced. In certain embodiments, the second, smaller amount of tradipitant may be about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount. Such dosage reductions may be suitable for an individual whose CYP3A4 genotype includes at least one, or exactly one *22 allele, and similarly, for an individual who is being co-administered tradipitant and a CYP3A4 inhibitor as described herein. In other embodiments, the second, smaller amount of tradipitant may be about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount. Such dosage reductions may be suitable for an individual whose CYP3A4 genotype includes at least one, or exactly two *22 alleles, and similarly, for an individual who is being co-administered tradipitant and a CYP3A4 inhibitor as described herein.

According to the method described herein, regardless of which condition is satisfied, namely, whether the individual is found to have a CYP3A4 genotype associated with normal metabolism of tradipitant and is administered the first amount of tradipitant, the individual is not administered a CYP3A4 inhibitor concurrently with the tradipitant and is therefore administered tradipitant in the first amount, or the individual is found to have a CYP3A4 genotype associated with decreased metabolism of tradipitant (relative to wildtype), or to be co-administered tradipitant with a CYP3A4 inhibitor, and is administered the second, smaller amount of tradipitant, the dose administered in both cases may be sufficient to achieve and maintain a plasma concentration level of tradipitant in the individual of at least about 100 ng/mL, e.g., 125 ng/mL or greater, 150 ng/mL or greater, 175 ng/mL or greater, 200 ng/mL or greater, or 225 ng/mL or greater.

In particular, the method may include instructing the individual to take tradipitant without food, e.g., to fast, and/or the individual taking tradipitant without food, e.g., fasting for a specified period of time prior to oral administration of the tradipitant. The period of time may be, for example, at least thirty (30) minutes, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, at least ten (10) hours, or a period of about one half (0.5) hour to 1.5 hour prior to administering the tradipitant. The method may also or alternatively include

instructing the individual to take tradipitant without food, e.g., to fast, and/or the individual taking tradipitant without food, e.g., fasting for a period of time following the administration of the tradipitant. The period of time may be, for example, at least one (1) hour, at least two (2) hours, at least four (4) hours, at least eight (8) hours, at least ten (10) hours, or a period of about two (2) hours to about 2.5 hours after administering the tradipitant. In still further embodiments, the individual may be instructed to take tradipitant without food, e.g., to fast, and/or the individual may take tradipitant without food, e.g., fast for a first period of time before administration of tradipitant and also to fast for a second period of time after administration of tradipitant. The first and second periods of time may be of the same duration or different durations, and may be independently selected from the durations described above.

According to another aspect of the invention, a method is provided for administering tradipitant to an individual in need thereof. The individual may, for example, be experiencing an acute manifestation of a tradipitant-responsive disease or disorder, or a chronic manifestation of a tradipitant-responsive disease or disorder. The method includes determining an effective amount of tradipitant for administration to the individual, based on a determination of whether or not the individual has fasted prior to administration. Tradipitant may then be administered in a solid immediate release form comprising the effective amount of tradipitant and one or more pharmaceutically acceptable excipients.

In a case in which the individual is in a fasted condition at the time of administration and is taking the tradipitant without food, a first effective amount of tradipitant may be administered. In a case in which the individual is in a fed condition at a time of administration, e.g., the tradipitant is taken with food or shortly after consuming food, a second effective amount of tradipitant may be administered, which is smaller than the first effective amount, as described elsewhere herein. In particular, individuals receiving tradipitant in the first amount may be administered an effective dose that is, e.g., 150-400 mg/day, 100-400 mg/day, 150 to 300 mg/day, 100-300 mg/day, 150 to 200 mg/day, 100-200 mg/day, about 170 mg/day, or about 85 mg/day, administered as, e.g., 75 to 200 mg bid, 50-200 mg bid, 75 to 150 mg bid, 50-150 mg bid, 75 to 100 mg bid, 50-100 mg bid, about 85 mg bid, or about 85 mg qd, while individuals receiving the second, smaller amount of tradipitant may receive a dose that is proportionally reduced. In certain embodiments, the second, smaller

amount of tradipitant may be about 60-90%, 60-85%, 60-80%, 60-75%, or 60-70% of the first amount; about 25-70%, 30-70%, 35-70%, 40-70%, 45-70%, 50-70%, 55-70%, or 60-70% of the first amount; about 35-95%, 40-90%, 50-80%, or 60-70% of the first amount; or about 66-68% of the first amount. Such dosage reductions may be suitable for an individual who takes tradipitant with food, or without fasting. In other embodiments, the second, smaller amount of tradipitant may be about 10-35%, 15-35%, 20-35%, 25-35%, or 30-35% of the first amount; about 30-70%, 30-65%, 30-60%, 30-55%, 30-50%, 30-45%, 30-40%, or 30-35% of the first amount; about 10-55%, 15-50%, 20-45%, 25-40%, or 30-35% of the first amount; or about 32% of the first amount. Such dosage reductions may be suitable for an individual who takes tradipitant with food as described herein. Also provided is a related method for determining an effective amount of tradipitant for administration to an individual in need thereof, comprising: determining the effective amount based on whether the individual is taking the tradipitant with or without food, e.g., whether the individual is in a fasted or fed condition at the time of administration. The respective amounts for each condition may be determined as described above.

The skilled artisan will appreciate that additional preferred embodiments may be selected by combining the preferred embodiments above, or by reference to the examples given herein.

Example 1: Role of CYP3A4 in the metabolism of Tradipitant

To investigate the role of CYP3A4 genotypes in the metabolism of tradipitant, pharmacokinetics are analyzed in view of CYP3A4 genotype in a phase III study of humans dosed with tradipitant. In the investigation, all CYP3A4 alleles (as recognized by the Human Cytochrome P450 Allele Nomenclature Database) are reviewed. The analysis includes a linear model that is tested on various ratios of parent compound (tradipitant) or its metabolites, including:

Ratio A = Sum of (M2 + M3 + M4)/M8, and

Ratio B = (tradipitant) / (M3).

After correction for covariates, including principal components (PCs), age, sex, and body mass index (BMI), CYP3A4*22 is identified as a variant of interest,

with a p-value of $1x10^{-5}$. The variants and their respective ratio distributions are displayed in **FIG. 1A** (ratio A) and **FIG. 1B** (ratio B). The effect of multiple alleles of interest is cumulative, as shown by the median ratios present in individuals having a CYP3A4 genotype of *22/*1, i.e. heterozygous for the *22 variant of interest (*22 het), compared with individuals having a CYP3A4 genotype of *22/*22 + *3/*1 genotype, i.e., homozygous for the *22 variant of interest. Tissue samples taken from homozygotes (*22/*22) exhibit a 1.7 to 2.5 fold reduction in mRNA or protein expression compared to wild type. This ultimately results in reduction of M3 and a shift to metabolism via other routes.

The graphs shown in **FIGS. 2A-2H** illustrate the plasma concentrations of tradipitant (**FIG. 2A**), metabolite M2 (**FIG. 2B**), metabolite M3 (**FIG. 2C**), metabolite M4 (**FIG. 2D**), metabolite M8 (**FIG. 2E**), ratio of tradipitant to M8 (**FIG. 2F**), ratio of all metabolites to M8 (i.e., (M2 + M3 + M4) / M8) (**FIG. 2G**), and ratio of tradipitant to M3 (**FIG. 2H**) in individuals in a study population. **FIGS. 2A-2D** show clearly greater median concentrations of tradipitant, M2, M3, and M4 in the *22 heterozygous group (*22 het) as compared to wild type. This reflects the reduced ability to clear tradipitant in individuals having a *22 allele. **FIG. 2F** illustrates a clearly greater median ratio of tradipitant to M8 in the *22 heterozygous group (*22 het) as compared to wild type (no *22 alleles).

FIG. 3 shows a graph relating apparent clearance of tradipitant with CYP3A4*22 status (missing, wild type, heterozygous, or homozygous), in which each circle represents the value from one subject, and the line represents the median value. The apparent clearance of tradipitant is plotted for individuals having a wild type (WT) genotype as compared to individuals having a heterozygous *22 (*22 het) genotype. The ratio of clearance (CL) in *22 het to WT is calculated as exp(median(HET) - median(WT)). Below these calculations, the P value is reported for a t test comparing the ETA values. This graph shows that the presence of a single CYP3A4*22 allele results in significantly different clearance of tradipitant, namely, about 66% of the clearance observed in wild type individuals. Post hoc ETAs are the following: log(individual value for clearance / typical value for clearance), where "typical value" is essentially the median value. Since the ratios are centered around 1.0 (one-half are > median, the other half < median), log of these values are centered at zero).

Due to the MAF of the *22 variant, no individuals having a *22/*22 homozygous genotype are identified in the study population. However, it would be expected that tradipitant clearance in a homozygous *22/*22 individual would be significantly lower still than the clearance observed in *22 het individuals. In the analysis, out of 2,060 samples, eleven (11) individuals are identified having *3 het/*22 het genotypes. In ten (10) of these individuals, both variants are on the same chromosome, while in one (1) individual, the variants are on separate chromosomes. Two (2) individuals are also identified as having a *3 het/*22 hom genotype.

These findings support a conclusion that variants in the CYP3A4 gene, and particularly the CYP3A4*22 allele, have functional significance with respect to metabolism of tradipitant. The presence of variants of interest, including *22, may lead to loss of metabolic activity, which may be cumulative with the number of alleles of interest present in an individual's gene sequence. Associated reductions in mRNA or protein expression may result in a clinically significant reduction in metabolism of tradipitant, e.g., heterozygotes may experience only 66% of the tradipitant clearance experienced by comparably dosed individuals having a wild type CYP3A4 genotype, i.e., reduction by 34%.

Example 2: A Four-Period, Two-Way Crossover Open Label Study Evaluating the Pharmacokinetics of a Single Dose of Tradipitant in Healthy Participants

To evaluate the pharmacokinetics and effect of food on the bioavailability of single-dose capsules containing 170 mg tradipitant and 85 mg tradipitant, an open label, four-period, two-way crossover study is performed. An overview of the study design is provided in **FIG. 4**. The study comprises two cohorts, each of which conducts a screening phase and an evaluation phase. Cohort 1 only conducts Period 1 and Period 2 (**FIG. 5**), while Cohort 2 only conducts Period 3 and Period 4 (**FIG. 6**). It is possible for a participant in Cohort 1 to be a Participant in Cohort 2.

The screening phase (Day -21 to Day -2, **FIGS. 5-6**) consists of a screening visit wherein an informed consent is obtained from potential participants, and their eligibility is initially assessed based on vital signs, body measurements, physical examination, ECG, clinical laboratory tests, drug and alcohol screen, and medical history. Clinical laboratory testing includes a pharmacogenetics sample for whole

genome sequencing. Participants may include men or women aged 18-55 years, inclusive at the time of screening; having a Body Mass Index (BMI) of ≥ 18.0 and ≤ 39.0 kg/m^2 (BMI = weight (kg)/[height (m)]^2); and female participants of childbearing potential must be non-pregnant and non-lactating. Participants must be in good health as determined by a medical and psychiatric history, physical examination, electrocardiogram, and serum chemistry and hematology; willing to comply with study procedures and restrictions; willing to provide a pharmacogenetic sample; and have negative test result for selected substances of abuse at screening. Individuals may be excluded from participating based on history (within the 12 months prior to screening) of psychiatric disorders; current clinically significant cardiovascular, respiratory, neurologic, hepatic, hematopoietic, renal, gastrointestinal, or metabolic dysfunction unless currently controlled and stable; history of intolerance and/or hypersensitivity to other NK-1 receptor antagonists; clinically significant deviation from normal in clinical laboratory results, vital signs measurements, or physical examination findings at screening as determined by the clinical investigator; major surgery, trauma (including broken pelvis/legs), illness (e.g. sepsis), or immobility for 3 or more days within the past month; active cancer or cancer treatment within the past 6 months prior to screening; central venous catheter in place or within the past month; impaired liver function indicated by AST, ALT, or bilirubin > 2 times the upper limit of normal, unless there is an isolated bilirubin > 2 times the upper limit of normal due to Gilbert's syndrome; pregnancy or recent pregnancy (within 6 weeks prior to screening) or women who are breastfeeding; history of drug or alcohol abuse as defined in DSM-V, Diagnostic Criteria for Drug and Alcohol Abuse, within the 12 months prior to screening and/or regular consumption of alcoholic drinks (> 2 drinks/day or > 14 drinks/week); randomization in a previous tradipitant trial; and participants at risk of suicide, in the opinion of the Investigator. Further exclusion criteria include participants who are unwilling or unable to follow the medication restrictions, or unwilling or unable to sufficiently wash-out from use of a restricted medication; any condition requiring the regular use of medication; routine consumption of caffeine including coffee, tea, and/or other caffeine-containing beverages or food averaging more than 3 cups a day (24 ounces); inability to be venipunctured and/or tolerate venous access; participants who had used tobacco products 3 months prior to dosing (tobacco users are defined as any participant who reported cigarette, cigar, tobacco, nicotine gum, nicotine patch, or electronic cigarette

use); participation in the evaluation of any investigational product for 30 days or within 5 half-lives (if-known), whichever is longer, before Day -1; use of prescription or OTC medications, including herbal products (e.g., St. John's wort), other than hormonal birth control within 1 week of first dose administration; use of any food or beverage containing alcohol, grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (e.g. kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), or charbroiled meat within 1 week of first dose administration until End of Study evaluation; abnormal diets (<1600 or > 3500 kcal/day), substantial changes in eating habits within one week of first dose administration until End of Study evaluation, or vegetarians; history (including family history) or current evidence of congenital long QT syndrome or known acquired QT interval prolongation; and history of liver disease and/or positive for one or more of the following serological results: a) a positive hepatitis C antibody test (anti-HCV), b) a positive HIV (ELISA and Western) test result, and/or c) positive hepatitis B surface antigen (HBsAg).

Following the screening period, each of the two evaluation phases consists of two periods for a total of four periods. Each period consists of a baseline visit and a single-dose treatment period with onsite observation for 48 hours and PK sampling for 72 hours. The four periods are separated by a washout of at least 11 days. The evaluation phases end with an end-of-study visit on Day 4 of Period 2 for cohort 1 (**FIG. 5**) and Day 4 of Period 4 for cohort 2 (**FIG. 6**). The baseline evaluations are repeated at the beginning of the second and fourth period. During the baseline visit the following assessments are performed: vital signs, body weight, clinical laboratory safety tests, drug, alcohol, and cotinine screening, physical examination, and urine and serum pregnancy tests if WOCBP, and any adverse events are recorded.

Within two hours prior to dosing on Day 1, pre-dose blood sampling for tradipitant and its metabolites (M2, M3, M4, M8) is collected. Participants are dispensed study medication under open label conditions. Each participant of cohort 1 (**FIG. 5**) is given a dose of 170 mg tradipitant in the form of two 85 mg tradipitant capsules by mouth (PO) in a fasted or fed condition at Visit 3, and the alternative treatment at Visit 6. Each participant of cohort 2 is given a dose of either 85 mg tradipitant given as one 85 mg tradipitant capsule PO under fasted or fed conditions at Visit 10, and the alternative treatment at Visit 13. Tradipitant capsules are white opaque, hard gelatin capsules provided as a strength of 85 mg. The 85 mg capsule

formulation also contains spray-dried lactose monohydrate, microcrystalline cellulose (Avicel PH102 and PH200), povidone, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate as excipients.

Participants take the study medication between 07:00 and 09:00. Participants dosed under fasted (10 hour fast) conditions take the study medication on an empty stomach with 240 mL of room temperature tap water, and swallow the capsule(s) whole, without chewing. Any other water is withheld from 1 hour before dosing to one hour after drug administration. Otherwise water intake is ad lib. Participants dosed with study medication in the fed condition commence consumption of a high-calorie, high-fat meal 30 minutes or less prior to administration of study medication, and finish the meal prior to dosing. The meal is consistent with the US FDA's suggested high-fat breakfast of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes, and eight oz. of whole milk. (U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry*, available at https://www.fda.gov/media/121313/download, p. 12, Appendix 1 (June 2022) (accessed November 11, 2022).)

In both fed and fasted conditions, food is provided 4 hours following dosing. Any subsequent meals and their contents are at the discretion of the investigational site, and are consistent across participants. The following foods and beverages are prohibited in any meal for the duration of the study: alcohol, grapefruit (juice), apple (juice), orange (juice), vegetables from the mustard green family (e.g. kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meat.

Pharmacokinetic (PK) blood samples are taken at the following time points for periods 1-4: pre-dose, and each of 0.5 hr., 1 hr., 1.5 hr., 2 hr., 2.5 hr., 3 hr., 4 hr., 6 hr., 8 hr., 12 hr., 18 hr., 24 hr., 30 hr., 36 hr., 48 hr., and 72 hr. post-dose, each +/- 5 minutes, after drug administration. Samples are analyzed for the following analytes: tradipitant, and metabolites M2, M3, M4, and M8. Participants are discharged from the site after 48 hours, and return to the site on Day 4 for a 72-hour blood sample.

The End of Study (EOS)/Early Discontinuation (ED) evaluation is performed after the last PK sample on Day 4 of Period 2 for cohort 1 and on Day 4 of Period 4

for cohort 2 or upon discontinuation if a participant withdraws prematurely from the study. During the EOS/ED evaluation, a physical examination is performed, vital signs and weight are assessed, and 12-lead ECG and clinical laboratory tests are performed. AEs and concomitant medication are recorded throughout the whole duration of the study.

Results

A total of fifteen (15) and sixteen (16) subjects enroll in Cohorts 1 and 2, respectively, and complete both periods. These 31 individuals comprise the PK analysis population. Five (5) subjects from cohort 1 also participated in cohort 2. The following abbreviations are used herein:

AUC	Area under the plasma concentration-time curve;
AUC(0-t)	Area under the plasma concentration-time curve to the last time with a concentration ≥ LOQ
AUC(inf)	Area under the plasma concentration-time curve to infinity
CI	Confidence interval
Cmax	Maximum plasma concentration
gMean	Geometric mean
hr	Hour
LSGMR	Least squares geometric mean ratio
mg	milligram
mL	milliliter
ng	nanogram
PK	pharmacokinetics
t	time
t½	elimination half-life
Tmax	Time of maximum plasma concentration
WSCV	Within-subject coefficient of variation
λz	elimination rate constant

Tradipitant

After administration of 170 mg in the fed state, the geometric mean (gMean) plasma concentrations of tradipitant (**FIGS. 7A-7B**) and values for Cmax, AUC(0-t),

and AUC(inf) (**Table 1**) are substantially higher than after oral administration under fasted conditions. The least squares geometric mean ratios (LSGMRs) were 703.87% for Cmax and 328.21% and 381.70% for AUC(0-t) and AUC(inf), respectively, (**Table 2**).

Table 1: Summary of pharmacokinetic parameters for tradipitant after oral administration of 170 mg of tradipitant to healthy volunteers under fed and fasted conditions

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	774 [29.6] (15)	112 [74.1] (15)
Tmax (hr)	4.00 (15) [2.00 – 8.00]	1.50 (15) [1.00 – 30.0]
AUC(0-t) (hr x ng/mL)	9,153 [41.2] (15)	2,793 [49.4] (15)
AUC(inf) (hr x ng/mL)	10,374 [51.4] (14)	3,526 [53.0] (8)
λz (1/hr)	0.0255 [37.1] (14)	0.0246 [30.1] (8)
t½ (hr)	27.2 [37.1] (14)	28.2 [30.1] (8)

* Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 2: Statistical comparison of pharmacokinetic parameters for tradipitant after oral administration of 170 mg of tradipitant to healthy volunteers under fed and fasted conditions

Parameter	**Least Squares Geometric Means**		**Least Squares Geometric Mean Ratio (%)**		**Within Subject CV (%)**	**Power* (%)**
	Fed	**Fasted**	**Estimate**	**90% CI**		
Cmax	777.82	110.51	703.87	546.99 → 905.75	40.4	67.5
AUC (0-t)	9,178.34	2,796.44	328.21	276.02 → 390.27	27.2	61.2
AUC (inf)	10,402.26	2,725.23	381.70	238.29 → 611.42	32.9	87.9

Based on analysis of natural log-transformed pharmacokinetic parameters.
*Power to detect a 20% difference at $\alpha = 0.05$.

The median Tmax increased from 1.50 hr under fasted conditions to 4.00 hr under fed conditions (**Table 1**).

The same significant increase was observed after administration of 85 mg in the fed state, as illustrated in **FIGS. 8A-8B** (gMean concentrations) and **Table 3** (Cmax and the AUCs) with LSGMRs of 437.59%, 234.21%, and 263.08% (**Table 4**). Administration in the fed state resulted in a 2-fold increase in Tmax (**Table 3**).

Table 3: Summary of pharmacokinetic parameters for tradipitant after oral administration of 85 mg of tradipitant to healthy volunteers under fed and fasted conditions

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	401 [36.9] (16)	84.7 [39.7] (16)
Tmax (hr)	4.00 (16) [1.53 – 6.00]	2.00 (16) [1.00 – 8.00]
AUC (0-t) (hr x ng/mL)	3,862 [41.7] (16)	1,649 [47.3] (16)
AUC (inf) (hr x ng/mL)	4,516 [51.9] (15)	1,839 [58.1] (10)
λz (1/hr)	0.0224 [29.0] (15)	0.0219 [39.0] (10)
t½ (hr)	31.0 [29.0] (15)	31.6 [39.0] (10)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 4: Statistical comparison of pharmacokinetic parameters for Tradipitant after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions

Parameter	**Least Squares Geometric Means**		**Least Squares Geometric Mean Ratio (%)**		**Within Subject CV (%)**	**Power* (%)**
	Fed	**Fasted**	**Estimate**	**90% CI**		
Cmax	401.00	84.67	473.59	408.09 → 549.60	24.2	65.6
AUC (0-t)	3,861.87	1,648.91	234.21	192.66 → 284.71	32.1	61.2
AUC (inf)	4,702.37	1,787.46	263.08	201.12 → 344.12	30.6	72.7

Based on analysis of natural log-transformed pharmacokinetic parameters.
*Power to detect a 20% difference at $\alpha = 0.05$.

For both doses, administration in the fed state results in significant increases in the gMean values for Cmax and AUC with longer median values for Tmax. This demonstrates an increase in the extent and a decrease in the rate of absorption.

Metabolite M2

Consistent with the effect of the fed state on the absorption of the parent compound, tradipitant, the geometric mean (gMean) plasma concentrations of Metabolite M2 (**FIGS. 9A-9B**) and values for Cmax, AUC(0-t), and AUC(inf) (**Table 5**) after administration of 170 mg are substantially higher after oral administration under fed conditions than after oral administration under fasted conditions. The LSGMRs were 654.35% for Cmax and 352.60% and 350.82% for AUC(0-t) and

AUC(inf), respectively (**Table 6**). The median Tmax remained unchanged, 4 hr, when the 170 mg capsule is dosed in the fed state (**Table 5**).

The same significant increase is observed after administration of 85 mg in the fed state, as illustrated in **FIGS. 10A-10B** (gMean concentrations) and **Table 7** (Cmax and the AUCs), with LSGMRs of 407.70%, 240.71%, and 238.83% (**Table 8**). The median Tmax remains unchanged (4 hr) when the 170 mg capsule is dosed in the fed state (**Table 7**). For both doses, there are significant increases in the gMean values for Cmax and AUC with no change in the median values for Tmax when administered in the fed state, demonstrating an increase in the extent of absorption.

Table 5: Summary of pharmacokinetic parameters for Metabolite M2 after oral administration of 170 mg of tradipitant to healthy volunteers under fed and fasted conditions

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	121 [33.9] (15)	18.7 [67.6] (15)
Tmax (hr)	4.00 (15) [2.50 – 8.00]	4.00 (15) [1.50 – 48.0]
AUC (0-t) (hr x ng/mL)	2,682 [45.8] (16)	761 [57.9] (15)
AUC (inf) (hr x ng/mL)	3,522 [48.2] (13)	803 [61.8] (6)
λz (1/hr)	0.0221 [36.1] (13)	0.0235 [14.7] (6)
t½ (hr)	31.4 [36.1] (13)	29.5 [14.7] (6)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 6: Statistical comparison of pharmacokinetic parameters for Metabolite M2 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	**Least Squares Geometric Means**		**Least Squares Geometric Mean Ratio (%)**		**Within Subject CV (%)**	**Power* (%)**
	Fed	**Fasted**	**Estimate**	**90% CI**		
Cmax	121.40	18.55	654.35	511.18 → 837.63	39.5	66.9
AUC (0-t)	2,686.63	761.94	352.60	298.32 → 416.77	26.2	61.7
AUC (inf)	3,582.62	1,021.22	350.82	177.98 → 691.50	42.9	94.0

Based on analysis of natural log-transformed pharmacokinetic parameters.
*Power to detect a 20% difference at $\alpha = 0.05$.

Table 7: Summary of pharmacokinetic parameters for Metabolite M2 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	57.7 [49.7] (16)	14.2 [55.8] (16)
Tmax (hr)	4.00 (16) [2.00 – 6.00]	4.00 (16) [1.50 – 48.0]
AUC (0-t) (hr x ng/mL)	1,221 [55.7] (16)	507 [58.8] (16)
AUC (inf) (hr x ng/mL)	1,553 [73.2] (14)	741 [92.9] (8)
λz (1/hr)	0.0194 [37.0] (14)	0.0159 [56.3] (8)
t½ (hr)	35.8 [37.0] (14)	43.7 [56.3] (8)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 1: Statistical comparison of pharmacokinetic parameters for Metabolite M2 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	**Least Squares Geometric Means**		**Least Squares Geometric Mean Ratio (%)**		**Within Subject CV (%)**	**Power* (%)**
	Fed	**Fasted**	**Estimate**	**90% CI**		
Cmax	57.73	14.16	407.70	338.64 → 490.83	30.5	60.8
AUC (0-t)	1,221.20	507.33	240.71	203.19 → 285.17	27.7	61.4
AUC (inf)	1,653.19	692.22	238.83	175.53 → 324.94	23.9	83.2

Based on analysis of natural log-transformed pharmacokinetic parameters.
*Power to detect a 20% difference at $\alpha = 0.05$.

Metabolite M3

Consistent with the effect of the fed state on the absorption of the parent compound, tradipitant, the geometric mean (gMean) plasma concentrations of Metabolite M3 (**FIGS. 11A-11B**) and values for Cmax, AUC(0-t), and AUC(inf) (**Table 9**) after administration of 170 mg tradipitant are substantially higher than after oral administration under fasted conditions. The LSGMRs are 526.84% for Cmax and 356.01% for AUC(0-t) (**Table 10**). The median Tmax is longer when the 170 mg capsule is dosed in the fed state (4 hr) compared to fasted conditions (3 hr) (**Table 9**).

The same significant increase is observed after administration of 85 mg tradipitant in the fed state, as illustrated in **FIGS. 12A-12B** (gMean concentrations) and **Table 11** (Cmax and the AUCs) with LSGMRs of 370.57%, 255.71%, and 263.76% (**Table 12**). The median Tmax is longer when the 85 mg capsule is dosed in the fed state (4 hr) compared to fasted conditions (3 hr) (**Table 11**). For both doses,

there are significant increases in the gMean values for Cmax and AUC with longer median values for Tmax when administered in the fed state, demonstrating an increase in the extent and a decrease in the rate of absorption.

Table 9: Summary of pharmacokinetic parameters for Metabolite M3 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	114 [17.1] (15)	21.9 [52.2] (15)
Tmax (hr)	4.00 (15) [3.00 – 8.00]	3.00 (15) [1.05 – 48.0]
AUC (0-t) (hr x ng/mL)	2,682 [40.3] (15)	757 [47.1] (15)
AUC (inf) (hr x ng/mL)	3,589 [41.2] (13)	835 [62.5] (7)
λz (1/hr)	0.0252 [47.2] (13)	0.0270 [32.4] (7)
t½ (hr)	27.5 [47.2] (13)	25.7 [32.4] (7)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 10: Statistical comparison of pharmacokinetic parameters for Metabolite M3 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	**Least Squares Geometric Means**		**Least Squares Geometric Mean Ratio (%)**		**Within Subject CV (%)**	**Power* (%)**
	Fed	**Fasted**	**Estimate**	**90% CI**		
Cmax	114.37	21.71	526.84	417.99 → 664.04	36.9	64.9
AUC (0-t)	2,685.20	754.25	356.01	303.15 → 418.09	25.2	62.7
AUC (inf)	— †	— †	— †	— †	— †	— †

Based on analysis of natural log-transformed pharmacokinetic parameters.
*Power to detect a 20% difference at α = 0.05.
†Could not be estimated due to missing values.

Table 11: Summary of pharmacokinetic parameters for Metabolite M3 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	63.5 [21.3] (16)	17.1 [35.1] (16)
Tmax (hr)	4.00 (16) [2.00 – 6.00]	3.02 (16) [1.50 – 12.0]
AUC (0-t) (hr x ng/mL)	1,337 [34.4] (16)	523 [43.4] (16)
AUC (inf) (hr x ng/mL)	1,567 [45.2] (15)	608 [56.4] (10)
λz (1/hr)	0.0248 [26.5] (15)	0.0230 [35.2] (10)
t½ (hr)	28.0 [26.5] (15)	30.2 [35.2] (10)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 12: Statistical comparison of pharmacokinetic parameters for Metabolite M3 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	Least Squares Geometric Means		Least Squares Geometric Mean Ratio (%)		Within Subject CV (%)	Power* (%)
	Fed	Fasted	Estimate	90% CI		
Cmax	63.55	17.15	370.57	317.07 → 433.09	25.4	63.7
AUC (0-t)	1,337.43	523.02	255.71	216.56 → 301.95	27.2	61.8
AUC (inf)	1,566.47	593.90	263.76	213.08 → 326.49	26.1	64.0

Based on analysis of natural log-transformed pharmacokinetic parameters.

*Power to detect a 20% difference at $\alpha = 0.05$.

Metabolite M4

Consistent with the effect of the fed state on the absorption of the parent compound, tradipitant, the geometric mean (gMean) plasma concentrations of Metabolite M4 (**FIGS. 13A-13B**) and values for Cmax, AUC(0-t), and AUC(inf) (**Table 13**) after administration of 170 mg tradipitant are substantially higher than after oral administration of the same dose under fasted conditions. The LSGMRs were 547.40% for Cmax, 357.77% for AUC(0-t), and 320.49% for AUC(inf) (**Table 14**). The median Tmax is longer when the 170 mg capsule is dosed in the fed state (6 hr) compared to fasted conditions (4 hr) (**Table 13**).

The same significant increase is observed after administration of 85 mg tradipitant in the fed state, as illustrated in **FIGS. 14A-14B** (gMean concentrations) and **Table 15** (Cmax and the AUCs), with LSGMRs of 339.57%, 243.58%, and 239.45% (**Table 16**). The median Tmax is longer when the 85 mg capsule is dosed in the fed state (6 hr) compared to fasted conditions (4.09 hr) (**Table 15**). For both doses, there are significant increases in the gMean values for Cmax and AUC with longer median values for Tmax when administered in the fed state, demonstrating an increase in the extent and a decrease in the rate of absorption.

Table 13: Summary of pharmacokinetic parameters for Metabolite M4 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter*	Fed	Fasted
Cmax (ng/mL)	116 [16.7] (15)	21.4 [54.0] (15)
Tmax (hr)	6.00 (15) [4.00 – 12.0]	4.00 (15) [3.00 – 48.0]
AUC (0-t) (hr x ng/mL)	3,074 [44.8] (15)	861 [54.9] (15)
AUC (inf) (hr x ng/mL)	3,627 [61.3] (15)	1,035 [62.7] (9)
λz (1/hr)	0.0301 [47.2] (15)	0.0242 [39.7] (9)
t½ (hr)	23.1 [47.2] (15)	28.6 [39.7] (9)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 14: Statistical comparison of pharmacokinetic parameters for Metabolite M4 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	Least Squares Geometric Means		Least Squares Geometric Mean Ratio (%)		Within Subject CV (%)	Power* (%)
	Fed	Fasted	Estimate	90% CI		
Cmax	116.30	21.25	547.40	439.26 → 682.15	35.0	63.6
AUC (0-t)	3,077.61	860.22	357.77	304.61 → 402.22	25.2	62.7
AUC (inf)	3,643.03	1,136.70	320.49	230.02 → 446.56	31.6	79.4

Based on analysis of natural log-transformed pharmacokinetic parameters.

*Power to detect a 20% difference at $\alpha = 0.05$.

Table 15: Summary of pharmacokinetic parameters for Metabolite M4 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter*	Fed	Fasted
Cmax (ng/mL)	59.0 [23.3] (16)	17.4 [46.4] (16)
Tmax (hr)	6.00 (16) [4.00 – 8.00]	4.09 (16) [3.00 – 36.0]
AUC (0-t) (hr x ng/mL)	1,482 [54.4] (16)	609 [56.5] (16)
AUC (inf) (hr x ng/mL)	1,752 [63.6] (16)	804 [74.3] (12)
λz (1/hr)	0.0258 [22.3] (16)	0.0214 [50.2] (12)
t½ (hr)	26.9 [22.3] (16)	32.4 [50.2] (12)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 16: Statistical comparison of pharmacokinetic parameters for Metabolite M4 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	Least Squares Geometric Means		Least Squares Geometric Mean Ratio (%)		Within Subject CV (%)	Power* (%)
	Fed	Fasted	Estimate	90% CI		
Cmax	58.98	17.37	339.57	285.03 → 404.55	28.7	61.0
AUC (0-t)	1,482.25	608.53	243.58	206.93 → 286.72	26.6	62.3
AUC (inf)	1,751.73	731.56	239.45	203.57 → 281.66	22.2	62.5

Based on analysis of natural log-transformed pharmacokinetic parameters.

*Power to detect a 20% difference at $\alpha = 0.05$.

Metabolite M8

Consistent with the effect of the fed state on the absorption of the parent compound, tradipitant, the geometric mean (gMean) plasma concentrations of Metabolite M8 (**FIGS. 15A-15B**) and values for Cmax, AUC(0-t), and AUC(inf) (**Table 17**) after administration of 170 mg tradipitant are substantially higher than after oral administration of the same dose under fasted conditions. The LSGMRs were 559.09% for Cmax, 365.76% for AUC(0-t), and 352.97% for AUC(inf) (**Table 18**). The median Tmax is shorter when the 170 mg capsule is dosed in the fed state (8 hr) compared to fasted conditions (30 hr) (**Table 17**).

The same significant increase is observed after administration of 85 mg in the fed state, as illustrated in **FIGS. 16A-16B** (gMean concentrations) and **Table 19** (Cmax and the AUCs) with LSGMRs of 428.64%, 293.76%, and 273.24% (**Table 20**). The median Tmax is shorter when the 85 mg capsule is dosed in the fed state (8 hr) compared to fasted conditions (15 hr) (**Table 19**).

For both doses, there are significant increases in the gMean values for Cmax and AUC with shorter median values for Tmax when administered in the fed state, demonstrating an increase in the extent and the rate of absorption.

Table 17: Summary of pharmacokinetic parameters for Metabolite M8 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	120 [21.0] (15)	21.7 [57.4] (15)
Tmax (hr)	8.00 (15) [6.00 – 12.0]	30.0 (15) [8.00 – 72.0]
AUC (0-t) (hr x ng/mL)	3,997 [44.3] (15)	1,099 [60.0] (15)
AUC (inf) (hr x ng/mL)	5,415 [72.2] (14)	1,359 [67.8] (8)
λz (1/hr)	0.0223 [53.3] (14)	0.0221 [30.9] (8)
t½ (hr)	31.1 [53.3] (14)	31.4 [30.9] (8)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 18: Statistical comparison of pharmacokinetic parameters for Metabolite M8 after oral administration of 170 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	**Least Squares Geometric Means**		**Least Squares Geometric Mean Ratio (%)**		**Within Subject CV (%)**	**Power* (%)**
	Fed	**Fasted**	**Estimate**	**90% CI**		
Cmax	120.47	21.55	559.09	464.26 → 673.30	29.3	60.9
AUC (0-t)	3,993.20	1,091.74	365.76	308.35 → 433.87	26.8	61.4
AUC (inf)	5,323.03	1,508.07	352.97	223.88 → 556.49	39.6	88.8

Based on analysis of natural log-transformed pharmacokinetic parameters.

*Power to detect a 20% difference at $\alpha = 0.05$.

Table 19: Summary of pharmacokinetic parameters for Metabolite M8 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter*	**Fed**	**Fasted**
Cmax (ng/mL)	56.9 [23.7] (16)	13.3 [51.0] (16)
Tmax (hr)	8.00 (16) [4.00 – 12.0]	15.0 (16) [6.00 – 48.0]
AUC (0-t) (hr x ng/mL)	1,865 [43.9] (16)	635 [58.4] (16)
AUC (inf) (hr x ng/mL)	2,276 [52.1] (14)	764 [62.2] (11)
λz (1/hr)	0.0229 [43.2] (14)	0.0191 [58.3] (11)
t½ (hr)	30.3 [43.2] (14)	36.3 [58.3] (11)

*Geometric mean [geometric %CV] (N) except Tmax for which the median (N) [Range] are reported.

Table 20: Statistical comparison of pharmacokinetic parameters for Metabolite M8 after oral administration of 85 mg of Tradipitant to healthy volunteers under fed and fasted conditions.

Parameter	Least Squares Geometric Means		Least Squares Geometric Mean Ratio (%)		Within Subject CV (%)	Power* (%)
	Fed	Fasted	Estimate	90% CI		
Cmax	56.92	13.28	428.64	346.05 → 530.94	35.4	62.8
AUC (0-t)	1,865.36	634.99	293.76	241.97 → 356.64	31.9	61.1
AUC (inf)	2.193.04	802.60	273.24	205.37 → 363.55	34.6	73.9

Based on analysis of natural log-transformed pharmacokinetic parameters.
*Power to detect a 20% difference at $\alpha = 0.05$.

Conclusions

The geometric mean values for Cmax and AUC(inf) after administration of both 85 mg and 170 mg of Tradipitant under fed conditions are compared in **Table 21**. Although the two doses represent different groups of subjects, the ratios of the geometric means are close to 2.0 for all comparisons, indicating dose proportionality of the two capsules under fed conditions.

Table 21: Comparison of pharmacokinetic parameters for Tradipitant and Metabolites M2, M3, M4, and M8 after oral administration of 85 mg and 170 mg of Tradipitant to healthy volunteers under fed conditions.

Assay	Cmax (ng/mL)*			AUC(inf) (hr x ng/mL)*		
	85 mg	170 mg	Ratio	85 mg	170 mg	Ratio
Tradipitant	401.00	773.90	1.93	4,516.18	10,373.66	2.30
Metabolite M2	57.73	120.61	2.09	1,553.36	3,521.68	2.27
Metabolite M3	63.55	114.17	1.80	1,567.30	3,589.29	2.29
Metabolite M4	58.98	116.04	1.97	1,751.73	3,626.71	2.07
Metabolite M8	56.92	120.49	2.12	2,275.71	5,415.35	2.38

*Geometric mean.

The geometric mean values for Cmax and AUC(inf) after administration of 85 mg and 170 mg of Tradipitant under fed conditions are compared in **Table 22**. Although the two doses represent different groups of subjects, the ratios of the geometric means for Cmax are less than proportional for tradipitant and the four metabolites, ranging from 1.23 to 1.64. For AUC(inf), only tradipitant is approximately proportional (ratio 1.92), with ratios for M2, M3, M4, and M8 ranging from 1.08 to 1.78. This indicates that while the parent compound may be dose

proportional with respect to the extent of exposure (AUC) under fasted conditions, for the four metabolites the relationship is less than proportional.

Table 22: Comparison of pharmacokinetic parameters for Tradipitant and Metabolites M2, M3, M4, and M8 after oral administration of 85 mg and 170 mg of Tradipitant to healthy volunteers under fasted conditions.

Assay	Cmax (ng/mL)*			AUC(inf) (hr x ng/mL)*		
	85 mg	170 mg	Ratio	85 mg	170 mg	Ratio
Tradipitant	84.67	112.07	1.32	1,839.37	3,525.92	1.92
Metabolite M2	14.16	18.73	1.32	741.22	802.63	1.08
Metabolite M3	17.15	21.95	1.28	607.63	835.11	1.37
Metabolite M4	17.37	21.42	1.23	804.00	1,034.81	1.29
Metabolite M8	13.28	21.74	1.64	764.06	1,359.49	1.78

*Geometric mean.

For both the 170 mg and 85 mg doses, administration in the fed state associates with substantial increases in the gMean values for Tradipitant Cmax, AUC(0-t), and AUC(inf), with longer median values for Tmax, demonstrating an increase in the extent and a decrease in the rate of absorption. The results with the four metabolites — M2, M3, M4, and M8 — are consistent with those of the parent compound with respect to Cmax and the AUCs, and Tmax, with the exception of M8, for which the median Tmax decreases under fed conditions.

Based on a comparison across the two dose groups under fed conditions, the ratios of the geometric means values for Cmax and AUC(inf) are close to 2.0 for all comparisons, indicating dose proportionality of the two capsules. Based on a comparison across the two dose groups under fasted conditions, the ratios of the geometric mean values for Cmax suggest less than dose proportionality for tradipitant and the four metabolites. AUC(inf) is close to dose proportional for tradipitant, but less than proportional for the four metabolites.

* * *

As used herein, the terms “first,” “second,” and the like, do not denote any order, quantity, or importance, but rather are used to distinguish one element from another, and the terms “a” and “an” herein do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The modifier “about” used in connection with a quantity is inclusive of the stated value and has the meaning dictated by the context (e.g., includes the degree of error associated with

measurement of the particular quantity). The suffix "(s)" as used herein is intended to include both the singular and the plural of the term that it modifies, thereby including one or more of that term (e.g., the metal(s) includes one or more metals). Ranges disclosed herein are inclusive and independently combinable (e.g., ranges of "up to about 25 mm, or, more specifically, about 5 mm to about 20 mm," is inclusive of the endpoints and all intermediate values of the ranges of "about 5 mm to about 25 mm," etc.).

While various embodiments are described herein, it will be appreciated from the specification that various combinations of elements, variations or improvements therein may be made by those skilled in the art, and are within the scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment disclosed, but that the invention will include all embodiments falling within the scope of the appended claims.

CLAIMS

What is claimed is:

1. A method of administering tradipitant to an individual in need thereof, comprising:
5 determining a CYP3A4 genotype of the individual; and
if the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, then administering tradipitant to the individual in a first amount, and
if the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, then administering tradipitant in a
10 second amount, wherein the second amount is smaller than the first amount.

2. The method of claim 1, wherein the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes at least one *22 allele.

15 3. The method of claim 1, wherein the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes two *22 alleles.

4. The method of claim 1 or claim 2, wherein the second, smaller amount is about 35-95% of the first amount.

20

5. The method of claim 1 or claim 3, wherein the second, smaller amount is about 10-55% of the first amount.

6. The method of claim 1, wherein the first amount is about 100-400 mg.

25

7. The method of claim 1, wherein the first amount is about 85 mg.

8. A method of determining an effective amount of tradipitant for administration to an individual in need thereof, comprising:

determining a CYP3A4 genotype of the individual from a biological sample; and

if the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, then determining that the effective amount of tradipitant is a first amount, and

if the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, then determining that the effective amount of tradipitant is a second amount,

wherein the second amount is smaller than the first amount.

9. The method of claim 8, wherein the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes at least one *22 allele.

10. The method of claim 8, wherein the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes two *22 alleles.

11. The method of claim 8 or claim 9, wherein the second, smaller amount is about 35-95% of the first amount.

12. The method of claim 8 or claim 10, wherein the second, smaller amount is about 10-55% of the first amount.

13. The method of claim 8, wherein the first amount is about 100-400 mg.

14. The method of claim 8, wherein the first amount is about 85 mg.

15. A method of administering tradipitant to an individual in need thereof, comprising:

orally administering to the individual a solid dosage form comprising tradipitant and one or more pharmaceutically acceptable excipients, without food.

16. The method of claim 15, further comprising:

instructing the individual to fast for at least 30 minutes prior to the administering.

17. The method of claim 15, further comprising:

instructing the individual to fast for at least 1 hour prior to the administering.

18. The method of claim 15, further comprising:

instructing the individual to fast for at least 2 hours prior to the administering.

19. The method of claim 15, further comprising:

instructing the individual to fast for at least 4 hours prior to the administering.

20. The method of claim 15, further comprising:

instructing the individual to fast for at least 8 hours prior to the administering.

21. The method of claim 15, further comprising:

instructing the individual to fast for at least 10 hours prior to the administering.

22. The method of claim 15, further comprising:

instructing the individual to fast for a period of 0.5 to 1.5 hour prior to the administering.

23. The method of claim 15, further comprising:

instructing the individual to fast for at least 30 minutes following the administering.

24. The method of claim 15, further comprising:

instructing the individual to fast for at least 1 hour following the administering.

25. The method of claim 15, further comprising:

instructing the individual to fast for at least 2 hours following the administering.

26. The method of claim 15, further comprising:

instructing the individual to fast for at least 4 hours following the administering.

27. The method of claim 15, further comprising:

instructing the individual to fast for a period of two (2) to 2.5 hours following the administering.

28. The method of claim 15, wherein the solid dosage form comprises tradipitant in an amount of 100-400 mg.

29. The method of claim 15, wherein the solid dosage form comprises tradipitant in an amount of 150-400 mg.

30. The method of claim 15, wherein the solid dosage form comprises tradipitant in an amount of 170 mg.

31. The method of claim 15, wherein the solid dosage form comprises tradipitant in an amount of 85 mg.

32. The method of claim 15, wherein the solid dosage form comprises a capsule or a tablet.

33. A method of administering tradipitant to an individual in need thereof, comprising:

determining a CYP3A4 genotype of the individual; and

if the individual has a CYP3A4 genotype associated with normal metabolism of tradipitant, then orally administering to the individual a solid dosage form comprising tradipitant in a first amount and one or more pharmaceutically acceptable excipients, without food, and

if the individual has a CYP3A4 genotype that is associated with decreased metabolism of tradipitant relative to wildtype, then orally administering to the individual a solid dosage form comprising tradipitant in a second amount and one or more pharmaceutically acceptable excipients, without food,

wherein the second amount is smaller than the first amount.

34. The method of claim 33, wherein the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes at least one *22 allele.

35. The method of claim 33, wherein the CYP3A4 genotype associated with decreased metabolism of tradipitant relative to wildtype includes two *22 alleles.

36. The method of claim 33 or claim 34, wherein the second, smaller amount is about 35-95% of the first amount.

37. The method of claim 33 or claim 35, wherein the second, smaller amount is about 10-55% of the first amount.

38. The method of claim 33, wherein the first amount is about 100-400 mg.

39. The method of claim 33, wherein the first amount is about 85 mg.

40. The method of claim 33, further comprising:

instructing the individual to fast for at least 30 minutes prior to the administering.

41. The method of claim 33, further comprising:
instructing the individual to fast for at least 1 hour prior to the administering.

42. The method of claim 33, further comprising:
instructing the individual to fast for at least 2 hours prior to the administering.

43. The method of claim 33, further comprising:
instructing the individual to fast for at least 4 hours prior to the administering.

44. The method of claim 33, further comprising:
instructing the individual to fast for at least 8 hours prior to the administering.

45. The method of claim 33, further comprising:
instructing the individual to fast for at least 10 hours prior to the administering.

46. The method of claim 33, further comprising:
instructing the individual to fast for a period of 0.5 to 1.5 hour prior to the administering.

47. The method of claim 33, further comprising:
instructing the individual to fast for at least 30 minutes following the administering.

48. The method of claim 33, further comprising:
instructing the individual to fast for at least 1 hour following the administering.

49. The method of claim 33, further comprising:
instructing the individual to fast for at least 2 hours following the administering.

50. The method of claim 33, further comprising:
instructing the individual to fast for at least 4 hours following the

administering.

51. The method of claim 33, further comprising:

instructing the individual to fast for a period of two (2) to 2.5 hours following the administering.

52. The method of claim 33, wherein the solid dosage form comprises a capsule or a tablet.

53. A method of administering tradipitant to an individual in need thereof, comprising:

determining an effective amount of tradipitant for administration to the individual, wherein the effective amount is determined based on whether or not the individual has fasted prior to administration; and

administering tradipitant in a solid immediate release form comprising the effective amount of tradipitant and one or more pharmaceutically acceptable excipients.

54. The method of claim 53, wherein the effective amount of tradipitant is a first effective amount if the individual is in a fasted condition at a time of administration, and wherein the effective amount is a second effective amount if the individual is in a fed condition at a time of administration.

55. The method of claim 54, wherein the first effective amount is larger than the second effective amount.

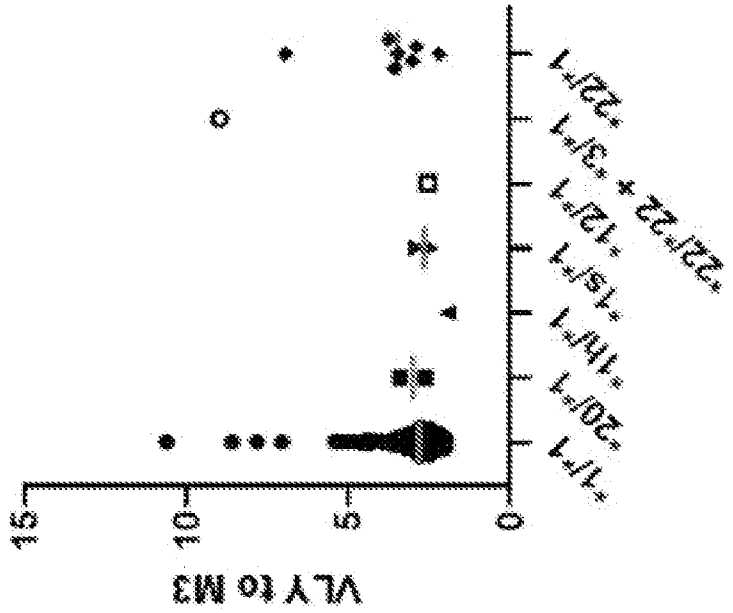
56. The method of claim 53, wherein the individual is experiencing an acute manifestation of a tradipitant-responsive disease or disorder.

57. The method of claim 53, wherein the individual is experiencing a chronic manifestation of a tradipitant-responsive disease or disorder.

58. A method for determining an effective amount of tradipitant for administration to an individual in need thereof, comprising:

determining the effective amount based on whether the individual is in a fasted or fed condition at the time of administration.

FIG. 1B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5
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*1A/*1
*15/*1
*3/*1
*12/*1
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*22/*1

FIG. 1A

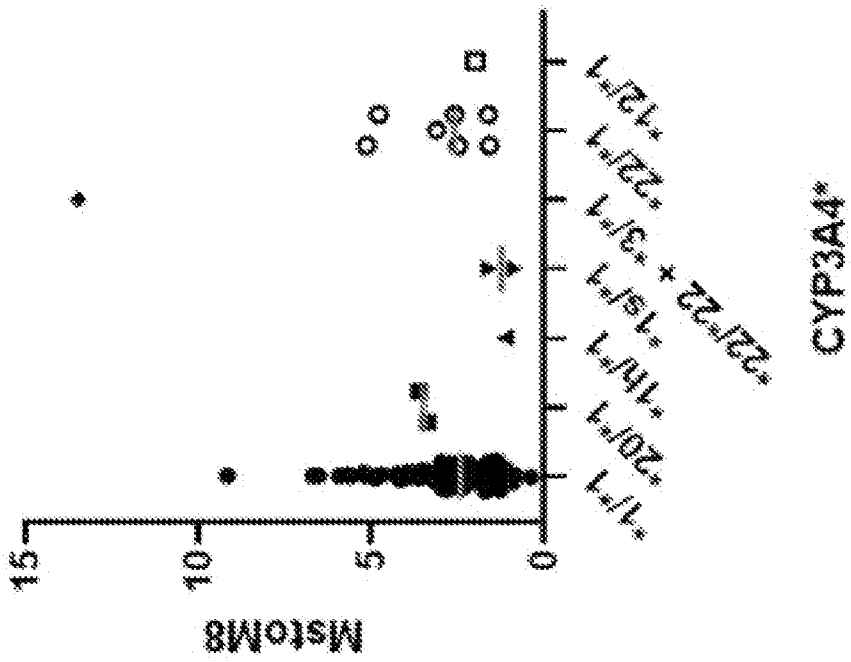

MistoM8
15
10
5
0
*1/*1
*20/*1
*1A/*1
*15/*1
*3/*1
*12/*1
*22/*22 + *3/*1
*22/*1
CYP3A4*

FIG. 2A

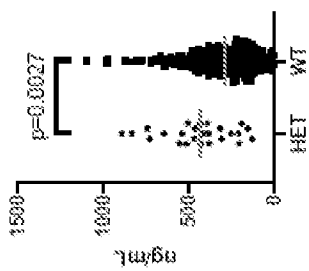


FIG. 2B

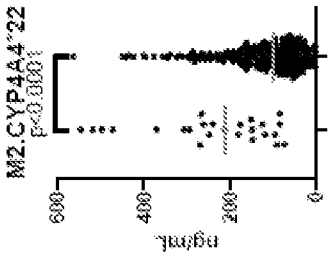


FIG. 2C

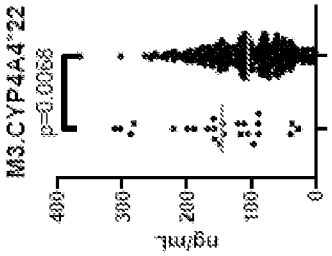


FIG. 2D

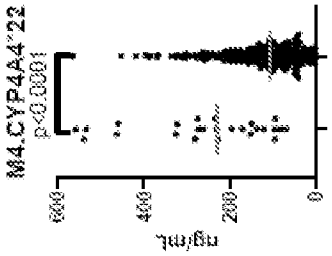


FIG. 2E

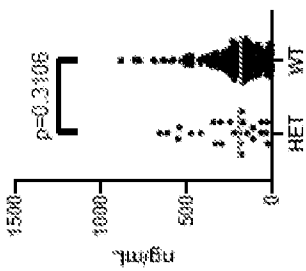


FIG. 2F

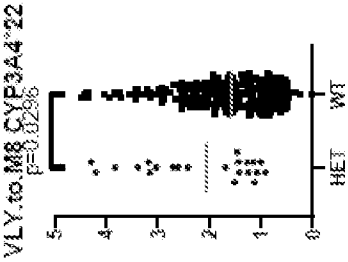


FIG. 2G

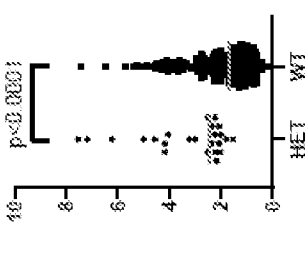


FIG. 2H

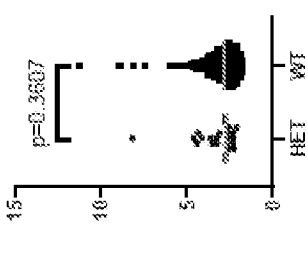


FIG. 3

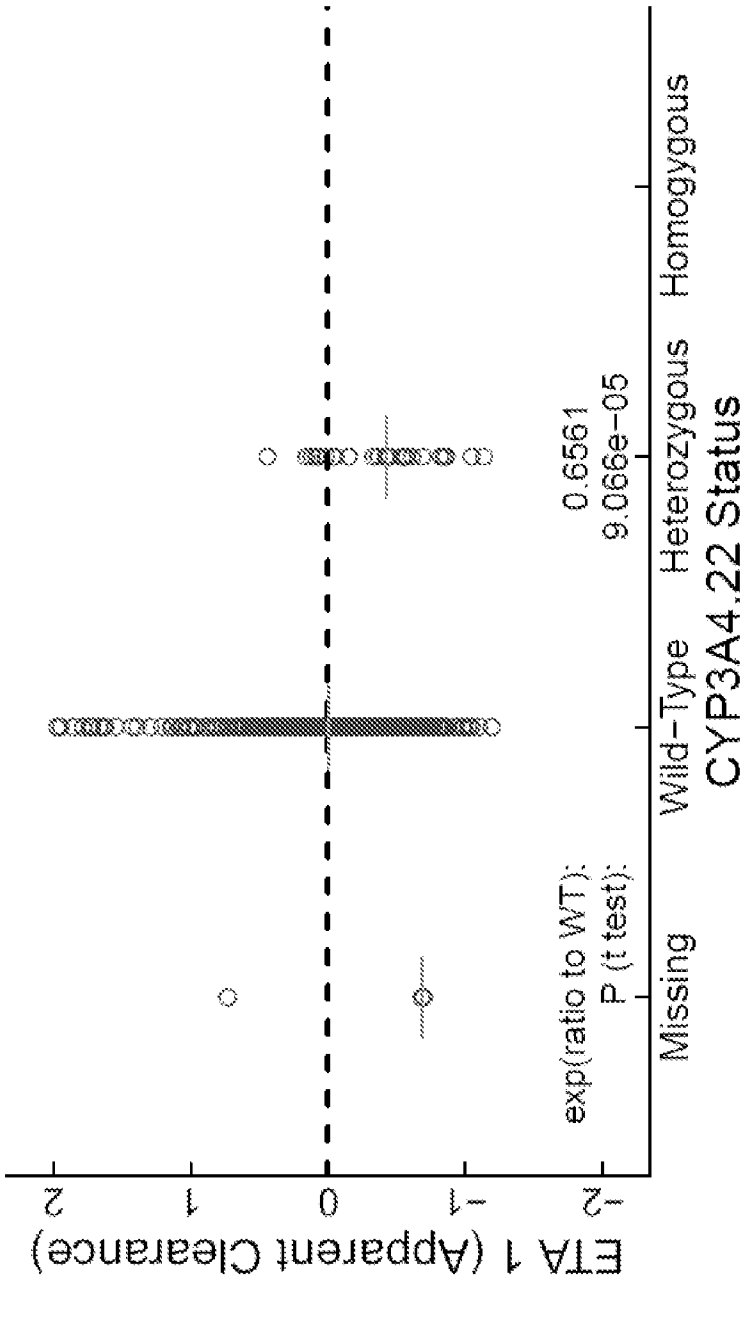

ETA 1 (Apparent Clearance)
2
1
0
−1
−2
exp(ratio to WT): 0.6561
P (t test): 9.066e−05
Missing
Wild−Type
Heterozygous
Homogygous
CYP3A4.22 Status

FIG. 4

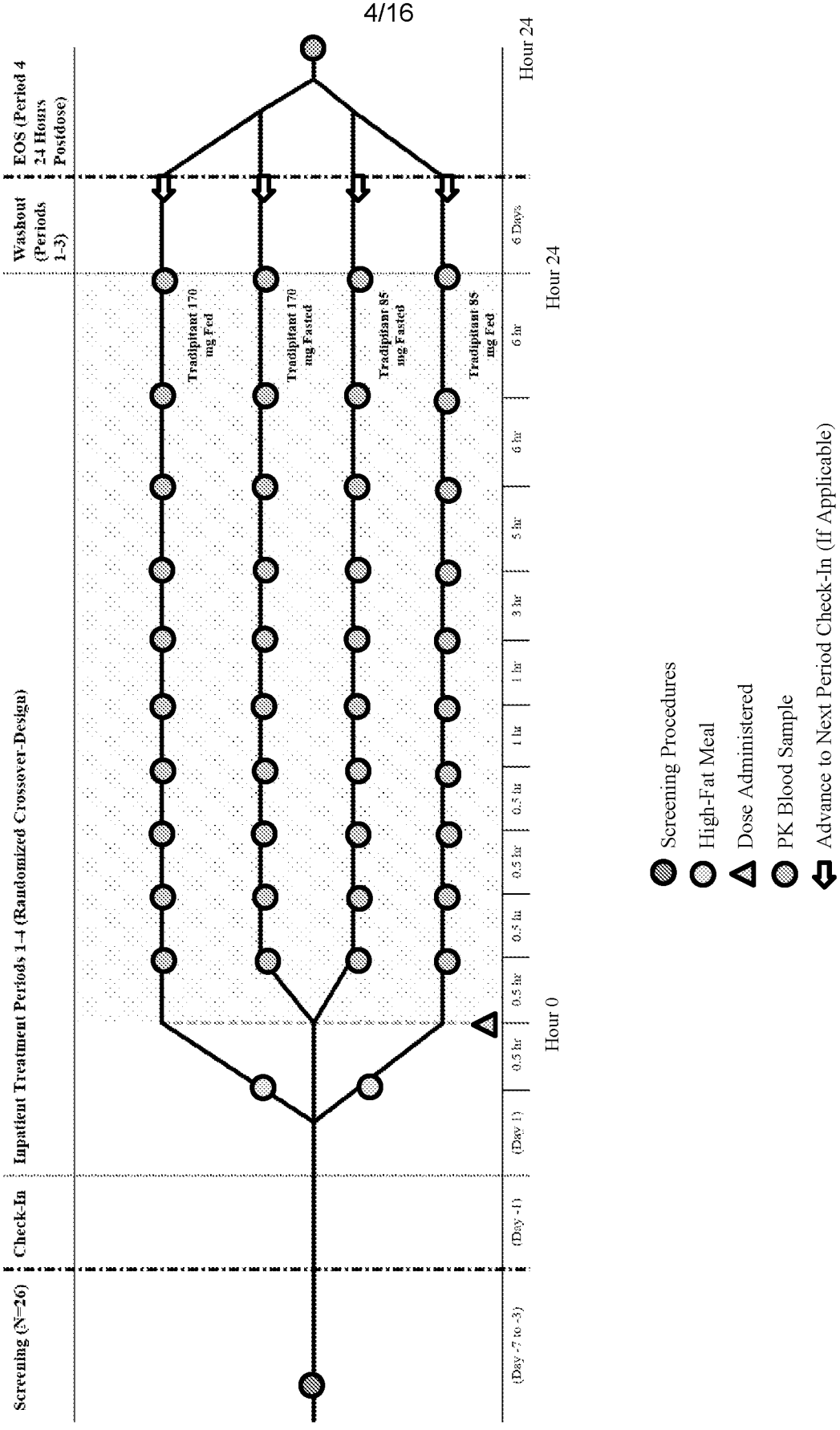

Screening (N=26)
Check-In
Inpatient Treatment Periods 1-4 (Randomized Crossover Design)
Washout (Periods 1-3)
EOS (Period 4 24 Hours Postdose)
(Day -7 to -3)
(Day -1)
(Day 1)
Hour 0
0.5 hr
0.5 hr
0.5 hr
0.5 hr
1 hr
1 hr
3 hr
5 hr
6 hr
6 hr
Hour 24
6 Days
Tradipitant 170 mg Fed
Tradipitant 170 mg Fasted
Tradipitant 85 mg Fasted
Tradipitant 85 mg Fed
Screening Procedures
High-Fat Meal
Dose Administered
PK Blood Sample
Advance to Next Period Check-In (If Applicable)
EOS Procedures

FIG. 5

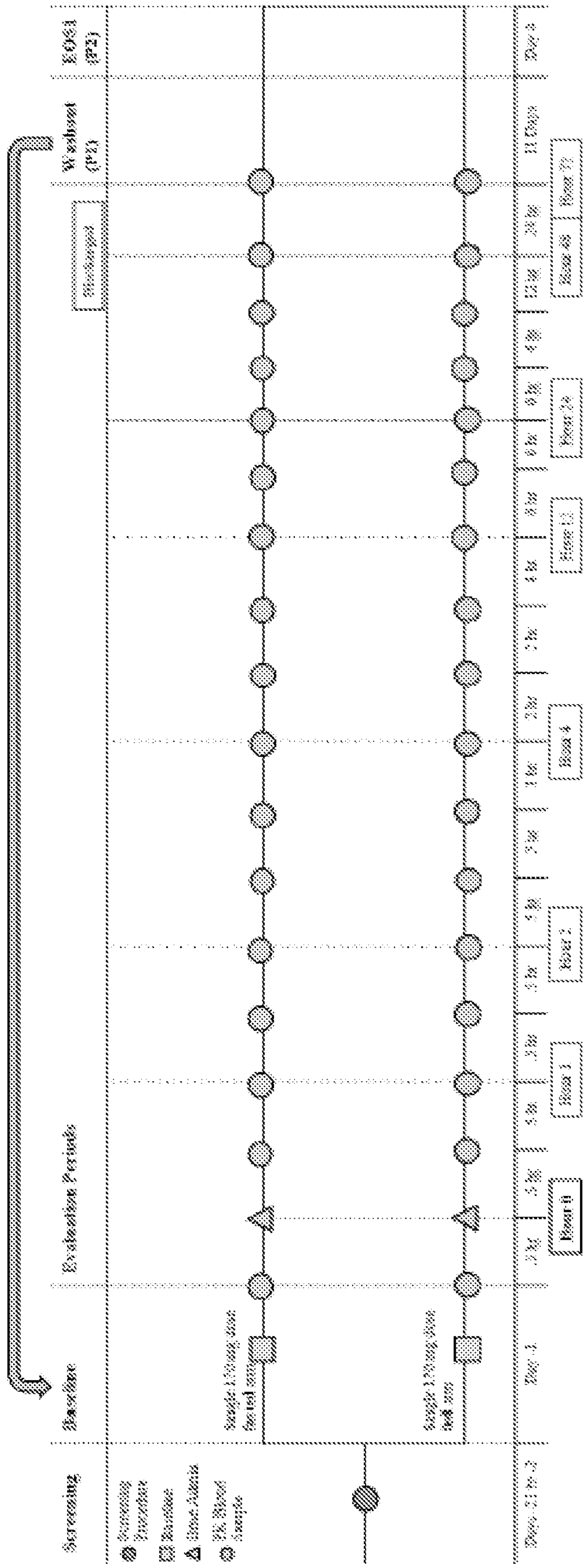


FIG. 6

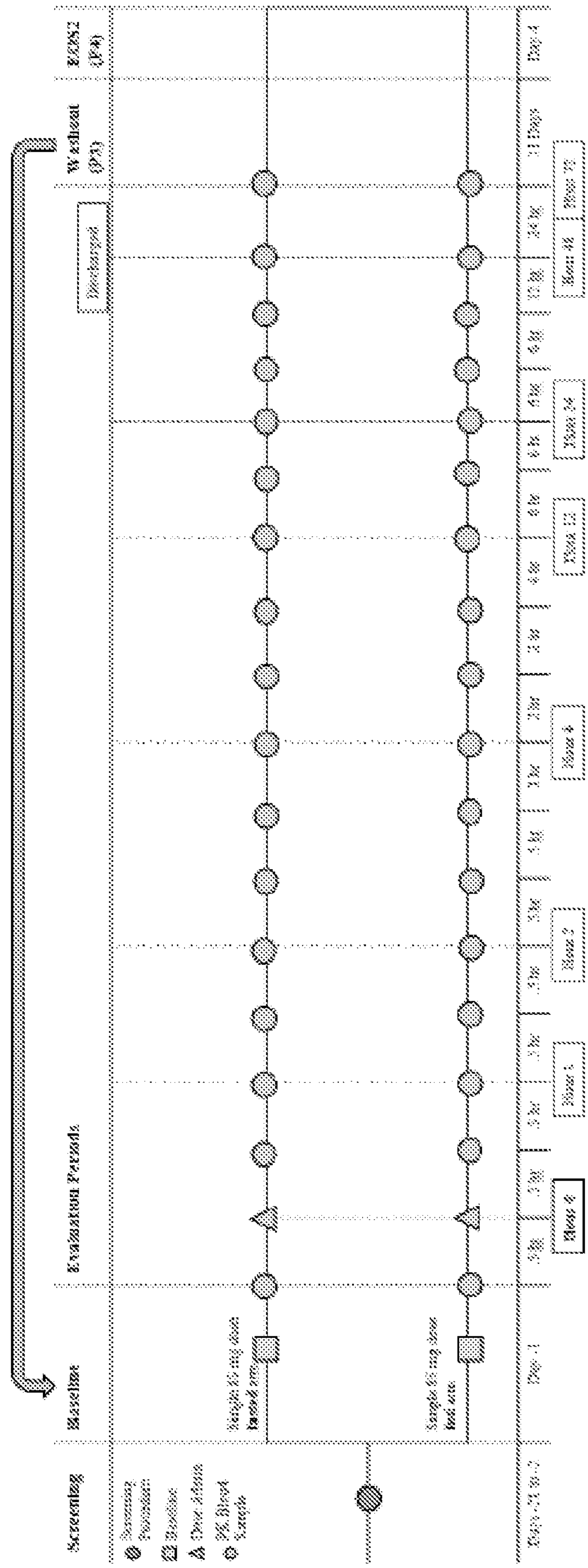


FIG. 7A

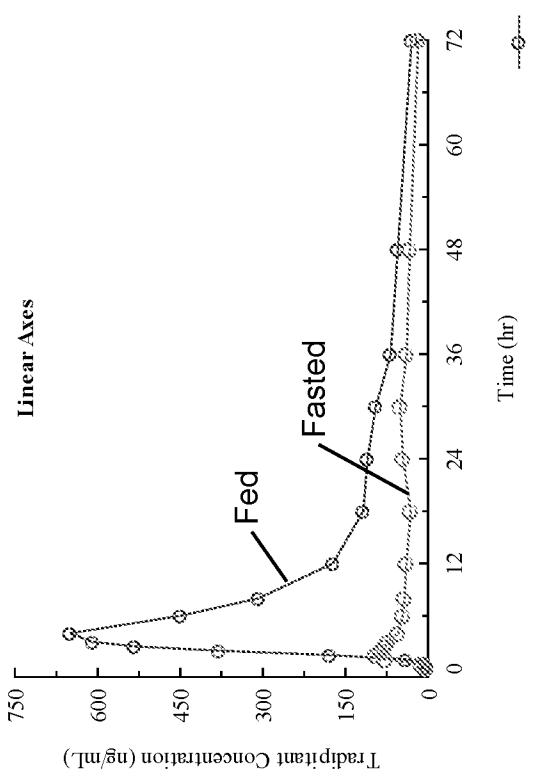

Linear Axes
Fed
Fasted
Tradiptiant Concentration (ng/mL)
750
600
450
300
150
0
0
12
24
36
48
60
72
Time (hr)
Fed
Fasted

FIG. 7B

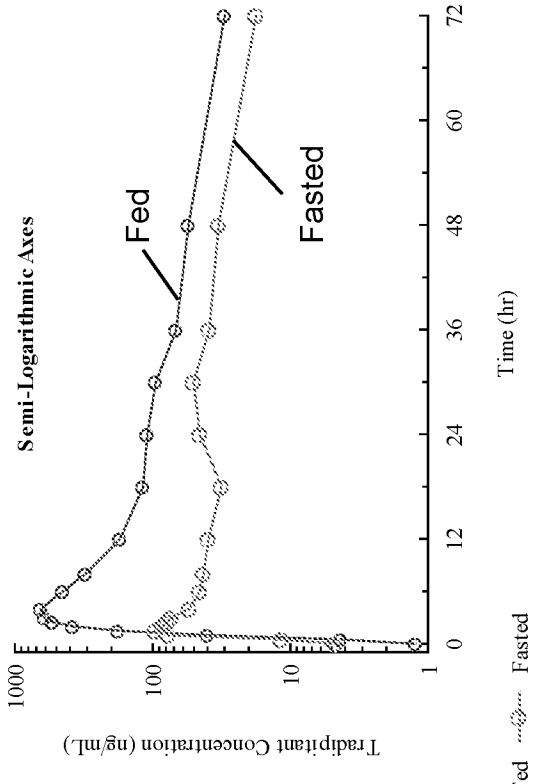

Semi-Logarithmic Axes
Fed
Fasted
Tradiptiant Concentration (ng/mL)
1000
100
10
1
0
12
24
36
48
60
72
Time (hr)
Fed
Fasted

FIG. 8A

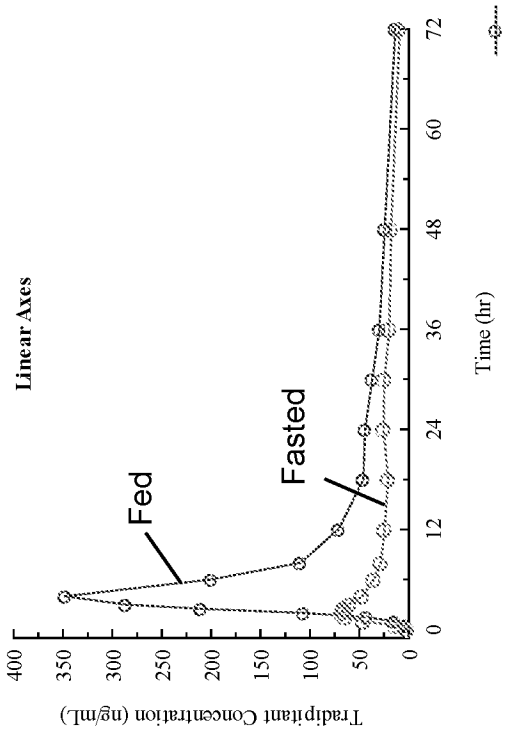
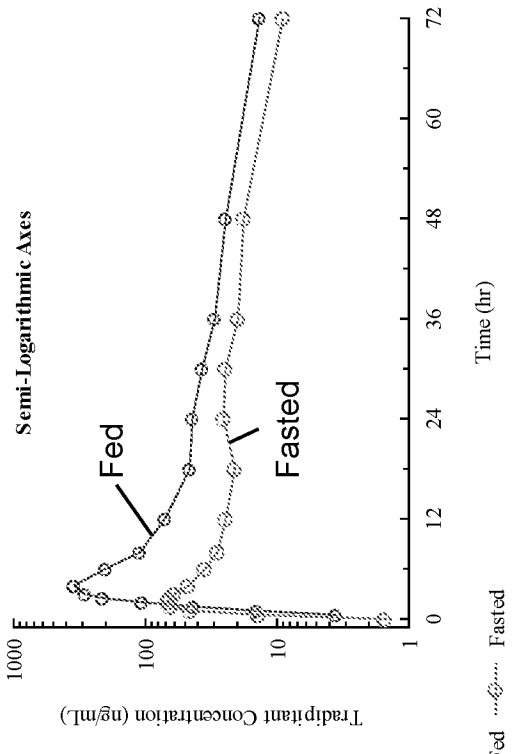

Linear Axes
Fed
Fasted
Tradipitant Concentration (ng/mL)
Time (hr)
0
50
100
150
200
250
300
350
400
0
12
24
36
48
60
72

FIG. 8B


Semi-Logarithmic Axes
Fed
Fasted
Tradipitant Concentration (ng/mL)
Time (hr)
1
10
100
1000
0
12
24
36
48
60
72

Fed
Fasted

FIG. 9A

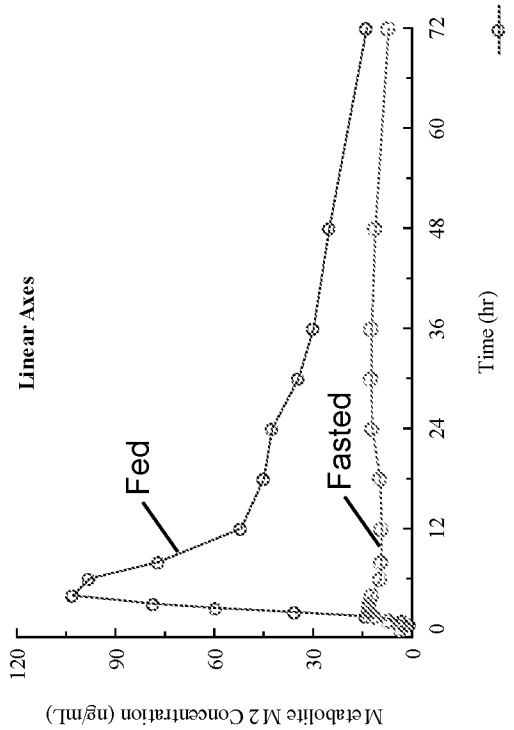

Linear Axes
Fed
Fasted
Metabolite M2 Concentration (ng/mL)
120
90
60
30
0
0
12
24
36
48
60
72
Time (hr)
Fed
Fasted

FIG. 9B

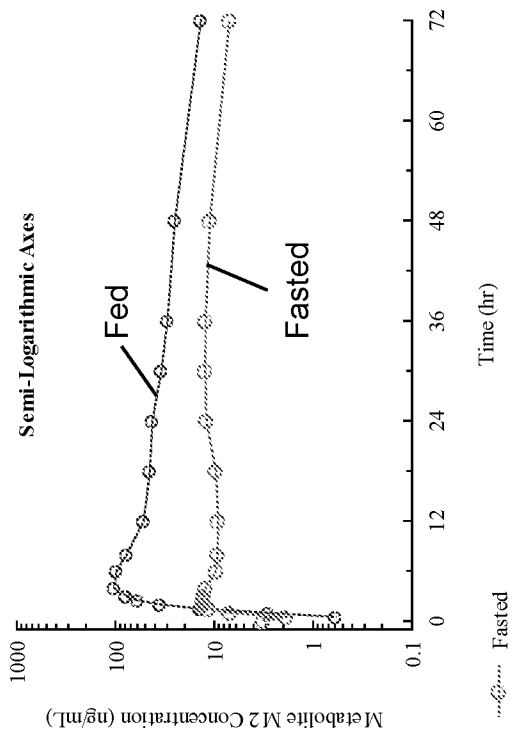

Semi-Logarithmic Axes
Fed
Fasted
Metabolite M2 Concentration (ng/mL)
1000
100
10
1
0.1
0
12
24
36
48
60
72
Time (hr)

FIG. 10A

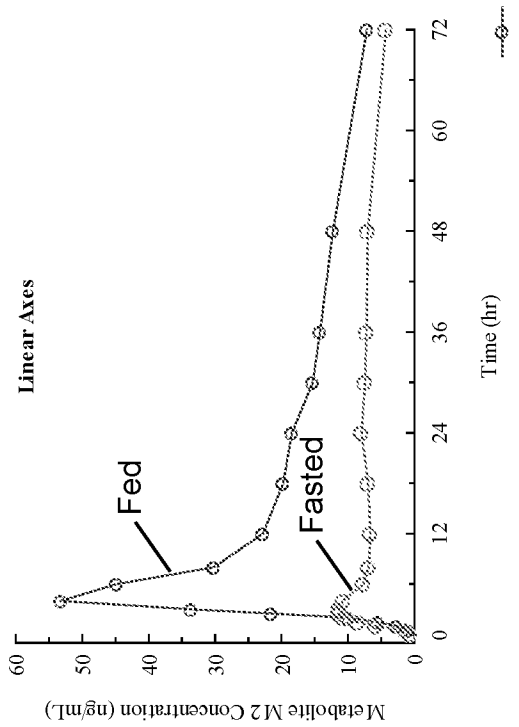


FIG. 10B

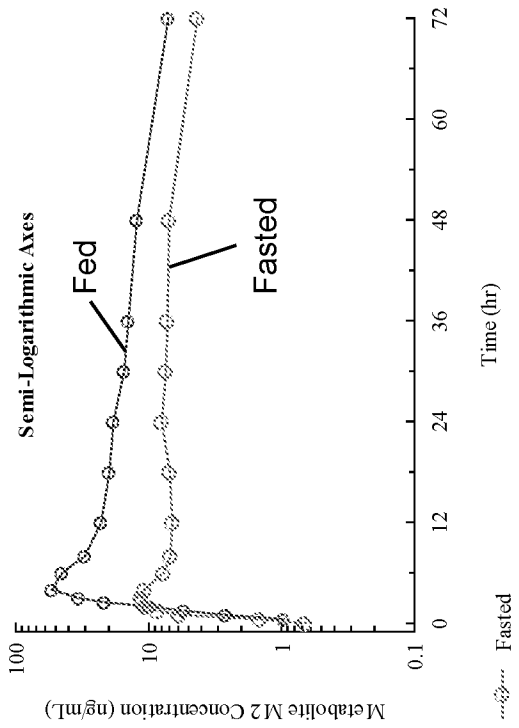


FIG. 11A

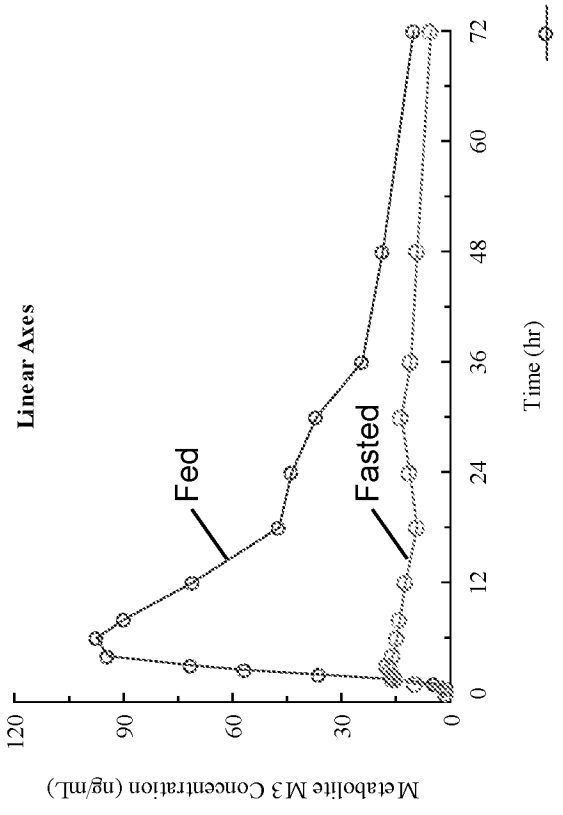


FIG. 11B

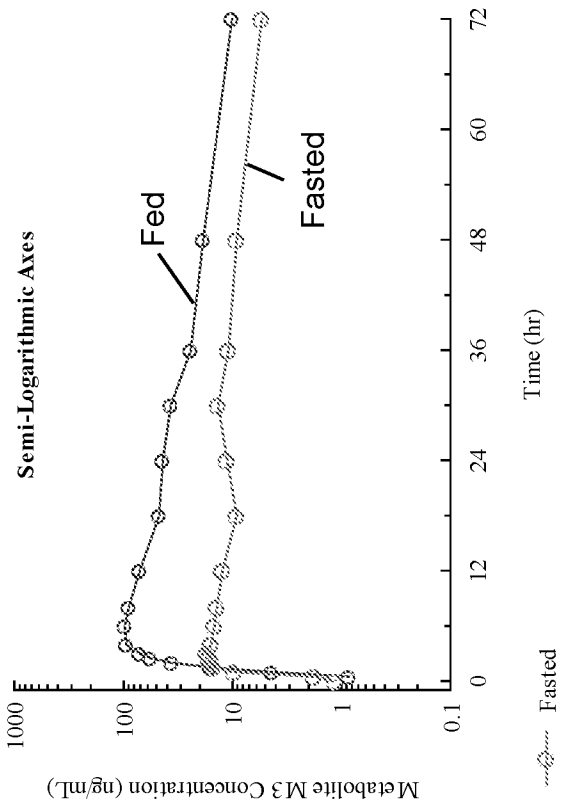


FIG. 12A

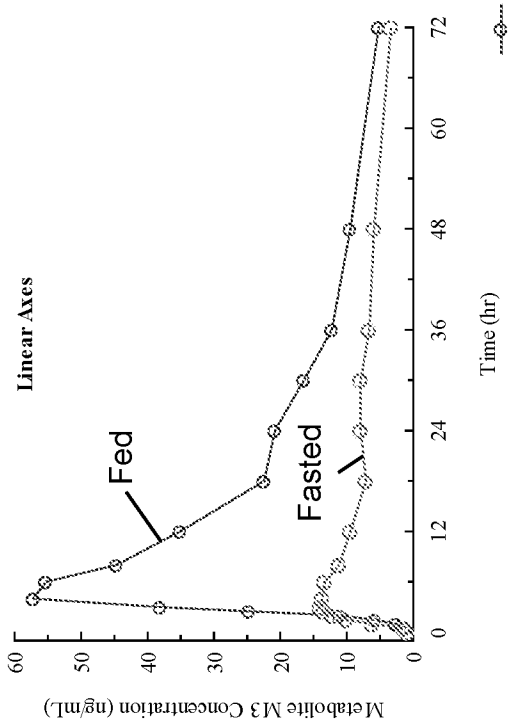


FIG. 12B

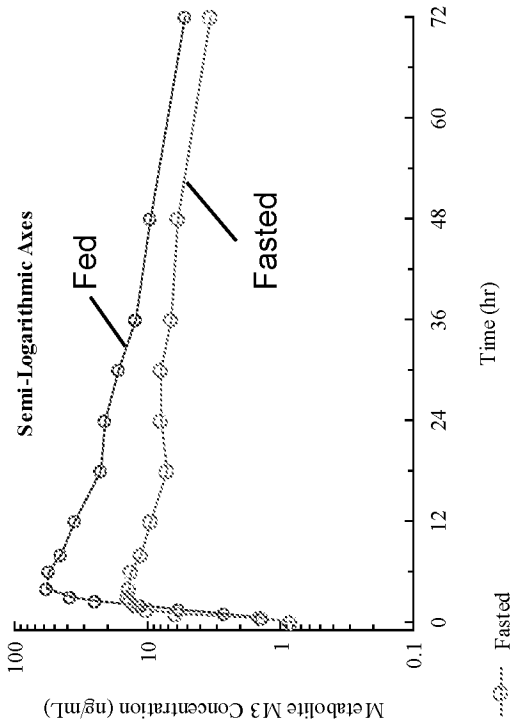


FIG. 13A

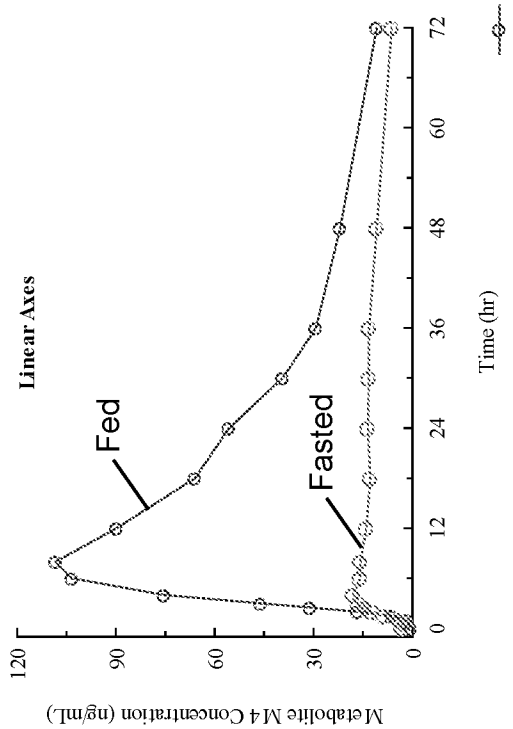


FIG. 13B

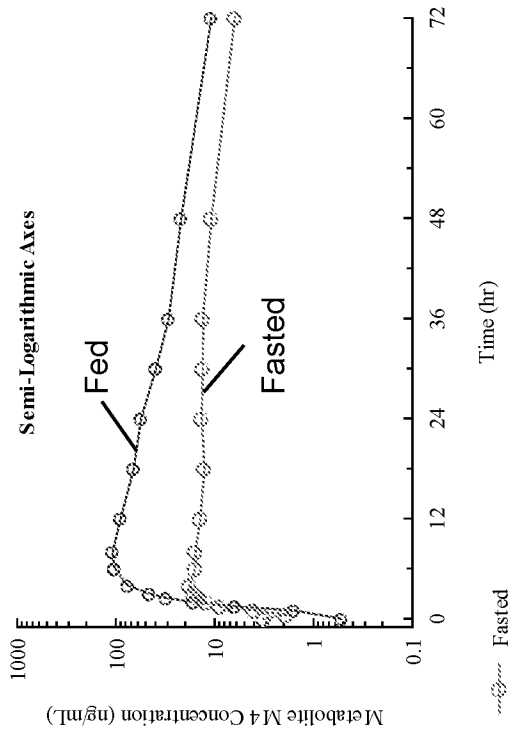


FIG. 14A

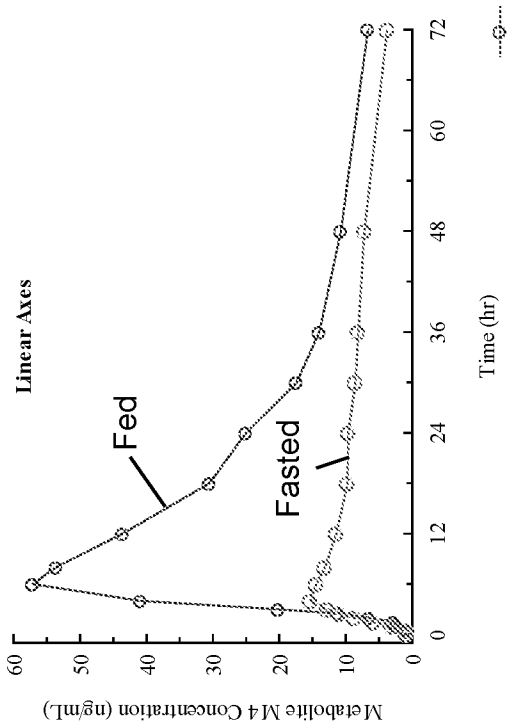


FIG. 14B

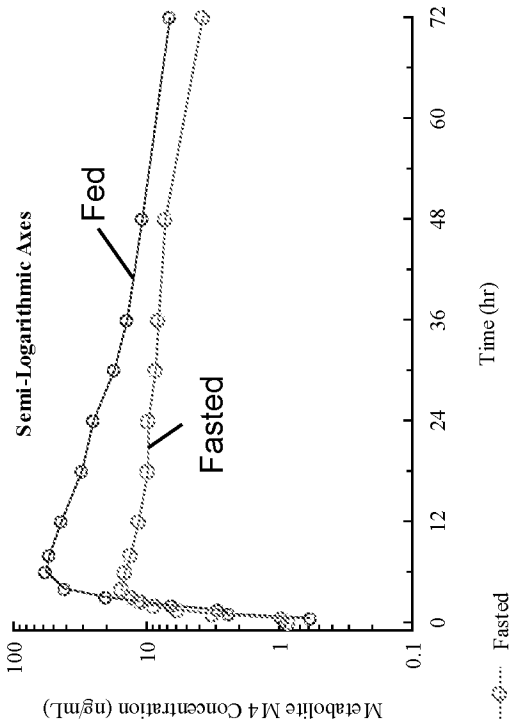


FIG. 15A

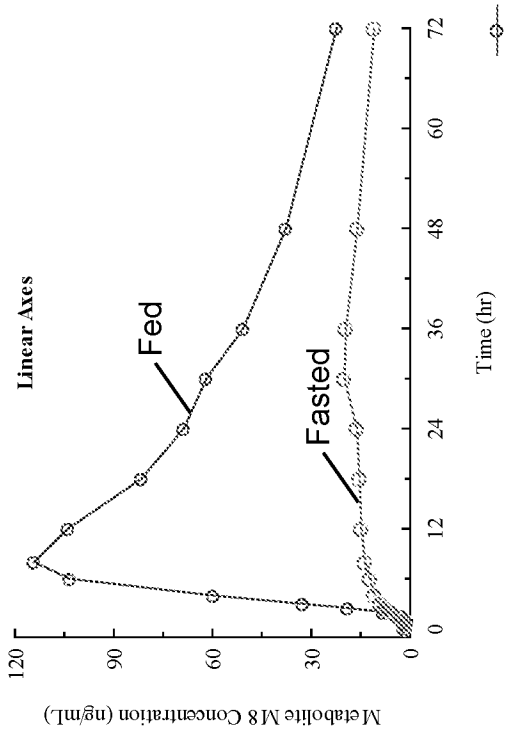


FIG. 15B

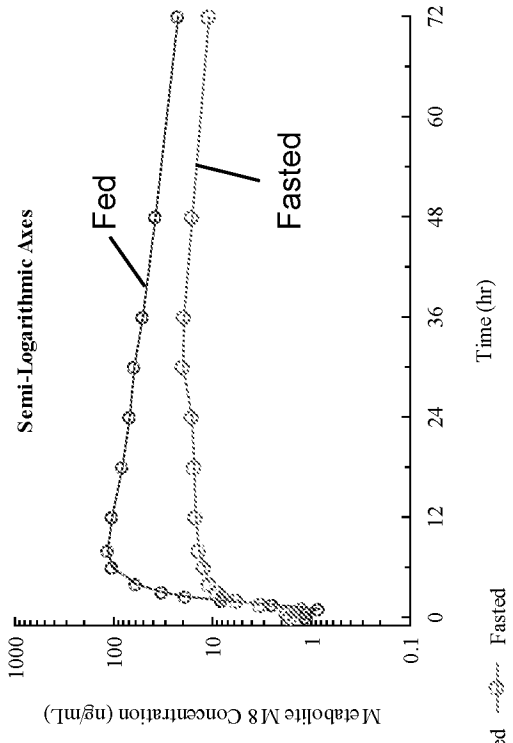


FIG. 16A

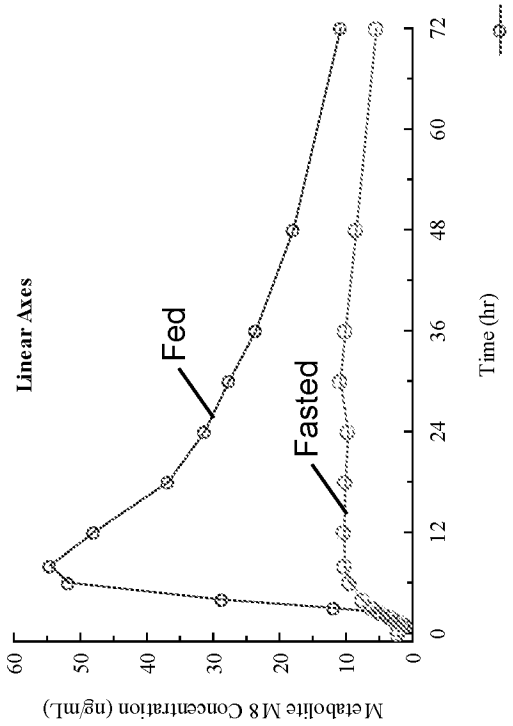
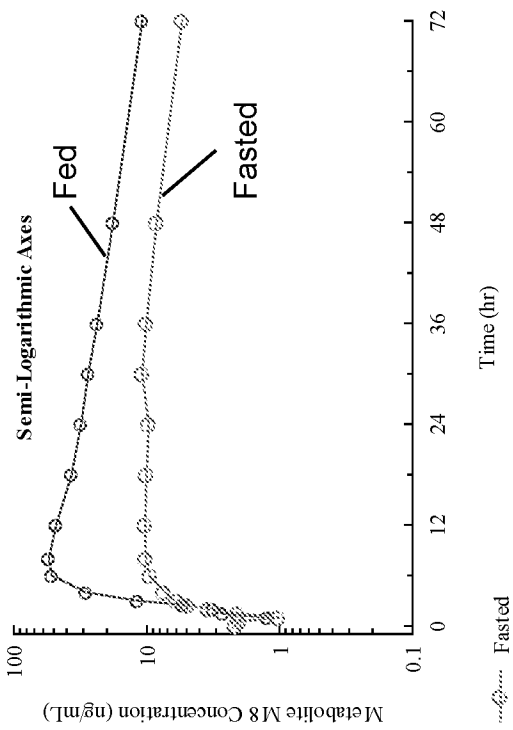


FIG. 16B



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/085520

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/444 A61P1/00 A61P1/08 A61P11/00 A61P17/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2020/030307 A1 (POLYMEROPOULOS MIHAEL H [US] ET AL) 30 January 2020 (2020-01-30)	1-58
Y	claims 1, 2, 6 paragraphs [0061], [0065], [0066], [0085], [0088]	1-14, 33-52

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2024	07/05/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Haider, Ursula

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	KHANNA LEHAR ET AL: "Clinical trial: a single-centre, randomised, controlled trial of tradipitant on satiation, gastric functions, and serum drug levels in healthy volunteers", ALIMENTARY PHARMACOLOGY & THERAPEUTICS, vol. 56, no. 2, 1 July 2022 (2022-07-01), pages 224-230, XP055975971, GB ISSN: 0269-2813, DOI: 10.1111/apt.17065 Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/doi/full-xml/10.1111/apt.17065> abstract items 2.5, 2.6 -----	15-32
X	US 2019/216779 A1 (BASTA STEVEN [US] ET AL) 18 July 2019 (2019-07-18) claim 1 embodiments 1, 3, 4, 11, 20; paragraph [0396] paragraphs [0087], [0094] -----	15-32
Y	ROSA I. SANCHEZ: "CYTOCHROME P450 3A4 IS THE MAJOR ENZYME INVOLVED IN THE METABOLISM OF THE SUBSTANCE P RECEPTOR ANTAGONIST APREPITANT", DRUG METABOLISM AND DISPOSITION, vol. 32, no. 11, 13 November 2004 (2004-11-13), pages 1287-1292, XP093155807, US ISSN: 0090-9556, DOI: 10.1124/dmd.104.000216 Retrieved from the Internet: URL:https://dx.doi.org/10.1124/dmd.104.000216> the whole document -----	1-14, 33-52
A	PIRMOHAMED ET AL: "Drug metabolism", MEDICINE - U K EDITION, THE MEDICINE PUBLISHING COMPANY, GB, vol. 36, no. 7, 1 July 2008 (2008-07-01), pages 355-359, XP022854245, ISSN: 1357-3039, DOI: 10.1016/J.MPMED.2008.04.002 [retrieved on 2008-06-21] the whole document ----- -/--	1-14, 33-52

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	GRANT R WILKINSON: "The effects f diet aging and disease-states on presystemic elimination and oral drug bioavailability in humans", ADVANCED DRUG DELIVERY REVIEWS, ELSEVIER, AMSTERDAM , NL, vol. 27, no. 2-3, 15 September 1997 (1997-09-15), pages 129-159, XP008112131, ISSN: 0169-409X, DOI: 10.1016/S0169-409X(97)00040-9 [retrieved on 1999-03-11] paragraph [02.2] -----	15-58

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/085520

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