

VENGLUSTAT IN COMBINATION WITH A STRONG OR MODERATE INHIBITOR OF CYP3A4

Provided herein are methods in which patients are administered venglustat in combination with inhibitors of cytochrome CYP3A4, such as itraconazole or fluconazole. The methods
5 may involve making specific adjustments to the venglustat dosage in order to optimise the clinical response of the patient.

BACKGROUND

Venglustat (also known as (*S*)-quinuclidin-3-yl 2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-ylcarbamate) is a small molecule drug which has been proposed to be useful in the treatment
10 of conditions including lysosomal storage diseases such as Gaucher disease (See, e.g., WO 2012/129084), proteinopathies such as Alzheimer's disease and Parkinson's disease (See, e.g., WO 2016/145046), cystic diseases such as polycystic kidney disease (See, e.g., WO 2014/043068), and ciliopathies such as Bardet-Biedl Syndrome (See, e.g., WO 2020/163337), the contents of each of which applications are hereby incorporated by reference in their
15 entirety. It has been suggested that venglustat, which is an inhibitor of the enzyme glucosylceramide synthase (GCS), might act in these treatments by: reducing glycolipid levels (e.g., in the case of lysosomal storage diseases); reducing protein aggregation (e.g., in the case of proteinopathies); decreasing apoptosis (e.g., in the case of cystic diseases); or improving the function of ciliary bodies in ciliated epithelial cells (e.g., in the case of
20 ciliopathies).

Small molecule GCS inhibitors, such as venglustat, are primarily intended for oral administration on a regular (e.g., daily) basis. Compounds administered orally may be subject to first-pass metabolic deactivation by the liver, which can reduce their oral bioavailability. Thus, oral dosage forms can sometimes require larger dosages to achieve therapeutic efficacy
25 than would be required if the active agent were administered via another route (e.g., intravenously). Moreover, there can be significant interactions between an orally administered drug and agents which act to modulate the metabolic pathway(s) for that drug (drug-drug interactions; DDIs).

In the case of venglustat, the hepatic enzyme cytochrome P₄₅₀ 3A4 (CYP3A4) has been
30 implicated in the metabolic pathway, although the clinical significance of CYP3A4 involvement has not been established (See, e.g., Peterschmitt *et al.*, Clin. Pharmacol. Drug

Dev. (2021) 10(1):86–98). Nevertheless, some of the clinical studies on venglustat have excluded participants who are undergoing concomitant treatment with moderate or strong inhibitors of CYP3A4 (See, e.g., Peterschmitt *et al.*, J. Parkinsons Dis. (2022) 12:557-570 and its supplementary information).

- 5 Patients in need of treatment for the above conditions may suffer from co-morbid disorders requiring additional pharmacological intervention. In many of these patients, there may be a particular need to co-administer one or more pharmacological agents which are CYP3A4 inhibitors, such that the combination of pharmacological agents might be contraindicated due to DDIs. There is, therefore, a need to develop safe and effective dosage regimens, dosage
10 forms, and treatment methods employing venglustat to account for CYP3A4-related metabolic effects.

SUMMARY

- The present disclosure describes clinical studies which have been carried out to assess the impact of a strong CYP3A4 inhibitor on venglustat exposure *in vivo*. It also describes *in*
15 *silico* investigations which assess the impact of various other CYP3A4 inhibitors on venglustat exposure. These results have enabled the development of venglustat dosage regimens, dosage forms, and treatment methods which are tailored for that drug when it is co-administered with specific CYP3A4 inhibitors.

- Thus, in a first aspect the disclosure provides a method for treating a disease or disorder in a
20 subject in need thereof, the method comprising administering to the subject an effective amount of venglustat or a pharmaceutically acceptable salt thereof, wherein said subject is concurrently being administered a strong or moderate inhibitor of CYP3A4.

- A further aspect provides a method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of venglustat
25 or a pharmaceutically acceptable salt thereof, wherein said subject is concurrently being administered an inhibitor of CYP3A4, whereby the plasma exposure (e.g., AUC) of venglustat is increased by between about 5% and 25% as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor. In embodiments, the venglustat or the pharmaceutically acceptable
30 salt thereof is administered in a dosage of about 12 mg per day or a dosage of about 15 mg per day (calculated as the free base).

In embodiments, the CYP3A4 inhibitor is a strong inhibitor which increases the plasma exposure of venglustat by between about 60% and 120% as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of between about 4 mg and 15 mg per day (calculated as the free base). In embodiments, the venglustat or the pharmaceutically acceptable salt thereof is administered in a dosage of about 8 mg per day (calculated as the free base).

In other embodiments, the CYP3A4 inhibitor is a moderate inhibitor which increases the plasma exposure of venglustat by between about 40% and 60% as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or the pharmaceutically acceptable salt thereof is administered in a dosage of between about 12 mg and 15 mg per day (calculated as the free base). In embodiments, the venglustat or the pharmaceutically acceptable salt thereof is administered in a dosage of about 15 mg per day (calculated as the free base).

In embodiments, the venglustat is in the form of venglustat free base, a pharmaceutically acceptable salt of venglustat, or a prodrug of venglustat, optionally venglustat L-malate salt.

In embodiments, the venglustat or the pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor are administered in combination, e.g., in the same pharmaceutical composition.

In embodiments, the venglustat or the pharmaceutically acceptable salt thereof is administered orally and the CYP3A4 inhibitor is administered transmucosally, intravenously, or orally.

In embodiments, the disease or disorder is selected from a lysosomal storage disease (e.g., Gaucher disease or Fabry disease), a proteinopathy (e.g., Alzheimer's disease, Parkinson's disease, or Huntington's disease), a cystic disease (e.g., polycystic kidney disease), and a ciliopathy (e.g., Bardet-Biedl syndrome).

In embodiments, the subject has a co-morbidity selected from a fungal infection, a viral infection, a bacterial infection, a mood disorder, and a cancer.

The disclosure also provides venglustat or a pharmaceutically acceptable salt thereof (or a combination of venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor, e.g., a composition comprising venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor) for use in a method as defined hereinbefore.

- 5 The disclosure also provides the use of venglustat or a pharmaceutically acceptable salt thereof (or a combination of venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor, e.g., a composition comprising venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor) in the manufacture of a medicament for use in a method as defined hereinbefore.
- 10 The disclosure also provides a method for optimizing (e.g., reducing) the dosage of venglustat in a subject being treated with or intended to be treated with venglustat or a pharmaceutically acceptable salt thereof, the method comprising administering to the subject a strong or moderate CYP3A4 inhibitor.

- The disclosure also provides a method for minimising the drug-drug interaction between
- 15 venglustat and a moderate or strong CYP3A4 inhibitor in a subject suffering from a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with said CYP3A4 inhibitor, as compared to the exposure resulting from
- 20 administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) adjusting the dosage of the venglustat or the pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25%.

- The disclosure also provides a method for establishing the correct dosage of venglustat or a
- 25 pharmaceutically acceptable salt thereof in a subject in need thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor;
- 30 and (ii) reducing the dosage of the venglustat or the pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25%.

The disclosure also provides a method for improving a dosage regimen of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof, the method comprising:

- (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) reducing the dosage of the venglustat or the pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25%.

- The disclosure also provides a method for managing the risk of venglustat/CYP3A4 inhibitor interaction in a subject having a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, the method comprising: (i) initiating treatment in the subject with venglustat or a pharmaceutically acceptable salt thereof at a standard indicated dose; (ii) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (iii) reducing the dosage if the change in plasma exposure is an increase of more than about 25%.

- The disclosure also provides the use of a strong or moderate CYP3A4 inhibitor in a method for: (a) establishing the correct dosage of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof; (b) improving a dosage regimen of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof; or (c) managing the risk of venglustat/CYP3A4 inhibitor interaction in a subject having a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, wherein the subject is being administered or is intended to be administered said CYP3A4 inhibitor.

The disclosure also provides a method for inhibiting CYP3A4 activity in a subject being treated with venglustat or a pharmaceutically acceptable salt thereof, the method comprising concurrently administering the venglustat or the pharmaceutically acceptable salt thereof with a strong or moderate CYP3A4 inhibitor.

- The disclosure also provides a method for improving the therapeutic response to venglustat treatment in a subject in need thereof, the method comprising concurrently administering

venglustat or a pharmaceutically acceptable salt thereof with a strong or moderate CYP3A4 inhibitor.

The disclosure also provides a pharmaceutical composition (e.g., an oral pharmaceutical dosage form) comprising venglustat or a pharmaceutically acceptable salt thereof, in
5 combination with a strong or moderate CYP3A4 inhibitor, and at least one pharmaceutically acceptable excipient.

In embodiments, the composition is formulated for oral administration. In embodiments, the composition is a dosage form selected from a capsule (e.g., a hard capsule) and a tablet (e.g., a chewable tablet, an orally disintegrating tablet, a dispersible tablet, or a classic tablet or
10 caplet).

The disclosure also provides a composition as defined hereinbefore, for use in a method as defined hereinbefore.

Additional features and advantages of the compositions and methods disclosed herein will be apparent from the following detailed description.

15 BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the study design of the clinical study described in Example 4.

Fig. 2 shows the mean (+SD) plasma concentrations of venglustat following single-dose administration of 15 mg venglustat alone (calculated as free base – open triangles); and following co-administration of 15 mg venglustat with repeated-dose itraconazole (100 mg
20 BID – open circles).

Fig. 3 shows observed (clinical study) and mean (with 5th and 95th percentile) predicted venglustat plasma concentrations in healthy male subjects following single oral dose of 11.2 mg (Fig. 3A), 18.6 mg (Fig. 3B), and 112 mg (Fig. 3C) venglustat (Cartesian scale). The grey lines represent the predictions from individual trials. The dashed lines represent the 5th and
25 95th percentile of the total virtual population. The black solid lines represent the simulated mean plasma concentration-time profiles. The open circles represent the individual observed concentrations from the clinical study.

Fig. 4 shows observed (clinical study) and mean (with 5th and 95th percentile) predicted venglustat plasma concentrations in healthy male subjects following single oral dose of 11.2 mg (Fig. 4A), 18.6 mg (Fig. 4B), and 112 mg (Fig. 4C) venglustat (semi-log scale). The grey lines represent the predictions from individual trials. The dashed lines represent the 5th and 95th percentile of the total virtual population. The black solid lines represent the simulated mean plasma concentration-time profiles. The open circles represent the individual observed concentrations from the clinical study.

Fig. 5 shows observed (clinical study) and mean (with 5th and 95th percentile) predicted venglustat plasma concentrations in healthy male subjects following repeated QD oral dose of 3.72 mg (Fig. 5A), 7.44 mg (Fig. 5B), and 14.9 mg (Fig. 5C) venglustat (Cartesian scale). The grey lines represent the predictions from individual trials. The dashed lines represent the 5th and 95th percentile of the total virtual population. The black solid lines represent the simulated mean plasma concentration-time profiles. The open circles represent the individual observed concentrations from the clinical study.

Fig. 6 shows observed (clinical study) and mean (with 5th and 95th percentile) predicted venglustat plasma concentrations in healthy male subjects following repeated QD oral dose of 3.72 mg (Fig. 6A), 7.44 mg (Fig. 6B), and 14.9 mg (Fig. 6C) venglustat (semi-log scale). The grey lines represent the predictions from individual trials. The dashed lines represent the 5th and 95th percentile of the total virtual population. The black solid lines represent the simulated mean plasma concentration-time profiles. The open circles represent the individual observed concentrations from the clinical study.

Fig. 7 shows simulated mean (with 5th and 95th percentile) venglustat plasma concentrations in healthy male subjects following single oral dose of 15 mg of venglustat without (Fig. 7A) and with (Fig. 7B) co-medication of itraconazole 100 mg BID (Cartesian scale). The simulated profiles are overlaid with individual observed venglustat concentrations (open circles). In each case, the black solid line represents simulated mean plasma concentration-time profiles of venglustat without itraconazole interaction, and the grey solid lines represent the 5th and 95th percentile of the total virtual population. The black dashed line represents the simulated mean plasma concentration-time profiles of venglustat with itraconazole interaction, and the grey dashed lines represent the 5th and 95th percentile of the total virtual population. The open circles represent the individual observed concentrations in the study of Example 4.

Fig. 8 shows simulated mean (with 5th and 95th percentile) venglustat plasma concentrations in healthy male subjects following single oral dose of 15 mg of venglustat without (Fig. 8A) and with (Fig. 8B) co-medication of itraconazole 100 mg BID (semi-log scale). The simulated profiles are overlayed with individual observed venglustat concentrations (open circles). In each case, the black solid line represents simulated mean plasma concentration-time profiles of venglustat without itraconazole interaction, and the grey solid lines represent the 5th and 95th percentile of the total virtual population. The black dashed lines represent the simulated mean plasma concentration-time profiles of venglustat with itraconazole interaction, and the grey dashed lines represent the 5th and 95th percentile of the total virtual population. The open circles represent the individual observed concentrations in the study of Example 4.

Fig. 9 shows observed (Example 4) and mean (with 5th and 95th percentile) predicted plasma concentrations of itraconazole (Fig. 9A) and its primary metabolite hydroxyitraconazole (Fig. 9B) in healthy male subjects following itraconazole 100 mg BID (Cartesian scale). The grey solid lines represent the predictions from individual trials. The dashed lines represent the 5th and 95th percentile of the total virtual population. The black solid lines represent the simulated mean plasma concentration-time profiles. The grey dots (at approximately 125, 160, and 220 hours) represent individual observed concentrations in the study of Example 4.

Fig. 10 shows observed (Example 4) and mean (with 5th and 95th percentile) predicted plasma concentrations of itraconazole (Fig. 10A) and its primary metabolite hydroxyitraconazole (Fig. 10B) in healthy male subjects following itraconazole 100 mg BID (semi-log scale). The grey solid lines represent the predictions from individual trials. The dashed lines represent the 5th and 95th percentile of the total virtual population. The black solid lines represent the simulated mean plasma concentration-time profiles. The grey dots (at approximately 125, 160, and 220 hours) represent individual observed concentrations in the study of Example 4.

DETAILED DESCRIPTION

Although specific embodiments of the present disclosure will now be described with reference to the preparations and schemes, it should be understood that such embodiments are by way of example only and merely illustrative of but a small number of the many possible specific embodiments which can represent applications of the principles of the present disclosure. Various changes and modifications will be obvious to those of skill in the art

given the benefit of the present disclosure and are deemed to be within the spirit and scope of the present disclosure as further defined in the appended claims.

Definitions

- Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, exemplary methods, devices, and materials are now described. All technical and patent publications cited herein are incorporated herein by reference in their entirety.
- 10 The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of tissue culture, immunology, molecular biology, microbiology, cell biology, and recombinant DNA, which are within the skill of the art. See, e.g., Michael R. Green and Joseph Sambrook, *Molecular Cloning* (4th ed., Cold Spring Harbor Laboratory Press 2012); the series Ausubel *et al.* eds. (2007) *Current Protocols in Molecular Biology*; the series
- 15 *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson *et al.* (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson *et al.* (1995) *PCR 2: A Practical approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Patent No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation*; *Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker
- 20 eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); Herzenberg *et al.* eds (1996) *Weir's Handbook of Experimental Immunology*; *Manipulating the Mouse Embryo: A Laboratory Manual*, 3rd edition (Cold Spring Harbor Laboratory Press (2002)); Sohail (ed.) (2004) *Gene Silencing by RNA Interference: Technology and Application* (CRC Press).
- 25
- 30 All numerical designations, e.g., pH, temperature, time, concentration, molecular weight, etc., including ranges, are approximations which are varied (+) or (-) by increments of, e.g., 0.1

or 1.0, where appropriate. It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term “about”, which is used to denote a conventional level of variability. For example, a numerical designation which is “about” a given value may vary by $\pm 10\%$ of said value; alternatively, the variation may be $\pm 5\%$, $\pm 2\%$,
5 or $\pm 1\%$ of the value. It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

As used in the specification and claims, the singular form “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. For example, the term “an inhibitor”
10 includes a plurality of inhibitors, including mixtures thereof. Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive. The term “including” is used herein to mean, and is used interchangeably with, the phrase “including but not limited to”.

As used herein, the term “comprising” or “comprises” is intended to mean that the
15 compositions and methods include the recited elements, but do not exclude others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude trace contaminants from the isolation and purification method and pharmaceutically acceptable
20 carriers, such as phosphate buffered saline, preservatives, and the like. “Consisting of” shall mean excluding more than trace elements of other ingredients and substantial method steps for administering the compositions of this disclosure or process steps to produce a composition or achieve an intended result. Embodiments defined by each of these transition terms are within the scope of this disclosure. Use of the term “comprising” herein is intended
25 to encompass both “consisting essentially of” and “consisting of”.

A “subject”, “individual”, or “patient” is used interchangeably herein, and refers to a human.

The term “healthy individual” as used herein typically denotes an individual who does not suffer from a condition which is amenable to treatment with venglustat. For example, a healthy individual may be an individual who does not suffer from a lysosomal storage disease
30 such as Gaucher disease, a proteinopathy such as Alzheimer’s disease or Parkinson’s disease, a cystic disease such as polycystic kidney disease, or a ciliopathy such as Bardet-Biedl

Syndrome. A healthy individual typically does not have any *GBA* mutations. Indeed, a healthy individual may lack mutations in any gene which encodes an enzyme involved in the glycosphingolipid pathway, for example mutations in the genes encoding ceramide synthase, glucosylceramide synthase, galactosylceramide synthase, lactosylceramide synthase, sphingomyelin synthase, ceramidase, glucocerebrosidase, saposin, galactosylceramide β -galactosidase, acid sphingomyelinase, arylsulphatase A, α -galactosidase A, β -hexosaminidase (e.g., Hex A or Hex B), sialidase, GM1- β -galactosidase, GM2 ganglioside activator protein, glucosyl transferase, and galactosyl transferase.

“Administering” is defined herein as a means of providing an agent (e.g., active ingredient) or a composition containing the agent to a subject in a manner that results in the agent being inside the subject’s body. Such an administration can be by any route including, without limitation, oral, dermal, transdermal, transmucosal (e.g., vaginal, rectal, buccal, or sublingual), by injection (e.g., subcutaneous, intravenous, intraperitoneal, intrathecal, intramuscular, intradermal), and by inhalation (e.g., pulmonary, intranasal). Pharmaceutical preparations are, of course, given by forms suitable for each administration route. Administration may also be local or systemic in nature. For example, while oral and injectable routes of administration generally provide systemic exposure, some routes of administration only provide local exposure, such as topical dermal administration and intradermal injection. Intranasal inhalation can provide either local or systemic exposure. The compositions and methods of the present disclosure are typically directed towards enteral, e.g. oral, administration.

As used herein, “concurrent” and “concurrently” when referring to a therapeutic use means administration of two or more active ingredients to a patient as part of a regimen for the treatment of a disease or disorder, whether the two or more active agents are given at the same or different times or whether given by the same or different routes of administrations. The terms “concomitant” and “in conjunction with” as used herein are intended to have an equivalent meaning. Concurrent administration of the two or more active ingredients may be at different times on the same day, or on different dates or at different frequencies. Concurrent administration of the two or more active agents may be intended to treat a single disease or disorder in the patient, but it is typically used herein to refer to the administration of two or more active agents which are effective in treating two or more different diseases or

disorders, e.g., wherein each active agent is effective in treating a separate disease or disorder independently of the other active agent(s).

As used herein, the term “simultaneously” when referring to a therapeutic use means administration of two or more active ingredients at or about the same time, typically by the same route of administration. This may refer to administering the two or more active ingredients in a single dosage form or in multiple separate dosage forms which are administered at or about the same time. For example, this may refer to administering to a patient a single oral tablet or capsule comprising two or more active ingredients, or administering two or more oral tablets or capsules comprising between them two or more active ingredients. The two or more active agents will typically be intended to treat two or more different diseases or disorders, e.g., each active agent is effective in treating a separate disease or disorder independently of the other active agent(s).

As used herein, the term “separately” when referring to a therapeutic use means administration of two or more active ingredients at or about the same time by different routes of administration, or administration of two or more active ingredients at different times by the same or different routes of administration. For example, the term “separately” includes administering one active ingredient by injection or inhalation while administering a separate active ingredient orally, when both administrations are taking place at about the same time. In addition, the term “separately” includes administering one active ingredient orally at a particular time of day, e.g. in the morning, while administering a separate active ingredient orally at a different time of day, e.g. one hour later, or three hours later, or in the afternoon or in the evening, or on a different day. Thus, separate administration would also encompass a dosing regimen under which, for example, one drug is taken on days 1, 3, 5, etc., and another drug is taken on days 2, 4, 6, etc. Again, the two or more active ingredients or drugs will typically be intended to treat two or more different diseases or disorders, e.g., each active agent is effective in treating a separate disease or disorder independently of the other active agent(s).

The phrase “at or about the same time” is understood to generally mean two events taking place with less than 30 minutes between them, e.g. less than 20 minutes, or less than 15 minutes, or less than 10 minutes, or less than 5 minutes. Where an event itself takes place over a period of time, e.g., an intravenous administration of a drug over a period of 60 minutes, “at or about the same time” would include any overlap between such periods of time

or the beginning of one such period of time within about 30 minutes of the ending of the previous period of time.

“Treating” or “treatment” of a disease includes: (1) inhibiting the disease, i.e. arresting or reducing the development of the disease or its clinical symptoms; and/or (2) relieving the disease, i.e. causing regression of the disease or its clinical symptoms. “Preventing” or “prevention” of a disease includes causing the clinical symptoms of the disease not to develop in a patient that may be predisposed to the disease but does not yet experience or display symptoms of the disease. A disease which is “amenable to treatment” with or “treatable by” a particular active agent is a disease which can be treated and/or prevented by the active agent in at least some patients who are suffering from the disease or who are predisposed to the disease.

The term “suffering” as it relates to the term “treatment” refers to a patient or individual who has been diagnosed with the disease. The term “suffering” as it relates to the term “prevention” refers to a patient or individual who is predisposed to the disease. A patient may also be referred to being “at risk of suffering” from a disease because of a history of disease in their family lineage or because of the presence of genetic mutations associated with the disease. A patient at risk of a disease has not yet developed all or some of the characteristic pathologies of the disease.

An “effective amount” or “therapeutically effective amount” is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications, or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent, and the route of administration. It is understood, however, that specific dose levels of the therapeutic agents of the present disclosure for any particular subject depend upon a variety of factors including, for example, the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the severity of the particular disorder being treated, and the form of administration. Typically, dosage-effect relationships from *in vitro* and/or *in vivo* tests initially can provide useful guidance on suitable doses for patient administration. In general, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective *in vitro*.

Determination of these parameters is well within the skill of the art. These considerations, as

well as effective formulations and administration procedures are well known in the art and are described in standard textbooks. Consistent with this definition, as used herein, the term “therapeutically effective amount” is an amount sufficient to treat (e.g., improve) one or more symptoms associated with a disease or disorder described herein, *ex vivo*, *in vitro*, or *in vivo*.

5 A “standard indicated dose” refers to the recommended amount of a therapeutic agent for a subject in the absence of variables which may require dose adjustment, e.g., concurrent administration with one or more additional agents as defined herein. Where such variables are present, an “adjusted dose” or “adjusted effective amount” may administered – this may be the same amount or a different amount of the therapeutic agent as compared with a “standard
10 indicated dose” or an “effective amount” for a different (e.g., an average) subject.

As used herein, “CYP” is an abbreviation for Cytochrome P450 (or Cytochrome Oxidase P450), a family of mammalian enzymes expressed predominantly in the liver which are largely responsible for the oxidative metabolism of many drugs. There are at least 57 common types of CYP enzymes, and these are group into families. The CYP 3A family
15 includes, among other enzymes, the related CYP3A4 and CYP3A5 enzymes, which collectively account for a large portion of mammalian drug metabolism. CYP3A4 is the predominant cytochrome involved in the metabolism of venglustat and it is responsible for about 80% of venglustat metabolism in human liver microsomes.

As used herein, the term “inhibitor” has its commonly recognized pharmacological meaning.
20 An inhibitor is thus a compound (typically a small molecule) which inhibits, either competitively or non-competitively (e.g., allosterically) the functioning of an enzyme, receptor, or other macromolecular target (e.g., protein). Inhibitors generally operate either by binding to the active site of an enzyme or receptor, blocking access by the normal substrate, or by binding to an allosteric site which results in a conformational change in the enzyme or
25 receptor which reduces the enzyme or receptor’s activity. Competitive inhibitors bind to the active site, and may cause either reversible or irreversible inhibition, the latter often by covalent attachment to the active site. Inhibition of an enzyme in the presence of a compound may also occur indirectly, e.g., if one or more metabolites of the compound are themselves inhibitors (e.g., reversible or irreversible, and/or competitive or non-competitive inhibitors) of
30 the enzyme.

As used herein, the term “CYP3A4 inhibitor” therefore refers to a small molecule compound which inhibits the enzymatic activity of the CYP3A4 enzyme, either competitively or non-

- competitively, and either reversibly or irreversibly. CYP3A4 inhibitors can be described as strong, moderate, or weak (See, e.g.: “Common Medications Classified as Weak, Moderate and Strong Inhibitors of CYP3A4”, EBM Consult (October 2015), which can be accessed at <https://www.ebmconsult.com/articles/medications-inhibitors-cyp3a4-enzyme>; and Flockhart
- 5 “Drug Interactions: Cytochrome P450 Drug Interaction Table”, Indiana University School of Medicine (2007), which can be accessed at <https://drug-interactions.medicine.iu.edu>).
- Examples of strong CYP3A4 inhibitors include clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, troleandomycin, voriconazole, ceritinib, and idelalisib. Examples of
- 10 moderate CYP3A4 inhibitors include fluconazole, amiodarone, erythromycin, miconazole, diltiazem, verapamil, delavirdine, amprenavir, fosamprenavir, conivaptan, chamomile, licorice, wild cherry, *echinacea angustifolia*, fluvoxamine, aprepitant, ciprofloxacin, crizotinib, cyclosporine, dronedarone, imatinib, isavuconazole, and tofisopam. Examples of weak CYP3A4 inhibitors include cimetidine, chlorzoxazone, cilostazol, clotrimazole,
- 15 fosaprepitant, istradefylline, ivacaftor, lomitapide, ranitidine, ranolazine, and ticagrelor.

- As used herein, the term “pharmaceutically acceptable excipient” encompasses any of the standard pharmaceutical excipients, including carriers such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. Pharmaceutical compositions also can include stabilizers and preservatives.
- 20 For examples of carriers, stabilizers, and adjuvants, see Remington’s Pharmaceutical Sciences (20th ed., Mack Publishing Co. 2000).

- As used herein, the term “pharmaceutically acceptable salt” means a pharmaceutically acceptable acid addition salt or a pharmaceutically acceptable base addition salt of a currently disclosed compound that may be administered without any resultant substantial undesirable
- 25 biological effect(s) or any resultant deleterious interaction(s) with any other component of a pharmaceutical composition in which it may be contained.

- Addition salts can be readily prepared using conventional techniques, e.g., by treating a base compound with a defined amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as, for example, methanol or ethanol.
- 30 Compounds that are positively charged, e.g., containing a quaternary ammonium, may also form salts with the anionic component of various inorganic and/or organic acids. Acids which can be used to prepare pharmaceutically acceptable acid addition salts are those which can

form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, malate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Bases which can be used to prepare the pharmaceutically acceptable base addition salts are those which can form non-toxic base addition salts, e.g., salts containing pharmacologically acceptable cations, such as, alkali metal cations (e.g., potassium and sodium), alkaline earth metal cations (e.g., calcium and magnesium), ammonium or other water-soluble amine addition salts such as *N*-methylglucamine (meglumine), lower alkanolammonium, and other such bases of organic amines. Addition salts of venglustat are typically acid addition salts. In embodiments, the pharmaceutically acceptable salt of venglustat is venglustat malate, in particular venglustat L-malate.

A mass quantity of venglustat referred to herein corresponds, unless explicitly stated otherwise, to a mass of venglustat calculated as free base. For example, a “15 mg dose of venglustat” refers to an amount of 15 mg of venglustat free base, or to an amount of a salt or prodrug of venglustat which provides an equivalent molar quantity (e.g., 20 mg of venglustat malate salt). Accordingly, references to “venglustat” throughout this specification include the pharmaceutically acceptable salts and prodrugs of venglustat, e.g. as described herein.

The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

The following abbreviations are used herein:

25	A β	amyloid-beta
	ADAM	advanced dissolution, absorption, and metabolism
	ADME	absorption, distribution, metabolism, and excretion
	ADPKD	autosomal dominant polycystic kidney disease
	AGP	α 1-acid glycoprotein
30	ARPKD	autosomal recessive polycystic kidney disease
	AUC	area under the plasma concentration to time curve

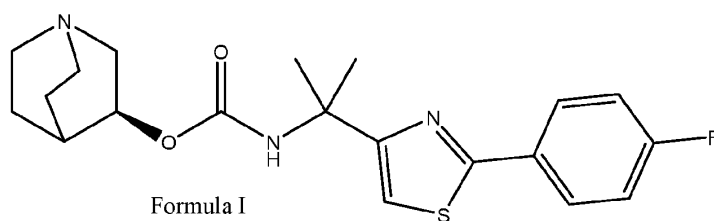
	AUC ₀₋₁₂	12-hour AUC (AUC ₀₋₂₄ = 24-hour AUC)
	AUC _{inf}	area under the plasma concentration to time curve (also AUC _∞)
	AUC _{last}	area under the plasma concentration to time curve from zero to t _{last}
	AUC _{tau}	area under the plasma concentration to time curve over the dosing interval
5	BBS	Bardet-Biedl syndrome
	B/P	blood-to-plasma ratio
	BID	twice daily (dosing)
	CDI	carbonyldiimidazole
	C _{max}	maximum observed plasma concentration
10	C _{trough}	plasma concentration just before TP2
	CL/F	apparent total body clearance from plasma
	CL _{int}	intrinsic clearance
	CL _{int-CYP2D6}	intrinsic metabolic clearance assigned to CYP2D6
	CL _{int-CYP3A4}	intrinsic metabolic clearance assigned to CYP3A4
15	CL _r	renal clearance
	CL _{uG,int}	gut intrinsic clearance
	CYP	cytochrome P450 (or cytochrome oxidase P450)
	DDI	drug-drug interaction(s)
	DMF	dimethylformamide
20	DNA	deoxyribonucleic acid
	EDTA	ethylenediaminetetraacetic acid
	f _a	fraction absorbed
	F _g	intestinal availability
	f _m	fractional metabolism
25	f _{u,gut}	fraction unbound in gut
	f _{u,mic}	percent unbound to human liver microsome proteins
	f _{u,p}	unbound fraction in plasma
	fe ₀₋₂₄	24-hour unchanged urinary excretion fraction
	GCS	glucosylceramide synthase
30	GD	Gaucher disease
	GI	gastrointestinal
	GM1	monosialotetrahexosylganglioside
	GM2	monosialotrihexosylganglioside
	Hex	β-hexosaminidase

	HIV	human immunodeficiency virus
	HCV	hepatitis C virus
	HLM	human liver microsomes
	HPC	hydroxypropyl cellulose
5	HPLC	high pressure/performance liquid chromatography
	HSA	human serum albumin
	IPA	isopropyl alcohol
	K _a	first order absorption rate constant
	K _i	inhibition constant
10	LC/MS	liquid chromatography mass spectrometry
	MDCKII	Madin-Darby canine kidney strain II
	MDR1	multidrug resistance mutation 1
	MS	mass spectrometry
	obs	observed
15	OH-itraconazole	hydroxyitraconazole
	P _{app}	apparent permeability coefficient
	P _{eff,man}	estimated <i>in vivo</i> permeability
	PBPK	physiologically-based pharmacokinetic
	Pgp	P-glycoprotein
20	PK	pharmacokinetics
	PKD	polycystic kidney disease
	POPPK	population pharmacokinetics
	pred	predicted
	QD	repeated once daily (dosing)
25	Q.S.	<i>quantum satis</i> – enough to make up the intended amount
	RB	round bottomed
	rHA	recombinant human albumin
	RNA	ribonucleic acid
	SAC	single-adjustment compartment
30	SAE	serious adverse event
	SD	single dose
	t _{1/2}	half-life
	t _{1/2z}	terminal half-life associated with the terminal slope
	t _{last}	time of last dose

	$t_{\max}$	time to peak concentration ($C_{\max}$)
	TBME	tert-butyl methyl ether
	TEAE	treatment-emergent adverse event
	THF	tetrahydrofuran
5	TID	three times daily (dosing)
	TP1	treatment period 1
	TP2	treatment period 2
	Tris	tris(hydroxymethyl)aminomethane
	TWEEN 20	polysorbate 20
10	TWEEN 80	polysorbate 80
	Wt. %	percentage by weight
	UPLCMS	ultra performance liquid chromatography mass spectrometry
	V_{ss}	apparent volume of distribution at steady state

15 Co-administration of venglustat with CYP3A4 inhibitors

Venglustat (free base) has a chemical structure according to Formula (I) below, and it may conveniently be provided in the form of a malate addition salt (e.g., prepared as described in the following Examples).



- 20 Venglustat is an oral GCS inhibitor under development for the treatment of Fabry disease, Gaucher disease, and GM2 gangliosidosis. Venglustat is primarily metabolized by CYP3A4.

Several CYP3A4 inhibitors are assessed in the examples which follow, including the strong CYP3A4 inhibitor, itraconazole, and the moderate CYP3A4 inhibitors, fluconazole, and fluvoxamine. Itraconazole is an antifungal medication which has also been explored as an
25 anticancer agent for patients with basal cell carcinoma, non-small cell lung cancer, and prostate cancer. It has also been studied for use in conjunction with other chemotherapeutic agents for advanced and metastatic basal cell carcinomas that cannot be treated surgically.

Itraconazole can be administered orally, topically, and intravenously. For oral administration, it is typically formulated as a tablet or capsule which may contain about 100 mg of the active per dose. Fluconazole is another antifungal medication. It can be administered orally or intravenously, and typical dosages are between 100 mg and 400 mg per day. Fluvoxamine is
5 a selective serotonin reuptake inhibitor having antidepressant properties. It is used to treat major depressive disorder and obsessive-compulsive disorder (OCD), as well as other anxiety disorders such as panic disorder, social anxiety disorder, and post-traumatic stress disorder. It is typically administered orally in a dosage starting at 50-100 mg daily which can be increased up to around 300 mg daily, if necessary.

- 10 The present disclosure and the Examples which follow describe the development and validation of a physiologically based pharmacokinetic (PBPK) model to assess the effect of CYP3A inhibitors on venglustat pharmacokinetics. The clinical studies and subsequent modelling which are described herein establish, for the first time, the quantitative relationship between CYP3A4 inhibition and changes in venglustat plasma exposure *in vivo*. Thus, based
15 on the studies described herein, the present disclosure provides dosage regimens for treatment with venglustat in patients being co-administered CYP3A4 inhibitors. In particular, the disclosure provides a validated approach to account for co-administration of a moderate or strong CYP3A4 inhibitor alongside venglustat, thereby enabling safe and effective treatments to be provided in these patient populations. The modelling described herein could be
20 extended to determine the impact of CYP3A4 inducers on venglustat pharmacokinetics, enabling similar assessments to be made, e.g., to optimize venglustat dosing in patients being co-administered CYP3A4 inducers.

- Accordingly, in one aspect the disclosure provides a method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective
25 amount of venglustat or a pharmaceutically acceptable salt thereof, wherein said subject is concurrently being administered a strong or moderate inhibitor of CYP3A4. In a related aspect, the disclosure provides venglustat or a pharmaceutically acceptable salt thereof for use in a method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of venglustat or a
30 pharmaceutically acceptable salt thereof, wherein said subject is concurrently being administered a strong or moderate inhibitor of CYP3A4. A further related aspect provides the use of venglustat in the manufacture of a medicament for use in a method for treating a

disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of venglustat and concurrently administering a strong or moderate inhibitor of CYP3A4.

In another aspect, the disclosure provides a method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination of (e.g., a composition comprising) venglustat or a pharmaceutically acceptable salt thereof and a strong or moderate inhibitor of CYP3A4. In a related aspect, the disclosure provides a combination of (e.g., a composition comprising) venglustat or a pharmaceutically acceptable salt thereof and a strong or moderate inhibitor of CYP3A4, for use in a method for treating a disease or disorder in a subject in need thereof. A further related aspect provides the use of venglustat or a pharmaceutically acceptable salt thereof and a strong or moderate inhibitor of CYP3A4 in the manufacture of a medicament for use in a method for treating a disease or disorder in a subject in need thereof.

In embodiments, the strong or moderate inhibitor of CYP3A4 is a competitive inhibitor of CYP3A4. In embodiments, one or more metabolites of the strong or moderate inhibitor of CYP3A4 is capable of inhibiting CYP3A4, e.g., such that the strong or moderate inhibitor can increase venglustat exposure through mechanism-based inhibition. In embodiments, the strong or moderate inhibitor of CYP3A4 is a triazole antifungal agent, e.g., itraconazole or fluconazole.

The disclosure also provides a method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of venglustat or a pharmaceutically acceptable salt thereof, wherein said subject is concurrently being administered an inhibitor of CYP3A4, whereby the plasma exposure (e.g., AUC) of venglustat is increased by at least about 25% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor. In a related aspect, the disclosure provides venglustat or a pharmaceutically acceptable salt thereof for use in a method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of venglustat or a pharmaceutically acceptable salt thereof, wherein the subject is concurrently being administered an inhibitor of CYP3A4, whereby the plasma exposure (e.g., AUC) of venglustat is increased by at least about 25% as compared to the exposure resulting from administration of venglustat or a

pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor. A further related aspect provides the use of venglustat or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in a method for treating a disease or disorder in a subject in need thereof, the method comprising
5 administering to the subject an effective amount of venglustat or a pharmaceutically acceptable salt thereof, wherein the subject is concurrently being administered an inhibitor of CYP3A4, whereby the plasma exposure (e.g., AUC) of venglustat is increased by at least about 25% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the
10 absence of said CYP3A4 inhibitor. Methods for determining the increase in plasma exposure for CYP3A4 inhibitors are described herein, including in detail in the following examples.

In another aspect, the disclosure provides a method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of a combination of (e.g., a composition comprising) venglustat or a
15 pharmaceutically acceptable salt thereof and an inhibitor of CYP3A4, whereby the plasma exposure (e.g., AUC) of venglustat is increased by at least about 25% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor. In a related aspect, the disclosure provides a combination of (e.g., a composition comprising)
20 venglustat or a pharmaceutically acceptable salt thereof and an inhibitor of CYP3A4, for use in a method for treating a disease or disorder in a subject in need thereof, whereby the plasma exposure (e.g., AUC) of venglustat is increased by at least about 25% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor. A
25 further related aspect provides the use of venglustat or a pharmaceutically acceptable salt thereof and an inhibitor of CYP3A4 in the manufacture of a medicament for use in a method for treating a disease or disorder in a subject in need thereof, whereby the plasma exposure (e.g., AUC) of venglustat is increased by at least about 25% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in
30 the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor.

In the foregoing aspects of the disclosure, the disease or disorder is amenable to treatment with venglustat (or a pharmaceutically acceptable salt thereof). Exemplary diseases and disorders which are treatable by venglustat are described herein.

5 In embodiments, the plasma exposure of venglustat is the AUC of venglustat, e.g., AUC_{0-12} , AUC_{0-24} , AUC_{last} , or AUC_{∞} . In embodiments, the plasma exposure of venglustat is the AUC_{last} of venglustat. In embodiments, the plasma exposure of venglustat is measured experimentally. In other embodiments, the plasma exposure of venglustat is estimated by modelling, e.g., by modelling as described herein.

10 In embodiments, the venglustat or the pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor are administered separately, e.g., in separate pharmaceutical compositions, by different modes of administration, and/or at different times (e.g., on different days, or at different times on the same day). In other embodiments, the venglustat or the pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor are administered in combination, e.g., in the same pharmaceutical composition.

15 In embodiments, the CYP3A4 inhibitor is a strong inhibitor. In embodiments, the inhibitor increases the plasma exposure of venglustat by at least about 50% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor. In
20 embodiments, the strong inhibitor increases the plasma exposure of venglustat by at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, 88%, 90%, 92%, 95%, 98%, or 100% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor. In embodiments, the strong inhibitor increases the plasma exposure of venglustat by
25 between about 50% and 400%, e.g., between about 55% and 300%, between about 60% and 200%, or between about 65% and 150%, as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor.

In embodiments, the strong inhibitor increases the plasma exposure of venglustat by between about 50% and 150% as compared to the exposure resulting from administration of
30 venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically

acceptable salt thereof is administered in a dosage which is an amount of from about 25% to 100% of the standard indicated dose for the disease or disorder being treated (e.g., an amount of from about 50% to 100% of the standard indicated dose). In embodiments, the strong inhibitor increases the plasma exposure of venglustat by between about 60% and 90% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage which is 100% of the standard indicated dose for the disease or disorder being treated. In other embodiments, the strong inhibitor increases the plasma exposure of venglustat by between about 90% and 120% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage which is an amount of from about 50% to 75% of the standard indicated dose for the disease or disorder being treated. In other embodiments, the strong inhibitor increases the plasma exposure of venglustat by between about 60% and 150% as compared to the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of between about 4 mg and 15 mg per day (calculated as the free base), e.g., a dosage of between about 8 mg and 12 mg per day (calculated as the free base).

In embodiments, the CYP3A4 inhibitor is a strong inhibitor, and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of about 8 mg per day (calculated as the free base), for example in a dosage of from about 7.0 mg to about 9.0 mg per day, e.g., about 7.5 mg or about 8.0 mg (calculated as the free base). A dosage of about 7.5 mg may be obtained, for example, by dividing a 15 mg tablet in half. A dosage of about 8.0 mg may be obtained, for example, by administering two 4 mg unit dosages (e.g., tablets or capsules). In other embodiments, the CYP3A4 inhibitor is a strong inhibitor, and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of about 15 mg per day (calculated as the free base). In embodiments, the strong inhibitor is itraconazole which is administered in a dosage of between about 50 mg and 400 mg per day, e.g., about 200 mg per day (such as a dosage of about 100 mg BID).

In other embodiments, the CYP3A4 inhibitor is a moderate inhibitor of CYP3A4. In
embodiments, the inhibitor increases the plasma exposure of venglustat by between about 5%
and 25% as compared to the exposure resulting from administration of venglustat or a
pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the
5 absence of said CYP3A4 inhibitor. In other embodiments, the inhibitor increases the plasma
exposure of venglustat by at least about 25% as compared to the exposure resulting from
administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage,
form, and regimen in the absence of said CYP3A4 inhibitor. In embodiments, the moderate
inhibitor increases the plasma exposure of venglustat by between about 25% and 75%, e.g.,
10 between about 30% and 65%, between about 35% and 60%, or between about 40% and 55%,
as compared to the exposure resulting from administration of venglustat or a
pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the
absence of said CYP3A4 inhibitor.

In embodiments, the moderate inhibitor increases the plasma exposure of venglustat by
15 between about 5% and 20% as compared to the exposure resulting from administration of
venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and
regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically
acceptable salt thereof is administered in a dosage which is 100% of the standard indicated
dose for the disease or disorder being treated. In embodiments, the venglustat or
20 pharmaceutically acceptable salt thereof is administered in a dosage of about 15 mg per day
(calculated as free base). In other embodiments, the moderate inhibitor increases the plasma
exposure of venglustat by between about 30% and 65% as compared to the exposure resulting
from administration of venglustat or a pharmaceutically acceptable salt thereof in the same
dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or
25 pharmaceutically acceptable salt thereof is administered in a dosage which is an amount of
from about 75% to 100% of the standard indicated dose for the disease or disorder being
treated. In embodiments, the moderate inhibitor increases the plasma exposure of venglustat
by between about 40% and 60% as compared to the exposure resulting from administration of
venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and
30 regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically
acceptable salt thereof is administered in a dosage which is 100% of the standard indicated
dose for the disease or disorder being treated. In other embodiments, the moderate inhibitor
increases the plasma exposure of venglustat by between about 40% and 60% as compared to

the exposure resulting from administration of venglustat or a pharmaceutically acceptable salt thereof in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of between about 10 mg and 15 mg per day (calculated as the free base), e.g., in a dosage of about 12 mg per day or about 15 mg per day. In embodiments, the CYP3A4 inhibitor is a moderate inhibitor and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of about 12 mg per day (calculated as the free base). In other embodiments, the CYP3A4 inhibitor is a moderate inhibitor and the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of about 15 mg per day (calculated as the free base). A dosage of about 12 mg may be achieved, for example, by administering three 4 mg unit dosages (e.g., tablets or capsules), or by administering two 6 mg unit dosages (e.g., tablets or capsules). A dosage of about 10 mg may be achieved, for example, by administering one 4 mg unit dosage (e.g., tablet or capsule) and one 6 mg unit dosage (e.g., tablet or capsule).

In embodiments, the CYP3A4 inhibitor is fluconazole which is administered in a dosage of between about 100 mg and 500 mg per day, e.g., about 200 mg or about 400 mg per day. In embodiments, the CYP3A4 inhibitor is fluvoxamine which is administered in a dosage of between about 50 mg and 300 mg per day. In other embodiments, the inhibitor of CYP3A4 is not fluvoxamine. In embodiments, the inhibitor of CYP3A4 is not cyclosporine. In embodiments, the inhibitor of CYP3A4 is not fluvoxamine or cyclosporine.

In embodiments, the method of the disclosure comprises administering to the subject an effective amount of venglustat or a pharmaceutically acceptable salt thereof, wherein the subject is concurrently being administered a CYP3A4 inhibitor selected from itraconazole and fluconazole. In other embodiments, the method comprises administering to the subject an effective amount of a combination of (e.g., a composition comprising) venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor selected from itraconazole and fluconazole. In a related aspect, the disclosure provides a combination of (e.g., a composition comprising) venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor selected from itraconazole and fluconazole, for use in a method for treating a disease or disorder amenable to treatment with venglustat in a subject in need thereof. A further related aspect provides the use of venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor selected from itraconazole and fluconazole in

the manufacture of a medicament for use in a method for treating a disease or disorder amenable to treatment with venglustat in a subject in need thereof.

In embodiments, the venglustat is in the form of venglustat free base, a pharmaceutically acceptable salt of venglustat, or a prodrug of venglustat. In one embodiment, the venglustat is
5 in the form of venglustat malate salt, e.g., venglustat L-malate, optionally in crystalline form.

In embodiments, the venglustat or pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor are administered simultaneously, optionally in the same pharmaceutical composition (e.g., oral pharmaceutical dosage form).

In embodiments, the venglustat or pharmaceutically acceptable salt thereof and the CYP3A4
10 inhibitor are administered separately. In embodiments, the method comprises administering a separate pharmaceutical composition comprising the CYP3A4 inhibitor (i.e., separate from the pharmaceutical composition or dosage form comprising the venglustat or pharmaceutically acceptable salt thereof).

In embodiments, the venglustat or pharmaceutically acceptable salt thereof is administered
15 orally. In embodiments, the CYP3A4 inhibitor is administered orally. In embodiments, the venglustat or pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor are administered orally.

In other embodiments, the CYP3A4 inhibitor is administered by transdermal, transmucosal, intravenous, intramuscular, subcutaneous, or intranasal administration. In embodiments, the
20 CYP3A4 inhibitor is administered transmucosally, intravenously, or orally. In embodiments, the CYP3A4 inhibitor is administered by transdermal, transmucosal, intravenous, intramuscular, subcutaneous, or intranasal administration and the venglustat or pharmaceutically acceptable salt thereof is administered orally. In embodiments, the venglustat or pharmaceutically acceptable salt thereof is administered orally and the CYP3A4
25 inhibitor is administered transmucosally, intravenously, or orally.

In embodiments, the venglustat or pharmaceutically acceptable salt thereof (and optionally the CYP3A4 inhibitor) is formulated as an oral pharmaceutical composition. In embodiments, the pharmaceutical composition comprises at least one pharmaceutically acceptable excipient as described herein. In embodiments, the pharmaceutical composition further comprises the
30 CYP3A4 inhibitor.

In embodiments, the oral pharmaceutical composition is a pill, capsule, caplet, tablet, dragee, powder, granule, film, lozenge, or liquid. In embodiments, the oral pharmaceutical composition is a capsule or tablet, e.g., a tablet. In an embodiment, the oral pharmaceutical composition is a formulation as described in international patent application No.

- 5 PCT/IB2021/056673 (published as WO 2022/018695), the entire content of which is incorporated by reference herein.

In embodiments, the formulation is a capsule having the following composition:

Ingredient	Amount (Wt. %)
Venglustat malate	12.2%
Microcrystalline cellulose (diluent)	Q.S. (~82%)
Croscarmellose sodium (disintegrant)	3.0%
Colloidal silica (glidant)	0.2%
Magnesium stearate (lubricant)	2.0%

- 10 In embodiments, the capsule contains 15 mg of venglustat (20.16 mg of venglustat malate), the fill mass of the capsule is 165 mg, and the formulation is packaged into a size #3 capsule shell.

In other embodiments, the formulation is a tablet having the following composition:

Ingredient	Amount (Wt. %)
Venglustat malate	13.4%
Mannitol	Q.S. (~68%)
Crospovidone (Type A)	8.0%
Low-sub HPC	5.0%
Colloidal silica	1.0%
Sodium stearyl fumarate	2.5%
Magnesium stearate	0.5%
Flavor	1.0%
Sweetener	1.0%

- 15 In embodiments, the tablet contains 15 mg of venglustat (20.16 mg of venglustat malate), the flavor is apricot flavor, the sweetener is sucralose, and the weight of the tablet is 150 mg.

In embodiments, the CYP3A4 inhibitor is itraconazole. In other embodiments, the CYP3A4 inhibitor is fluconazole.

In embodiments, the disease or disorder is selected from a lysosomal storage disease, a proteinopathy, a cystic disease, and a ciliopathy.

In embodiments, the disease or disorder is a lysosomal storage disease selected from Fabry disease, Gaucher disease (e.g., GD type 1, type 2, or type 3), a GM1-gangliosidosis, a GM2-gangliosidosis (e.g., GM2-activator deficiency, Tay-Sachs disease, Sandhoff disease, or AB Variant), Niemann-Pick disease (e.g., Type C), and Krabbe disease. In embodiments, the disease or disorder is Gaucher disease or Fabry disease. In an embodiment, the disease or disorder is type 3 Gaucher Disease (GD3).

In embodiments, the disease or disorder is a proteinopathy selected from Alzheimer's disease, Parkinson's disease, Lewy Body Dementia, Pick's disease, progressive supranuclear palsy, dementia pugilistica, parkinsonism linked to chromosome 17, Lytico-Bodig disease, tangle predominant dementia, Argyrophilic grain disease, ganglioglioma, gangliocytoma, meningioangiomatosis, subacute sclerosing panencephalitis, lead encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, corticobasal degeneration, frontotemporal dementia, frontotemporal lobar degeneration, and Huntington's disease. In embodiments, the proteinopathy is selected from Alzheimer's disease, Parkinson's disease, and Huntington's disease. In embodiments, the proteinopathy is characterized by tau protein aggregates, alpha-synuclein protein aggregates, and/or amyloid-beta (A β) aggregates in the central nervous system.

In embodiments, the disease or disorder is a cystic disease selected from polycystic kidney disease, polycystic liver disease, and polycystic ovary disease. In embodiments, the cystic disease is polycystic kidney disease (PKD), e.g., autosomal dominant PKD (ADPKD) or autosomal recessive PKD (ARPKD).

In embodiments, the disease or disorder is a ciliopathy selected from Joubert syndrome, Meckel-Gruber syndrome, Senior-Loken syndrome, Orofaciodigital syndrome type I, Leber's congenital amaurosis, Bardet-Biedl syndrome (BBS), Alström syndrome, Jeune asphyxiating thoracic dystrophy, Ellis van Creveld syndrome, Sensenbrenner syndrome, primary ciliary dyskinesia, and combinations thereof. In embodiments, the ciliopathy is BBS.

In embodiments, the subject has a co-morbidity which can be treated with said CYP3A4 inhibitor. In embodiments, the co-morbidity is selected from a fungal infection, a viral

infection (e.g., infection with HIV or HCV), a bacterial infection, a mood disorder (e.g., depression or an anxiety disorder), and a cancer.

Dose adjustment

As described herein, the concurrent administration of the venglustat or pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor can increase the plasma exposure (e.g., AUC) of venglustat, for instance by about 50% to about 200%. This may permit an adjusted (e.g., lower) dose of venglustat to be used compared to the standard indicated dose for the disease or disorder being treated.

Thus, in a further aspect the disclosure provides a method for treating a disease or disorder amenable to treatment with venglustat in a subject in need thereof, the method comprising administering to the subject a strong or moderate CYP3A4 inhibitor and concurrently administering an adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof. In a related aspect, the present disclosure provides venglustat or a pharmaceutically acceptable salt thereof for use in a method for treating a disease or disorder amenable to treatment with venglustat in a subject in need thereof, the method comprising administering to the subject a strong or moderate CYP3A4 inhibitor and concurrently administering an adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof. In another related aspect, the present disclosure provides the use of venglustat or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in a method of treating a disease or disorder in a subject, wherein the method comprises concurrent administration of a CYP3A4 inhibitor, and wherein the amount of the venglustat or pharmaceutically acceptable salt thereof in the medicament is an adjusted effective amount. In embodiments, the CYP3A4 inhibitor is selected from itraconazole and fluconazole. In embodiments, the CYP3A4 inhibitor is not fluvoxamine.

In another aspect, the disclosure provides a method for treating a disease or disorder amenable to treatment with venglustat in a subject in need thereof, the method comprising administering to the subject a combination of (e.g., a composition comprising) a strong or moderate CYP3A4 inhibitor and venglustat or a pharmaceutically acceptable salt thereof, wherein the venglustat or pharmaceutically acceptable salt thereof is administered in an adjusted effective amount. In a related aspect, the present disclosure provides a combination of (e.g., a composition comprising) venglustat or a pharmaceutically acceptable salt thereof

and a strong or moderate CYP3A4 inhibitor, for use in a method for treating a disease or disorder amenable to treatment with venglustat in a subject in need thereof, the method comprising administering to the subject an adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof. In another related aspect, the present disclosure provides the use of a combination of (e.g., a composition comprising) venglustat or a pharmaceutically acceptable salt thereof and a strong or moderate CYP3A4 inhibitor in the manufacture of a medicament for use in a method of treating a disease or disorder amenable to treatment with venglustat in a subject, wherein the amount of the venglustat or pharmaceutically acceptable salt thereof in the medicament is an adjusted effective amount.

10 In embodiments, the CYP3A4 inhibitor is selected from itraconazole and fluconazole. In embodiments, the CYP3A4 inhibitor is not fluvoxamine.

In embodiments, the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is an amount of from about 25% to 100% of the standard indicated dose for the disease or disorder being treated (e.g., an amount of from about 50% to 100% of the standard indicated dose). In embodiments, the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is at least about 50% of the standard indicated dose for the disease or disorder being treated, e.g., at least about 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% of the standard indicated dose. In embodiments, the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is less than 100% of the standard indicated dose for the disease or disorder being treated, e.g., less than about 99%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, or 55% of the standard indicated dose. In embodiments, the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is an amount of from about 50% to about 99% of the standard indicated dose for the disease or disorder being treated, e.g., from about 55% to about 95%, from about 60% to about 90%, or from about 65% to about 75% of the standard indicated dose. In embodiments, the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is an amount of about 50% of the standard indicated dose for the disease or disorder being treated, e.g., about 55%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% of the standard indicated dose.

In embodiments, the CYP3A4 inhibitor is a strong inhibitor (e.g., itraconazole) and the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is an amount of from about 50% to 100% of the standard indicated dose for the disease or disorder being treated. In embodiments, the adjusted effective amount of venglustat or a

pharmaceutically acceptable salt thereof is 100% of the standard indicated dose for the disease or disorder being treated (e.g., a dose of about 15 mg per day). In other embodiments, the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is an amount of from about 50% to 100% of the standard indicated dose for the disease or disorder being treated, e.g., from about 50% to about 90%, from about 50% to about 80%, from about 50% to about 70%, or from about 50% to about 60% of the standard indicated dose. In 5
embodiments, the standard indicated dose of venglustat or a pharmaceutically acceptable salt thereof is about 15 mg per day (calculated as the free base) and the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is about 8 mg per day (calculated 10
as the free base), e.g. from about 7.0 mg to about 9.0 mg per day, such as about 7.5 mg or about 8.0 mg (calculated as the free base). A dosage of about 7.5 mg may be obtained, for example, by dividing a 15 mg tablet in half. A dosage of about 8.0 mg may be achieved, for example, by administering two 4 mg unit dosages (e.g., tablets or capsules).

In other embodiments, the CYP3A4 inhibitor is a moderate inhibitor (e.g., fluconazole) and 15
the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is an amount of from about 70% to 100% of the standard indicated dose for the disease or disorder being treated. In embodiments, the adjusted effective amount of venglustat or a pharmaceutically acceptable salt thereof is 100% of the standard indicated dose for the disease or disorder being treated. In other embodiments, the adjusted effective amount of 20
venglustat or a pharmaceutically acceptable salt thereof is an amount of from about 75% to 100% of the standard indicated dose for the disease or disorder being treated, e.g., from about 80% to 100%, from about 85% to 100%, from about 90% to 100%, or from about 95% to 100% of the standard indicated dose. In embodiments, the standard indicated dose of venglustat is about 15 mg per day and the adjusted effective amount of venglustat or a 25
pharmaceutically acceptable salt thereof is from about 10 mg to 15 mg per day, e.g., about 12 mg per day or about 15 mg per day (calculated as the free base). A dosage of about 12 mg may be achieved, for example, by administering three 4 mg unit dosages (e.g., tablets or capsules), or by administering two 6 mg unit dosages (e.g., tablets or capsules). A dosage of about 10 mg may be achieved, for example, by administering one 4 mg unit dosage (e.g., 30
tablet or capsule) and one 6 mg unit dosage (e.g., tablet or capsule).

In embodiments, the venglustat or pharmaceutically acceptable salt thereof, and/or the CYP3A4 inhibitor, are as defined herein.

In embodiments, the subject being treated, and/or the disease or disorder to be treated, are as defined herein.

In a further aspect, the present disclosure provides a method for optimizing (e.g., reducing) the dosage of venglustat in a subject being treated with or intended to be treated with venglustat or a pharmaceutically acceptable salt thereof, the method comprising administering to the subject a strong or moderate CYP3A4 inhibitor, e.g., as defined herein. In embodiments, the strong or moderate CYP3A4 inhibitor is administered concurrently with the venglustat or pharmaceutically acceptable salt thereof. In a related aspect, the present disclosure provides a strong or moderate CYP3A4 inhibitor, e.g. as defined herein, for use in a method for optimizing (e.g., reducing) the dosage of venglustat in a subject being treated with or intended to be treated with venglustat or a pharmaceutically acceptable salt thereof. In a further aspect, the present disclosure provides the use of a strong or moderate CYP3A4 inhibitor, e.g. as defined herein, in the manufacture of a medicament for use in a method for optimizing (e.g., reducing) the dosage of venglustat in a subject being treated with or intended to be treated with venglustat or a pharmaceutically acceptable salt thereof. In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor. In embodiments, the CYP3A4 inhibitor is selected from itraconazole and fluconazole.

In another aspect, the disclosure provides a method for minimising the drug-drug interaction between venglustat and a moderate or strong CYP3A4 inhibitor (e.g., as defined herein) in a subject suffering from a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with said CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) adjusting the dosage of the venglustat or pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25% increase.

In embodiments, the determining the change in plasma exposure of venglustat involves measuring the change in plasma exposure after administration of venglustat and/or the CYP3A4 inhibitor, e.g., in one or more healthy subjects. In other embodiments, the determining the change in plasma exposure of venglustat involves predicting the change in plasma exposure, e.g., using a computer implemented model as described herein. In

embodiments, the plasma exposure is determined as the AUC as defined herein. In embodiments, the AUC is AUC_{0-12} , AUC_{0-24} , AUC_{last} , or AUC_{∞} . In embodiments, the plasma exposure of venglustat is the AUC_{last} of venglustat.

- In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor. In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor and/or the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced if the change in plasma exposure is an increase of more than about 50%. In embodiments, the reduced dosage is an adjusted effective amount as defined herein. In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor and the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced by an amount of between about 0% and 75% (e.g., between about 0% and 50%) if the change in plasma exposure is an increase of between about 50% and 200%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced by an amount of between about 5% and 50%, e.g., between about 10% and 50%, between about 25% and 50%, or between about 40% and 50%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced to an amount of between about 4 and 15 mg per day (calculated as free base) if the change in plasma exposure is an increase of between about 50% and 200%, e.g., an amount of between about 7 and 15 mg per day if the change in plasma exposure is an increase of between about 50% and 200%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced to an amount of about 8 mg per day (calculated as the free base), e.g., from about 7.0 to about 9.0 mg per day, such as about 7.5 mg or about 8.0 mg (calculated as the free base). A dosage of about 7.5 mg may be obtained, for example, by dividing a 15 mg tablet in half. A dosage of about 8.0 mg may be achieved, for example, by administering two 4 mg unit dosages (e.g., tablets or capsules).
- In another aspect, the disclosure provides a method for establishing the correct dosage of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) reducing the dosage of the venglustat or the pharmaceutically

acceptable salt thereof if the change in plasma exposure is an increase of more than about 25%.

In a related aspect, the disclosure provides a method for improving a dosage regimen of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) reducing the dosage of the venglustat or the pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25%.

In embodiments, the determining the change in plasma exposure of venglustat involves measuring the change in plasma exposure after administration of venglustat and/or the CYP3A4 inhibitor, e.g., in one or more healthy subjects. In other embodiments, the determining the change in plasma exposure of venglustat involves predicting the change in plasma exposure, e.g., using a computer implemented model as described herein. In embodiments, the plasma exposure is determined as the AUC as defined herein. In embodiments, the AUC is AUC_{0-12} , AUC_{0-24} , AUC_{last} , or AUC_{∞} . In embodiments, the plasma exposure of venglustat is the AUC_{last} of venglustat.

In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor. In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor and/or the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced if the change in plasma exposure is an increase of more than about 50%. In embodiments, the reduced dosage is an adjusted effective amount as defined herein. In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor and the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced by an amount of between about 0% and 50% if the change in plasma exposure is an increase of between about 50% and 200%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced by an amount of between about 5% and 50%, e.g., between about 10% and 50%, between about 25% and 50%, or between about 40% and 50%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced to an amount of between about 4 and 15 mg per day (calculated as free base) if the change in plasma exposure is an increase of

between about 50% and 200%, e.g., an amount of between about 7 and 15 mg per day if the change in plasma exposure is an increase of between about 50% and 200%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced to an amount of about 8 mg per day (calculated as the free base), e.g., from about 7.0 to about 9.0 mg per day, such as about 7.5 mg or about 8.0 mg (calculated as the free base). A dosage of about 7.5 mg may be obtained, for example, by dividing a 15 mg tablet in half. A dosage of about 8.0 mg may be achieved, for example, by administering two 4 mg unit dosages (e.g., tablets or capsules).

Another aspect of the disclosure provides a method for managing the risk of venglustat/CYP3A4 inhibitor interaction in a subject having a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, the method comprising: (i) initiating treatment in the subject with venglustat or a pharmaceutically acceptable salt thereof at a standard indicated dose (e.g., a dose as described herein); (ii) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (iii) reducing the dosage if the change in plasma exposure is an increase of more than about 25%.

In embodiments, the determining the change in plasma exposure of venglustat involves measuring the change in plasma exposure after administration of venglustat and/or the CYP3A4 inhibitor, e.g., in one or more healthy subjects. In other embodiments, the determining the change in plasma exposure of venglustat involves predicting the change in plasma exposure, e.g., using a computer implemented model as described herein. In embodiments, the plasma exposure is determined as the AUC as defined herein. In embodiments, the AUC is AUC_{0-12} , AUC_{0-24} , AUC_{last} , or AUC_{∞} . In embodiments, the plasma exposure of venglustat is the AUC_{last} of venglustat.

In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor. In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor and/or the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced if the change in plasma exposure is an increase of more than about 50%. In embodiments, the reduced dosage is an adjusted effective amount as defined herein. In embodiments, the CYP3A4 inhibitor is a strong

CYP3A4 inhibitor and the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced by an amount of between about 0% and 50% if the change in plasma exposure is an increase of between about 50% and 200%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced by an amount of
5 between about 5% and 50%, e.g., between about 10% and 50%, between about 25% and 50%, or between about 40% and 50%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced to an amount of between about 4 and 15 mg per day (calculated as free base) if the change in plasma exposure is an increase of between about 50% and 200%, e.g., an amount of between about 7 and 15 mg per day if the
10 change in plasma exposure is an increase of between about 50% and 200%. In embodiments, the dosage of the venglustat or the pharmaceutically acceptable salt thereof is reduced to an amount of about 8 mg per day (calculated as the free base), e.g., from about 7.0 to about 9.0 mg per day, such as about 7.5 mg or about 8.0 mg (calculated as the free base). A dosage of about 7.5 mg may be obtained, for example, by dividing a 15 mg tablet in half. A dosage of
15 about 8.0 mg may be achieved, for example, by administering two 4 mg unit dosages (e.g., tablets or capsules).

In another aspect, the disclosure provides the use of a strong or moderate CYP3A4 inhibitor in a method for: (a) establishing the correct dosage of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof; (b) improving a dosage regimen of
20 venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof; or (c) managing the risk of venglustat/CYP3A4 inhibitor interaction in a subject having a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, wherein the subject is being administered or is intended to be administered said CYP3A4 inhibitor. In embodiments, said method is a method as described herein.

25 Other methods

In another aspect, the present disclosure provides a method for inhibiting CYP3A4 activity in a subject being treated with venglustat or a pharmaceutically acceptable salt thereof, the method comprising concurrently administering the venglustat or pharmaceutically acceptable salt thereof with a strong or moderate CYP3A4 inhibitor. In a related aspect, the present
30 disclosure provides a strong or moderate CYP3A4 inhibitor for use in a method for inhibiting CYP3A4 activity in a subject being treated with venglustat or a pharmaceutically acceptable salt thereof, the method comprising concurrently administering the venglustat or

pharmaceutically acceptable salt thereof with the CYP3A4 inhibitor. In a further aspect, the present disclosure provides the use of a strong or moderate CYP3A4 inhibitor in the manufacture of a medicament for inhibiting CYP3A4 activity in a subject being treated with venglustat or a pharmaceutically acceptable salt thereof. In embodiments, the CYP3A4
5 inhibitor is a strong CYP3A4 inhibitor. In embodiments, the CYP3A4 inhibitor is selected from itraconazole and fluconazole. In embodiments, the CYP3A4 inhibitor is not fluvoxamine.

In another aspect, the disclosure provides a method for improving the therapeutic response to venglustat treatment in a subject in need thereof, the method comprising concurrently
10 administering venglustat or a pharmaceutically acceptable salt thereof with a strong or moderate CYP3A4 inhibitor. In a related aspect, the present disclosure provides a strong or moderate CYP3A4 inhibitor for use in a method for improving the therapeutic response to venglustat treatment in a subject in need thereof. In a further aspect, the present disclosure provides the use of a strong or moderate CYP3A4 inhibitor in the manufacture of a
15 medicament for improving the therapeutic response to venglustat treatment in a subject in need thereof. In embodiments, the CYP3A4 inhibitor is a strong CYP3A4 inhibitor. In embodiments, the CYP3A4 inhibitor is selected from itraconazole and fluconazole. In embodiments, the CYP3A4 inhibitor is not fluvoxamine.

In embodiments, the venglustat or pharmaceutically acceptable salt thereof and/or the
20 CYP3A4 inhibitor are as defined herein.

In embodiments, the concurrent administration of venglustat or a pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor permits a lower dose of the venglustat or pharmaceutically acceptable salt thereof to be used compared to the standard indicated dose for the disease or disorder being treated. In embodiments, the lower dose of the venglustat or
25 a pharmaceutically acceptable salt thereof is an adjusted effective amount as described herein.

In embodiments, the concurrent administration of the venglustat or pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor results in an increase in plasma AUC for venglustat of at least about 25% compared to the plasma AUC resulting from administration
30 of the venglustat or pharmaceutically acceptable salt thereof in the absence of the CYP3A4 inhibitor.

In embodiments, the subject is being treated for a disease or disorder as defined herein.

In various aspects and embodiments of the present disclosure, a change in the plasma exposure of venglustat on concomitant administration of a strong or moderate CYP3A4 inhibitor is determined by a computer implemented method, e.g., as described in the
5 examples which follow.

Forms of venglustat

The present disclosure contemplates salt forms of venglustat, e.g., venglustat in the form of a pharmaceutically acceptable salt.

Compounds that are basic in nature are generally capable of forming a wide variety of
10 different salts with various inorganic and/or organic acids. Although such salts are generally pharmaceutically acceptable for administration to animals and humans, it is often desirable in practice to initially isolate a compound from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a
15 pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds can be readily prepared using conventional techniques, e.g. by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as, for example, methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.
20 Compounds that are positively charged, e.g., containing a quaternary ammonium, may also form salts with the anionic component of various inorganic and/or organic acids.

Acids which can be used to prepare pharmaceutically acceptable salts of venglustat are those which can form non-toxic acid addition salts, e.g., salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or
25 acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, malate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

In one embodiment, the pharmaceutically acceptable salt is a succinate salt. In another embodiment, the pharmaceutically acceptable salt is a 2-hydroxysuccinate salt, e.g., an (*S*)-2-
30 hydroxysuccinate salt. In another embodiment, the pharmaceutically acceptable salt is a

hydrochloride salt (i.e., a salt with HCl). In another embodiment, the pharmaceutically acceptable salt is a malate salt, e.g., an L-malate salt.

The present disclosure also contemplates prodrugs of venglustat. The pharmaceutically acceptable prodrugs disclosed herein are derivatives which can be converted *in vivo* into venglustat. The prodrugs, which may themselves have some activity, become pharmaceutically active *in vivo* when they undergo, for example, solvolysis under physiological conditions or enzymatic degradation. Methods for preparing prodrugs of venglustat would be apparent to one of skill in the art based on the present disclosure.

In one embodiment, the carbamate moiety of venglustat is modified. For example, the carbamate moiety may be modified by the addition of water and/or one or two aliphatic alcohols. In this case, the carbon-oxygen double bond of the carbamate moiety adopts what could be considered a hemiacetal or acetal functionality. In one embodiment, the carbamate moiety may be modified by the addition of an aliphatic diol such as 1,2-ethanediol.

In one embodiment, the amino group on the quinuclidine moiety is modified. For example, the amino group may be modified to form an acid derivative or a quaternary ammonium salt. The derivative can be formed, for example, by reacting venglustat with an acetylating agent such as an acid chloride, or with an agent such as an alkyl halide.

The present disclosure further embraces hydrates, solvates, and polymorphs of venglustat. For example, the venglustat may be in one or more crystalline forms as described in, e.g., international patent application No. PCT/US2014/027081 (published as WO 2014/152215). In one embodiment, the venglustat is in the form of the crystalline Form A of the malate salt as described in PCT/US2014/027081.

Isotopically-labeled compounds are also within the scope of the present disclosure. As used herein, an "isotopically-labeled compound" refers to a presently disclosed compound including pharmaceutical salts and prodrugs thereof, each as described herein, in which one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds presently disclosed include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

Pharmaceutical compositions

In another aspect, the present disclosure provides a pharmaceutical composition (e.g., an oral pharmaceutical dosage form) comprising venglustat, in combination with a CYP3A4 inhibitor as defined herein, and at least one pharmaceutically acceptable excipient. The composition may be adapted for use in any of the methods disclosed herein.

The pharmaceutically acceptable excipient can be any such excipient known in the art including those described in, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). Pharmaceutical compositions of the compounds presently disclosed may be prepared by conventional means known in the art including, for example, mixing at least one presently disclosed compound with a pharmaceutically acceptable excipient.

Thus, in embodiments the disclosure provides an oral pharmaceutical dosage form comprising venglustat and a pharmaceutically acceptable excipient, in combination with a CYP3A4 inhibitor (e.g., selected from itraconazole and fluconazole), wherein the dosage form is formulated to provide, when administered orally, an amount of venglustat sufficient to treat a disease or disorder as described according to any of the methods herein.

In embodiments, the venglustat is in solid crystal form (e.g., crystalline malate salt Form A of venglustat). In other embodiments, the venglustat is in solid amorphous form. In embodiments, the dosage form comprises an amorphous solid dispersion comprising the venglustat and/or the CYP3A4 inhibitor with the pharmaceutically acceptable excipient.

In embodiments, the dosage form is a capsule (e.g., a hard capsule) or a tablet (e.g., a chewable tablet, an orally-disintegrating tablet, a dispersible tablet, or a classic tablet or caplet), optionally wherein said dosage form comprises from about 2 to about 30 mg of venglustat (measured as the equivalent amount of free base), e.g., from about 4 mg to about 20 mg, or from about 8 mg to about 12 mg, or about 4 mg, or about 6 mg, or about 8 mg, or about 12 mg, or about 15 mg of venglustat (measured as the equivalent amount of free base).

In embodiments, the dosage form is a classic tablet or caplet (e.g., for swallowing), a chewable tablet, an orally disintegrating tablet, or a dispersible tablet.

In embodiments, the pharmaceutically acceptable excipient comprises one or more of (a) diluent/filler (e.g., cellulose or microcrystalline cellulose, mannitol, or lactose), (b) binder (e.g., povidone, methylcellulose, ethylcellulose, hydroxypropyl cellulose (such as low-substituted hydroxypropyl cellulose), or hydroxypropyl methylcellulose), (c) disintegrant
5 (e.g., crospovidone, sodium starch glycolate, or croscarmellose sodium), (d) lubricant (e.g., magnesium stearate or sodium stearyl fumarate), (e) a glidant (e.g., silica or talc), (f) sweetener (e.g., sucralose, acesulfame potassium, aspartame, saccharine, neotame, or advantame), (g) flavor (e.g., apricot flavor), and (h) dye or colorant.

In embodiments, the pharmaceutically acceptable excipient comprises one or more
10 hydrophilic water-soluble or water swellable polymers. In embodiments, the polymer is selected from the group consisting of natural or modified cellulosic polymers, or any mixture thereof.

In embodiments, any one or more pharmaceutically acceptable excipients are present in an amount of 0.01 to 80% by weight, e.g., 0.1 to 60%, or 0.1 to 40%, or 0.1 to 30%, 0.01 to
15 15%, or 0.01 to 10%, or 0.1 to 20%, or 0.1 to 15% or 0.1 to 10%, or 0.5 to 10%, or 0.5 to 5%, or 1 to 5%, or 2.5 to 5%, or 1 to 3%, or 0.1 to 1% by weight. In embodiments, the dosage form comprises (a) from 5-95% by weight of diluent(s)/filler(s), e.g., 60-70% or 70-80%, or 65-75%, or 65-70%, or about 68%; (b) from 0.5-5% by weight of lubricant(s), e.g., 1-5%, or 2-4%, or 2-3%, or about 3%; (c) from 2-15% by weight of disintegrant(s), e.g., 4-12%, or 6-
20 10%, or 7-9%, or about 8%; (d) from 0-12% by weight of binder(s), e.g., 2-10%, or 2-8%, or 3-7%, or 4-6%, or about 5%; (e) from 0-5% by weight of glidant(s), e.g., 0.15-4%, or 1-3%, or 1-2%, or about 1%; and (f) from 0-2% by weight of flavor(s), 0-2% by weight of sweetener(s) and/or 0-2% by weight of color(s), e.g., about 1% each of flavor(s), sweetener(s), and/or color(s). In embodiments, the venglustat is present in an amount of from
25 3% to 20% by weight (measured as free base). In embodiments, the CYP3A4 inhibitor is present in an amount of from 10% to 90% by weight.

In embodiments, the dosage form is a tablet comprising a mixture of venglustat (e.g., venglustat malate), the CYP3A4 inhibitor, and one or more pharmaceutically acceptable excipients. In embodiments, the tablet is formed by direct compression of a mixture of
30 venglustat (e.g., venglustat malate), the CYP3A4 inhibitor, and one or more pharmaceutically acceptable excipients.

In embodiments, the dosage form is a hard-shelled capsule, e.g., wherein said capsule contains a mixture of venglustat (e.g., venglustat malate), the CYP3A4 inhibitor, and one or more pharmaceutically acceptable excipients. The venglustat, CYP3A4 inhibitor, and other diluents/carriers may be comprised as granules or pellets, or as a powder, said granules, pellets, or powder being contained within the shell of the capsule.

In embodiments, the venglustat and/or CYP3A4 inhibitor is present in (a) a mean particle size of 5 to 150 μm , e.g., 5 to 120 μm , 5 to 100 μm , 10 to 100 μm , 15 to 85 μm , 20 to 60 μm , 30 to 40 μm ; and/or (b) a D90 of 120 μm or less, e.g., 50 to 100 μm , 70 to 90 μm , or 60 to 80 μm ; and/or (c) a D10 of 30 μm or less, e.g. 10 to 25 μm , 10 to 20 μm or less, or 11 to 14 μm

- 10 In embodiments, the venglustat and the CYP 3A4 inhibitor are mixed together to form the oral pharmaceutical dosage form, optionally wherein the dosage form is homogenous with respect to the distribution of the venglustat and the CYP 3A4 inhibitor. In embodiments, the venglustat and the CYP 3A4 inhibitor are released over substantially the same period of time in the gastrointestinal cavity.
- 15 In embodiments, the venglustat and the CYP 3A4 inhibitor are comprised in separate portions of the composition or dosage form, e.g., in separate compartments, granules or layers. In embodiments, the venglustat and the CYP 3A4 inhibitor are separated by a pharmacologically inert barrier, layer, or shell. In embodiments, the venglustat and the CYP3A4 inhibitor are released over substantially different periods of time in the
- 20 gastrointestinal cavity or in different regions of the gastrointestinal cavity (e.g., mouth, stomach, duodenum, ileum, or jejunum).

- In embodiments, the dosage form is formulated for immediate release of the venglustat and/or immediate release of the CYP3A4 inhibitor. In embodiments, the dosage form is formulated for sustained release of the venglustat and/or sustained release of the CYP3A4 inhibitor. In
- 25 embodiments, the dosage form is formulated for delayed release of the venglustat and/or delayed release of the CYP3A4 inhibitor.

In embodiments, the plasma AUC of venglustat after a single oral dose of 15 mg averages at least 3400 ng-h/mL, e.g., 3400 to 6200 ng-h/mL, or 4000 to 5600 ng-h/mL, or 4400 to 5200 ng-h/mL.

A pharmaceutical composition or dosage form of the present disclosure can include an agent and another carrier, e.g., compound or composition, inert or active, such as a detectable agent, label, adjuvant, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant, or the like. Carriers also include pharmaceutical excipients and additives, for example, proteins, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars, and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1 to 99.99% by weight or volume. Exemplary protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. Carbohydrate excipients are also intended within the scope of this disclosure, examples of which include but are not limited to monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), and myoinositol.

Carriers which may be used include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Additional carriers include polymeric excipients/additives such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrans (e.g., cyclodextrins, such as 2-hydroxypropyl- β -cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (e.g., phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

The present disclosure also provides pharmaceutical compositions, and kits comprising said compositions, which contain venglustat (or a pharmaceutically acceptable salt or prodrug thereof) and a CYP3A4 inhibitor as described herein. The present disclosure further provides

a kit comprising a first pharmaceutical composition comprising venglustat or a pharmaceutically acceptable salt thereof, e.g. as described herein, and a second pharmaceutical composition comprising a strong or moderate CYP3A4 inhibitor as described herein.

- 5 The pharmaceutical compositions can be formulated so as to provide slow, extended, or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes, and/or microspheres. The pharmaceutical compositions can also optionally contain opacifying agents and may be of a composition that releases the active
10 ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner, e.g., by using an enteric coating. Examples of embedding compositions include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more pharmaceutically acceptable carriers, excipients, or diluents well known in the art (see, e.g., Remington's). The
15 compounds presently disclosed may be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,119,742; 3,492,397; 3,538,214; 4,060,598; and 4,173,626.

- In solid dosage forms for oral administration (e.g., capsules, tablets, pills, dragees, powders,
20 granules, and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, excipients, or diluents, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, microcrystalline cellulose, calcium phosphate, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, pregelatinized
25 maize starch, polyvinyl pyrrolidone, hydroxypropyl methylcellulose, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, sodium starch glycolate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, sodium
30 lauryl sulphate, acetyl alcohol, and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, silica, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents.

In the case of capsules, tablets, and pills, the pharmaceutical compositions can also comprise buffering agents. Solid compositions of a similar type can also be prepared using fillers in soft and hard-filled gelatin capsules, and excipients such as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

- 5 A tablet can be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared using binders (for example, gelatin or hydroxypropylmethyl cellulose), lubricants, inert diluents, preservatives, disintegrants (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-actives, and/or dispersing agents. Molded tablets can be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets and other solid dosage forms, such as dragees, capsules, pills, and granules, can optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the art.

- In embodiments, the pharmaceutical compositions are administered orally in a liquid form.
- 15 Liquid dosage forms for oral administration of an active ingredient include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. Liquid preparations for oral administration may be presented as a dry product for constitution with water or other suitable vehicle before use. In addition to the active ingredient, the liquid dosage forms can contain inert diluents commonly used in the art, such as, for example, water
- 20 or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (e.g., cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. In addition to inert diluents, the liquid pharmaceutical compositions can
- 25 include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents, and the like. Suspensions, in addition to the active ingredient(s) can contain suspending agents such as, but not limited to, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof. Suitable liquid preparations may be prepared by conventional means with a
- 30 pharmaceutically acceptable additive(s) such as a suspending agent (e.g., sorbitol syrup, methyl cellulose, or hydrogenated edible fats); emulsifying agent (e.g., lecithin or acacia);

non-aqueous vehicle (e.g., almond oil, oily esters, or ethyl alcohol); and/or preservative (e.g., methyl or propyl p-hydroxybenzoates, or sorbic acid). The active ingredient(s) can also be administered as a bolus, electuary, or paste.

5 In some embodiments of the methods described herein, the pharmaceutical composition may take the form of tablets or lozenges formulated for buccal administration in a conventional manner.

In some embodiments of the methods described herein, the pharmaceutical compositions are administered by non-oral means such as by topical application, transdermal application, injection, and the like. In related embodiments, the pharmaceutical compositions are
10 administered parenterally by injection, infusion, or implantation (e.g., intravenous, intramuscular, intra-arterial, subcutaneous, and the like).

In some embodiments of the methods described herein, the presently disclosed compounds may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit
15 dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain a formulating agent such as a suspending, stabilizing, and/or dispersing agent recognized by those of skill in the art. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free
20 water, before use.

In some embodiments of the methods described herein, the pharmaceutical compositions can be in the form of sterile injections. The pharmaceutical compositions can be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other
25 sterile injectable medium immediately before use. To prepare such a composition, the active ingredient is dissolved or suspended in a parenterally acceptable liquid vehicle. Exemplary vehicles and solvents include, but are not limited to, water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution, and isotonic sodium chloride solution. The
30 pharmaceutical composition can also contain one or more preservatives, for example, methyl, ethyl, or n-propyl p-hydroxybenzoate. To improve solubility, a dissolution enhancing or

solubilising agent can be added or the solvent can contain 10-60% w/w of propylene glycol or the like.

In some embodiments of the methods described herein, the pharmaceutical compositions can contain one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous
5 solutions, dispersions, suspensions or emulsions, or sterile powders, which can be reconstituted into sterile injectable solutions or dispersions just prior to use. Such pharmaceutical compositions can contain antioxidants; buffers; bacteriostats; solutes, which render the formulation isotonic with the blood of the intended recipient; suspending agents; thickening agents; preservatives; and the like.

10 Examples of suitable aqueous and nonaqueous carriers, which can be employed in any of the pharmaceutical compositions described herein include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by
15 the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. In some embodiments, in order to prolong the effect of an active ingredient, it is desirable to slow the absorption of the compound from gastrointestinal administration, or from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate
20 of absorption of the active ingredient then depends upon its rate of dissolution which, in turn, can depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered active ingredient may be accomplished by dissolving or suspending the compound in an oil vehicle. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents that delay absorption
25 such as aluminum monostearate and gelatin.

Controlled release parenteral compositions can be in form of aqueous suspensions, microspheres, microcapsules, magnetic microspheres, oil solutions, oil suspensions, emulsions, or the active ingredient can be incorporated in biocompatible carrier(s), liposomes, nanoparticles, implants, or infusion devices. Materials for use in the preparation of
30 microspheres and/or microcapsules include, but are not limited to, biodegradable/bioerodible polymers such as polyglactin, poly-(isobutyl cyanoacrylate), poly(2-hydroxyethyl-L-glutamine), and poly(lactic acid). Biocompatible carriers which can be used when

formulating a controlled release parenteral formulation include carbohydrates such as dextrans, proteins such as albumin, lipoproteins, or antibodies. Materials for use in implants can be non-biodegradable, e.g., polydimethylsiloxane, or biodegradable such as, e.g., poly(caprolactone), poly(lactic acid), poly(glycolic acid), or poly(ortho esters).

- 5 In some embodiments of the methods described herein, for topical administration, a presently disclosed compound may be formulated as an ointment or cream. Presently disclosed compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.
- 10 In other aspects, the disclosure provides a dosage form or pharmaceutical composition as described herein for use in therapy, e.g., for use in a method as defined herein.

Having been generally described herein, the follow non-limiting examples are provided to further illustrate the disclosure.

EXAMPLES

- 15 Example 1A: Synthesis of (S)-quinuclidin-3-yl 2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-ylcarbamate (venglustat)

- To a stirred solution of 4-fluorothiobenzamide (8.94 g, 57.6 mmol) in ethanol (70 mL) was added ethyl 4-chloroacetoacetate (7.8 mL, 58 mmol). The reaction was heated at reflux for 4 hours, treated with an addition aliquot of ethyl 4-chloroacetoacetate (1.0 mL, 7.4 mmol), and
20 refluxed for an additional 3.5 hours. The reaction was then concentrated and the residue was partitioned between ethyl acetate (200 mL) and aqueous NaHCO₃ (200 mL). The organic layer was combined with a backextract of the aqueous layer (ethyl acetate, 1 x 75 mL), dried (Na₂SO₄), and concentrated. The resulting amber oil was purified by flash chromatography using a hexane/ethyl acetate gradient to afford ethyl 2-(2-(4-fluorophenyl)thiazol-4-yl)acetate
25 as a low melting, nearly colourless solid (13.58 g, 89%).

To a stirred solution of ethyl 2-(2-(4-fluorophenyl)thiazol-4-yl)acetate (6.28 g, 23.7 mmol) in DMF (50 mL) was added sodium hydride [60% dispersion in mineral oil] (2.84 g, 71.0 mmol). The frothy mixture was stirred for 15 minutes before cooling in an ice bath and adding iodomethane (4.4 mL, 71 mmol). The reaction was stirred overnight, allowing the

cooling bath to slowly warm to room temperature. The mixture was then concentrated and the residue partitioned between ethyl acetate (80 mL) and water (200 mL). The organic layer was washed with a second portion of water (1 x 200 mL), dried (Na₂SO₄) and concentrated. The resulting amber oil was purified by flash chromatography using a hexane/ethyl acetate
5 gradient to afford ethyl 2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropanoate as a colourless oil (4.57 g, 66%).

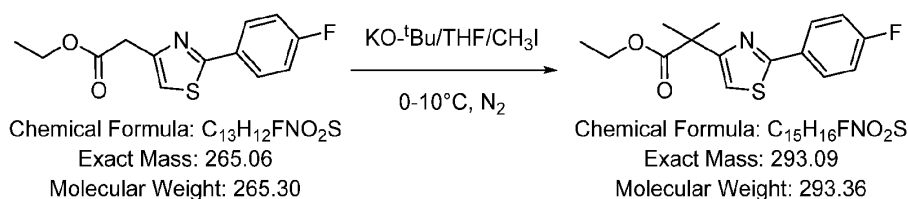
To a stirred solution of ethyl 2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropanoate (4.56 g, 15.5 mmol) in 1:1:1 THF/ethanol/water (45 mL) was added lithium hydroxide monohydrate (2.93 g, 69.8 mmol). The reaction was stirred overnight, concentrated, and redissolved in
10 water (175 mL). The solution was washed with ether (1 x 100 mL), acidified by the addition of 1.0 N HCl (80 mL) and extracted with ethyl acetate (2 x 70 mL). The combined extracts were dried (Na₂SO₄) and concentrated to afford 2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropanoic acid as a white solid (4.04 g, 98%). This material was used in the next step without purification.

15 To a stirred and cooled (0 °C) solution of 2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropanoic acid (4.02 g, 15.2 mmol) in THF (100 mL) was added trimethylamine (4.2 mL, 30 mmol) followed by isobutyl chloroformate (3.0 mL, 23 mmol). The reaction was stirred cold for another 1 hour before adding a solution of sodium azide (1.98 g, 30.5 mmol) in water (20 mL). The reaction was stirred overnight, allowing the cooling bath to slowly
20 warm to room temperature. The mixture was then diluted with water (100 mL) and extracted with ethyl acetate (2 x 60 mL). The combined extracts were washed with aqueous NaHCO₃ (1 x 150 mL) and brine (1 x 100 mL), dried (Na₂SO₄) and concentrated. After coevaporating with toluene (2 x 50 mL), the resulting white solid was taken up in toluene (100 mL) and refluxed for 4 hours. (S)-3-quinuclidinol (3.87 g, 30.4 mmol) was then added and reflux was
25 continued overnight. The reaction was concentrated and the residue partitioned between ethyl acetate (100 mL) and aqueous NaHCO₃ (150 mL). The organic layer was washed with water (1 x 150 mL), dried (Na₂SO₄) and concentrated. The resulting off-white solid was purified by flash chromatography using a chloroform/methanol/ammonia gradient to afford the title
30 compound as a white solid (4.34 g, 73%). ¹H NMR (400 MHz, CDCl₃) δ 7.96-7.88 (m, 2H), 7.16-7.04 (m, 3H), 5.55 (br s, 1H), 4.69-4.62 (m, 1H), 3.24-3.11 (m, 1H), 3.00-2.50 (m, 5H), 2.01-1.26 (m, 11H) ppm. ¹³C NMR (400 MHz, CDCl₃) δ 166.4, 165.1, 163.8 (d, J=250.3 Hz), 162.9, 155.0, 130.1 (d, J=3.3 Hz), 128.4 (d, J= 8.5 Hz), 115.9 (d, J= 22.3 Hz), 112.5, 71.2,

55.7, 54.2, 47.5, 46.5, 28.0, 25.5, 24.7, 19.6 ppm. Purity: 100 % UPLCMS (210 nm & 254 nm); retention time 0.83 min; (M+1) 390.

Example 1B: Preparation of (S)-Quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate (venglustat) in free base form

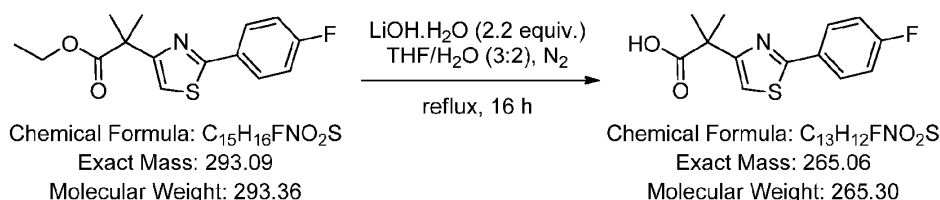
5 **Step 1: Dimethylation with methyl iodide**



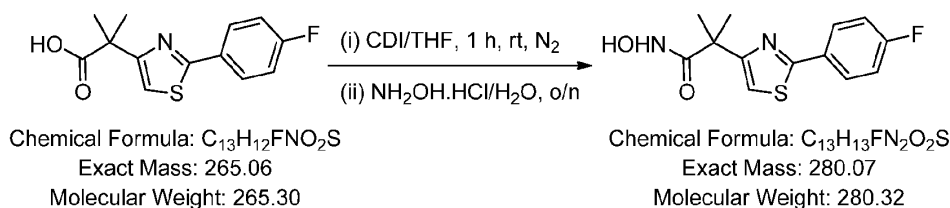
A 3N RB flask was equipped with a thermometer, an addition funnel and a nitrogen inlet. The flask was flushed with nitrogen and potassium tert-butoxide (MW 112.21, 75.4 mmol, 8.46 g, 4.0 equiv., white powder) was weighed out and added to the flask via a powder funnel
10 followed by the addition of THF (60 mL). Most of the potassium tert-butoxide dissolved to give a cloudy solution. This mixture was cooled in an ice-water bath to 0-2°C (internal temperature). In a separate flask, the starting ester (MW 265.3, 18.85 mmol, 5.0 g, 1.0 equiv.) was dissolved in THF (18 mL + 2 mL as rinse) and transferred to the addition funnel. This solution was added dropwise to the cooled mixture over a period of 25-30 min, keeping the
15 internal temperature below 5°C during the addition. The reaction mixture was cooled back to 0-2°C. In a separate flask, a solution of methyl iodide (MW 141.94, 47.13 mmol, 6.7 g, 2.5 equiv.) in THF (6 mL) was prepared and transferred to the addition funnel. The flask containing the methyl iodide solution was then rinsed with THF (1.5 mL) which was then transferred to the addition funnel already containing the clear colorless solution of methyl
20 iodide in THF. This solution was added carefully dropwise to the dark brown reaction mixture over a period of 30-40 min, keeping the internal temperature below 10°C at all times during the addition. After the addition was complete, the slightly turbid mixture was stirred for an additional 1 h during which time the internal temperature dropped to 0-5°C. After stirring for an hour at 0-5°C, the reaction mixture was quenched with the slow dropwise
25 addition of 5.0 M aqueous HCl (8 mL) over a period of 5-7 min. The internal temperature was maintained below 20°C during this addition. After the addition, water (14 mL) was added and the mixture was stirred for 2-3 min. The stirring was stopped and the two layers were allowed to separate. The two layers were then transferred to a 250 mL 1N RB flask and

the THF was evaporated *in vacuo* as much as possible to obtain a biphasic layer of THF/product and water. The two layers were allowed to separate. A THF solution of the Step 1 product was used in the next reaction.

Step 2: Hydrolysis of the ethyl ester with LiOH monohydrate

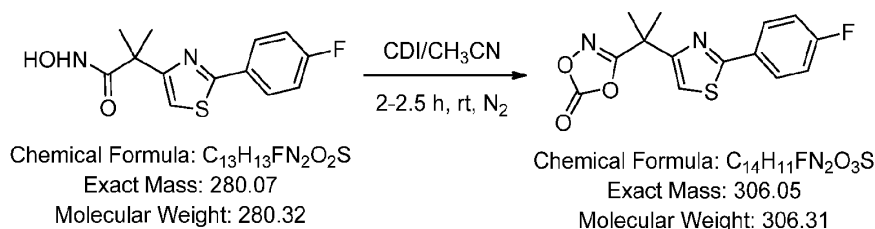


The crude ester in THF was added to the reaction flask. Separately, LiOH.H₂O (MW 41.96, 75.0 mmol, 3.15 grams, 2.2 equiv.) was weighed out in a 100 mL beaker to which a stir bar was added. Water (40 mL) was added and the mixture was stirred until all the solid dissolved to give a clear colorless solution. This aqueous solution was then added to the 250 mL RB flask containing the solution of the ester in tetrahydrofuran (THF). A condenser was attached to the neck of the flask and a nitrogen inlet was attached at the top of the condenser. The mixture was heated at reflux for 16 hours. After 16 hours, the heating was stopped and the mixture was cooled to room temperature. The THF was evaporated *in vacuo* to obtain a brown solution. An aliquot of the brown aqueous solution was analyzed by HPLC and LC/MS for complete hydrolysis of the ethyl ester. Water (15 mL) was added and this aqueous basic solution was extracted with TBME (2 x 40 mL) to remove the t-butyl ester. The aqueous basic layer was cooled in an ice-water bath to 0-10°C and acidified with dropwise addition of concentrated HCl to pH ~ 1 with stirring. To this gummy solid in the aqueous acidic solution was added TBME (60 mL) and the mixture was shaken and then stirred vigorously to dissolve all the acid into the TBME layer. The two layers were transferred to a separatory funnel and the TBME layer was separated out. The pale yellow aqueous acidic solution was re-extracted with TBME (40 mL) and the TBME layer was separated and combined with the previous TBME layer. The aqueous acidic layer was discarded. The combined TBME layers are dried over anhydrous Na₂SO₄, filtered and evaporated *in vacuo* to remove TBME and obtain the crude acid as an orange/dark yellow oil that solidified under high vacuum to a dirty yellow colored solid. The crude acid was weighed out and crystallized by heating it in heptane/TBME (3:1, 5 mL/g of crude) to give the acid as a yellow solid.

Step 3: Formation of hydroxamic acid with NH₂OH.HCl

The carboxylic acid (MW 265.3, 18.85 mmol, 5.0 g, 1.0 equiv.) was weighed and transferred to a 25 mL 1N RB flask under nitrogen. THF (5.0 mL) was added and the acid readily dissolved to give a clear dark yellow to brown solution. The solution was cooled to 0-2°C (bath temperature) in an ice-bath and N, N'-carbonyldiimidazole (CDI; MW 162.15, 20.74 mmol, 3.36 g, 1.1 equiv.) was added slowly in small portions over a period of 10-15 minutes. The ice-bath was removed and the solution was stirred at room temperature for 1 h. After 1 h of stirring, the solution was again cooled in an ice-water bath to 0-2°C (bath temperature).

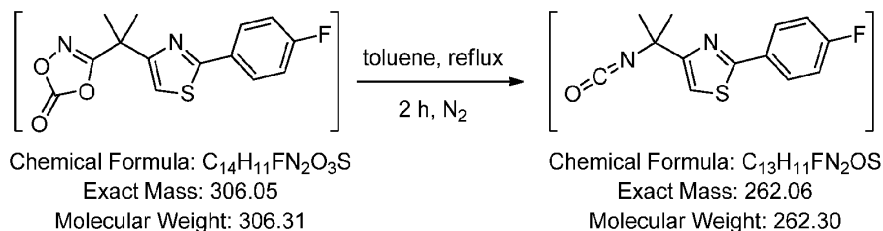
Hydroxylamine hydrochloride (NH₂OH.HCl; MW 69.49, 37.7 mmol, 2.62 g, 2.0 equiv.) was added slowly in small portions as a solid over a period of 3-5 minutes as this addition was exothermic. After the addition was complete, water (1.0 mL) was added to the heterogeneous mixture dropwise over a period of 2 minutes and the reaction mixture was stirred at 0-10°C in the ice-water bath for 5 minutes. The cooling bath was removed and the reaction mixture was stirred under nitrogen at room temperature overnight for 20-22 h. The solution became clear as all of the NH₂OH.HCl dissolved. After 20-22 h, an aliquot of the reaction mixture was analyzed by High Pressure Liquid Chromatography (HPLC). The THF was then evaporated *in vacuo* and the residue was taken up in dichloromethane (120 mL) and water (60 mL). The mixture was transferred to a separatory funnel where it was shaken and the two layers allowed to separate. The water layer was discarded and the dichloromethane layer was washed with 1N hydrochloride (HCl; 60 mL). The acid layer was discarded. The dichloromethane layer was dried over anhydrous Na₂SO₄, filtered and the solvent evaporated *in vacuo* to obtain the crude hydroxamic acid as a pale yellow solid that was dried under high vacuum overnight.

Step 3 continued: Conversion of hydroxamic acid to cyclic intermediate (not isolated)

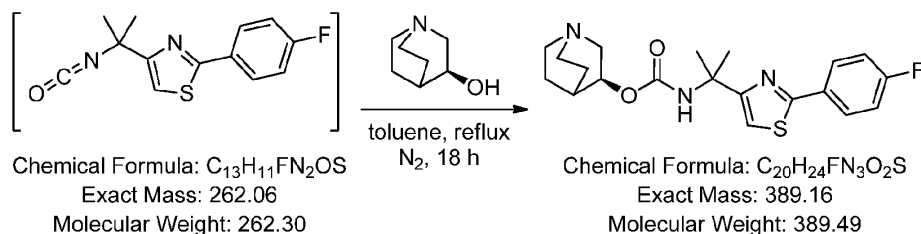
The crude hydroxamic acid (MW 280.32, 5.1 g) was transferred to a 250 mL 1N RB flask with a nitrogen inlet. A stir bar was added followed by the addition of acetonitrile (50 mL).

- 5 The solid was insoluble in acetonitrile. The yellow heterogeneous mixture was stirred for 2-3 minutes under nitrogen and CDI (MW 162.15, 20.74 mmol, 3.36 g, 1.1 equiv.) was added in a single portion at room temperature. No exotherm was observed. The solid immediately dissolved and the clear yellow solution was stirred at room temperature for 2-2.5 h. After 2-2.5 h, an aliquot was analyzed by HPLC and LC/MS which showed conversion of the
- 10 hydroxamic acid to the desired cyclic intermediate.

The acetonitrile was then evaporated *in vacuo* to give the crude cyclic intermediate as reddish thick oil. The oil was taken up in toluene (60 mL) and the reddish mixture was heated to reflux for 2 hours during which time, the cyclic intermediate released CO_2 and rearranged to the isocyanate (see below).



15

Step 3 continued: Conversion of the isocyanate to the free base

The reaction mixture was cooled to 50-60°C and (*S*)-(+)-quinuclidinol (MW 127.18, 28.28 mmol, 3.6 g, 1.5 equiv.) was added to the mixture as a solid in a single portion. The mixture was re-heated to reflux for 18 h. After 18 h, an aliquot was analyzed by HPLC and LC/MS which showed complete conversion of the isocyanate to the desired product. The reaction mixture was transferred to a separatory funnel and toluene (25 mL) was added. The mixture was washed with water (2 x 40 mL) and the water layers were separated. The combined water layers were re-extracted with toluene (30 mL) and the water layer was discarded. The combined toluene layers were extracted with 1N HCl (2 x 60 mL) and the toluene layer (containing the O-acyl impurity) was discarded. The combined HCl layers were transferred to a 500 mL Erlenmeyer flask equipped with a stir bar. This stirring clear yellow/reddish orange solution was basified to pH 10-12 by the dropwise addition of 50% w/w aqueous NaOH. The desired free base precipitated out of solution as a dirty yellow gummy solid which could trap the stir bar. To this mixture was added isopropyl acetate (100 mL) and the mixture was stirred vigorously for 5 minutes when the gummy solid went into isopropyl acetate. The stirring was stopped and the two layers were allowed to separate. The yellow isopropyl acetate layer was separated and the basic aqueous layer was re-extracted with isopropyl acetate (30 mL). The basic aqueous layer was discarded and the combined isopropyl acetate layers were dried over anhydrous Na₂SO₄, filtered into a pre-weighed RB flask and the solvent evaporated *in vacuo* to obtain the crude free base as beige to tan solid that was dried under high vacuum overnight.

Step 3 continued: Recrystallization of the crude free base

The beige to tan colored crude free base was weighed and re-crystallized from heptane/isopropyl acetate (3:1, 9.0 mL of solvent/g of crude free base). The appropriate amount of heptane/isopropyl acetate was added to the crude free base along with a stir bar and the mixture was heated to reflux for 10 min (free base was initially partially soluble but dissolved to give a clear reddish orange solution when heated to reflux). The heat source was removed and the mixture was allowed to cool to room temperature with stirring when a white precipitate formed. After stirring at room temperature for 3-4 h, the precipitate was filtered off under hose vacuum using a Buchner funnel, washed with heptane (20 mL) and dried under hose vacuum on the Buchner funnel overnight. The precipitate was transferred to a crystallizing dish and dried at 55°C overnight in a vacuum oven. ¹H NMR (400 MHz, CDCl₃) δ 8.04 – 7.83 (m, 2H), 7.20 – 6.99 (m, 3H), 5.53 (s, 1H), 4.73 – 4.55 (m, 1H), 3.18 (dd, *J* =

14.5, 8.4 Hz, 1H), 3.05 – 2.19 (m, 5H), 2.0 – 1.76 (m, 11H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 166.38, 165.02, 162.54, 162.8-155.0 (d, C-F), 130.06, 128.43, 128.34, 116.01, 115.79, 112.46, 71.18, 55.70, 54.13, 47.42, 46.52, 27.94, 25.41, 24.67, 19.58 ppm.

Example 2: Preparation of crystalline forms of (S)-Quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate (venglustat) salts

Crystalline salts of (S)-Quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate may be formed from the free base prepared as described in Example 1B.

For example, the free base of (S)-Quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate (about 50 mmol) is dissolved in IPA (140 ml) at room temperature and filtered.

- 10 The filtrate is added into a 1 L round bottomed flask which is equipped with an overhead stirrer and nitrogen in/outlet. L-malic acid (about 50 mmol) is dissolved in IPA (100 + 30 ml) at room temperature and filtered. The filtrate is added into the above 1 L flask. The resulting solution is stirred at room temperature (with or without seeding) under nitrogen for 4 to 24 hours. During this period of time crystals form. The product is collected by filtration and
- 15 washed with a small amount of IPA (30 ml). The crystalline solid is dried in a vacuum oven at 55 °C for 72 hours to yield the desired malate salt.

Crystal forms of other salts (e.g., acid addition salts with succinic acid or HCl) may be prepared in an analogous manner.

Example 3: Clinical studies of venglustat in healthy volunteers

- 20 Several phase 1 studies were conducted in healthy volunteers to determine venglustat pharmacokinetics, pharmacodynamics, safety, and tolerability and to assess food effects on pharmacokinetics. The studies assessed single-dose administration and food-effect (clinical trial reference NCT01674036) and repeated-dose administration (clinical trial reference NCT01710826) of venglustat L-malate salt.
- 25 Study NCT01674036 was split into two parts. The first part (referenced as TDU12766 herein) was a double-blind, randomized, placebo-controlled, sequential ascending single dose study. The second part (referenced as FED12767 herein) was an open-label, randomized, 2-sequence, 2-period, 2-treatment crossover study with a minimum wash-out period; to obtain preliminary information on the pharmacokinetics, tolerability, and safety of venglustat after

single oral doses in fed and fasted conditions. Study NCT01710826 was a double-blind, randomized, placebo-controlled study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of an ascending 14-day repeated oral doses of venglustat in healthy male and female subjects (referenced as TDR12768 herein).

- 5 Details of the study design, drug, assessment, parameters measured, and results are described in detail by Peterschmitt *et al.* (Clin. Pharmacol. Drug Dev. (2021) 10(1):86–98) and in the corresponding clinicaltrials.gov entries for the two trials cited above. Some of the conclusions are summarised below.

Venglustat pharmacokinetics following a single dose

- 10 In the single ascending-dose study (TDU12766), across the single oral doses of venglustat malate evaluated (2–150 mg), venglustat was absorbed with a median $t_{\max}$ of 3.00 to 5.50 hours and eliminated with a geometric mean $t_{1/2}$ of 28.9 hours. On Day 14, mean CL/F ranged from 5.18 to 6.43 L/h across the dose groups. Exposure increased close to dose-proportionally throughout the dose range: a 75-fold dose increase resulted in 97.3-, 89.2-, and
15 85.9-fold increases in geometric mean $C_{\max}$, AUC_{last} , and AUC_{inf} , respectively. Mean 48-hour urinary excretion fractions were 14.7% to 23.5% over the 2- to 150-mg dose range. In the study, a total of 4 mild treatment-emergent adverse events (TEAEs) were reported in the 50-150 mg dose groups. There were no adverse events reported in the 2-25 mg dose group.

Food effect

- 20 In the preliminary assessment of the effect of food on venglustat pharmacokinetics, administration of 5 mg venglustat malate with a high-fat meal had no effect on venglustat exposure compared with fasting conditions. Fed/fasted geometric mean ratios were 0.92 and 0.91 for $C_{\max}$ and AUC_{last} , respectively. Within-subject variability (i.e., fed versus fasted) accounted for less than half the total subject variability. Median $t_{\max}$ was 6.00 hours whether
25 fed or fasting. 1 subject reported a mild TEAE in the fed phase of the study.

Venglustat pharmacokinetics following multiple dosing

In the repeated ascending-dose study (TDR12768) in subjects receiving 5, 10, or 20 mg venglustat malate once daily for 14 days, venglustat was absorbed with a median $t_{\max}$ of 2.00 to 5.00 hours postdose on Days 1 and 14. Steady state appeared to be reached within 5 days

of repeated dosing. Venglustat exposure increased close to dose-proportionally over the dose range of 5–20 mg venglustat malate: this 4-fold dose increase resulted in 3.76- and 3.69-fold increases in geometric mean $C_{\max}$ and AUC_{0-24} values, respectively, on Day 14. After 14 days of administration, pooled venglustat accumulation ratios were 2.10 for $C_{\max}$ and 2.22 for AUC_{0-24} , independent of dose and sex. Dose and sex also had no effect on $t_{1/2}$. Point estimates for within-subject variability were approximately 14% for $C_{\max}$ and 13% for AUC_{0-24} . After 14 once-daily doses of venglustat malate, the 24-hour unchanged urinary excretion fraction of venglustat (mean fe_{0-24}) ranged between 26.3% and 33.1%. Mean $CL_{R(0-24)}$ ranged between 1.49 and 2.07 L/h, approximately 3.18- to 3.86-fold lower than observed plasma CL/F . The geometric mean plasma Day 14/Day 1 ratios of 4 β -hydroxycholesterol showed no marked difference between placebo and venglustat-treated groups, indicating minimal induction of CYP3A4. 17 subjects reported a total of 32 mild TEAEs during the study, including 10 TEAEs in the placebo group and 22 TEAEs in the 5-, 10-, and 20-mg dose groups. In the venglustat malate dose groups, the TEAEs reported by the investigator as study drug-related were constipation, diarrhea, dry mouth, flatulence, pruritus, and fatigue.

Conclusions

Following a single oral dose of venglustat malate, venglustat demonstrated linear pharmacokinetics, rapid absorption (median $t_{\max}$, 3.00–5.50 hours), systemic exposure unaffected by food, low apparent total body clearance (mean CL/F , 5.18–6.43 L/h), and pooled geometric mean $t_{1/2z}$ of 28.9 hours. Following repeated once-daily oral doses for 14 days, apparent steady state occurred within 5 days of repeated dosing, with pooled accumulation ratios of 2.10 for $C_{\max}$ and 2.22 for AUC_{0-24} , and no statistically significant effect of dose or sex on accumulation. At the doses and dosing regimens tested, venglustat showed a favorable safety and tolerability profile with no severe adverse events (SAEs) or deaths. There were several TEAEs in the single dose and multiple dose groups.

Example 4: Clinical study of venglustat co-administered with itraconazole

Study Design

A Phase I, single-center, open-label, 2-period, single-sequence, non-randomized, drug-drug interaction (DDI) study was conducted to assess the effect of multiple dose itraconazole 100-mg BID on the pharmacokinetics of single-dose venglustat in healthy male subjects under fed conditions with a washout duration of 7 days between treatment periods. The duration of

Treatment Period 1 (TP1) was 1 day, and the duration of Treatment Period 2 (TP2) was 13 days (see Figure 1).

8 subjects were enrolled in and completed the study. Subjects were males of 20-43 years of age with a mean age of 28.8. Venglustat (malate salt form) was administered to subjects on day 1 of TP1 as a hard capsule comprising 15 mg of venglustat (measured as free base, corresponding to approximately 20 mg of venglustat malate). Blood samples were collected predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144 and 168 hours following the dose on Day 1. Samples were processed to obtain plasma and plasma concentration of venglustat was determined by HPLC-tandem MS with a lower quantification limit of 0.5 ng/mL. Subjects then proceeded to a 7-day washout period.

At the conclusion of the washout period, TP2 began. Subjects were administered itraconazole as a commercial capsule comprising 100 mg of itraconazole twice per day from Day 1 to Day 12 of TP2 (just after eating breakfast and dinner). On Day 6 of TP2, venglustat malate was co-administered to subjects as a hard capsule comprising 15 mg of venglustat (measured as free base) in addition to the itraconazole dose. Blood samples were collected predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144 and 168 hours post-dose on Day 6, as well as pre-dose on Day 8 and Day 10, and 12-hours post-dose on Day 12. All samples were processed to obtain plasma and plasma concentration of venglustat free base was determined on all Day 6 samples by HPLC-tandem MS with a lower quantification limit of 0.5 ng/mL. The samples from predose through 12 hours post-dose on Day 6, and the Day 8, 10 and 13 samples were also analyzed for itraconazole and hydroxyitraconazole concentration by HPLC-tandem MS with lower quantification limits of 1 ng/mL and 2 ng/mL, respectively.

The primary endpoints of the study were to assess the effects of multiple-dose itraconazole (100 mg BID) on the pharmacokinetics of single-dose venglustat (15 mg, measured as free base). The secondary endpoints were to assess the safety and tolerability of single-dose venglustat with and without co-administration of multiple-dose itraconazole and to assess the pharmacokinetics of itraconazole/hydroxyitraconazole.

Subjects were also monitored for any adverse events (reported by the subject or observed by investigators), and physical examination and clinical laboratory evaluations were conducted (hematology, biochemistry, urinalysis). Subjects' body temperature, body weight, vital signs

(heart rate, supine and standing systolic blood pressure, diastolic blood pressure) and 12-lead electrocardiogram are also recorded.

Results

Overall, venglustat and itraconazole were well-tolerated in all subjects. No serious adverse events, adverse events of special interest, or adverse events leading to study discontinuation were reported. Two subjects reported treatment-emergent adverse events, one during TP1 and one during TP2. Both were mild in nature. One subject reported infrequent bowel movements on Day 4 of TP1, which was considered not related to venglustat. The infrequent bowel movements were treated with a daily dose of 5.5oz prune juice for 5 days. One subject reported a maculopapular rash on Day 6 of TP2, about 3 hours after coadministration of venglustat and itraconazole. Such a rash is listed as a common adverse event on the FDA label for itraconazole, and it was treated with 50mg diphenhydramine (an antihistamine) daily for 6 days.

Figure 2 shows the mean plasma concentrations of venglustat in the presence and absence of itraconazole. The pharmacokinetic results are summarized in Table 1 below.

Table 1: *Venglustat PK parameters following a single dose administration of venglustat alone (TP1) and following single dose venglustat co-administered with repeated-dose itraconazole (TP2) – Mean ± SD (geometric mean) [CV%]*

Drug	PK parameters	Treatment	
		Venglustat (TP1)	Venglustat + Itraconazole (TP2)
Venglustat	C _{max} (ng/mL)	57.5 ± 19.6 (54.4) [34]	63.2 ± 17.0 (61.0) [27]
	t _{max} (hr) ^a	4.50 (3.00 – 8.00)	5.50 (3.00 – 8.00)
	AUC _{last} (ng·h/mL)	2330 ± 884 (2200) [38]	4110 ± 1290 (3930) [31]
	AUC (ng·h/mL)	2400 ± 937 (2260) [39]	4810 ± 1630 (4580) [34]
	t _{last} (hr) ^a	168.0 (168.0 – 168.0)	168.0 (168.0 – 168.3)
	t _{1/2z} (hr)	31.2 ± 3.66 (31.0) [12]	58.7 ± 6.49 (58.4) [11]
	CL/F (L/h)	7.05 ± 2.48 (6.65) [35]	3.44 ± 1.15 (3.28) [33]

Itraconazole	$C_{\max}$ (ng/mL)	-	656 ± 167 (637) [25]
	C_{trough} (ng/mL)	-	314 ± 59.7 (309) [19]
	$t_{\max}$ (hr) ^a	-	4.50 (3.00 – 5.00)
	AUC_{0-12} (ng·h/mL)	-	5090 ± 1240 (4970) [24]
Hydroxy-itraconazole	$C_{\max}$ (ng/mL)	-	951 ± 194 (935) [20]
	C_{trough} (ng/mL)	-	749 ± 140 (737) [19]
	$t_{\max}$ (hr) ^a	-	5.00 (4.00 – 5.02)
	AUC_{0-12} (ng·h/mL)	-	9550 ± 1820 (9400) [19]

^a Median (min – max)

AUC_{last} = area under the plasma concentration to time curve from zero to t_{last} (where t_{last} = time to last concentration above limit of quantification); AUC = area under the curve extrapolated to infinity (calculated as $AUC_{\text{last}} + C_{\text{last}}/\lambda_z$); $C_{\max}$ = maximum observed plasma concentration; C_{trough} = plasma concentration just before TP2; $t_{\max}$ = time to $C_{\max}$; $t_{1/2z}$ = terminal half-life associated with the terminal slope (calculated as $0.693/\lambda_z$); CL/F = apparent total body clearance from plasma (calculated as dose/AUC); and AUC_{0-12} = 12-hour AUC.

These results demonstrate that repeated oral doses of 100 mg of itraconazole BID, a strong CYP3A4 inhibitor, with a single dose of 15 mg venglustat increased venglustat AUC_{last} and AUC by 1.79 fold (90% CI: 1.61 – 1.99) and 2.03 fold (90% CI: 1.81 – 2.27), respectively, confirming that venglustat is a CYP3A4 substrate *in vivo*. The $C_{\max}$ of venglustat was increased by 1.12-fold, while $t_{1/2z}$ was increased by 1.88-fold. Venglustat and itraconazole were well-tolerated when given alone or in co-administration.

15 Example 5: Development and verification of a PBPK model for venglustat plasma concentrations

The objective of this study was to develop and verify a PBPK model using the available *in vitro* and *in vivo* PK information, and to predict venglustat PK for venglustat alone or co-

administered with a CYP3A inhibitor in healthy subjects using the PBPK model to support dose recommendations.

The venglustat PBPK model was developed based on *in vitro* / *in vivo* absorption, distribution, metabolism, and excretion (ADME) data and PK data from Phase 1 clinical studies in healthy subjects (Example 3). Simcyp default “Sim-Healthy Volunteers” population was used for the generation of virtual population. The PBPK model performance was confirmed using observed venglustat single dose and repeated dosing PK data from Phase 1 studies in healthy adult subjects. The simulated results of the drug-drug interaction were verified using results from an *in vivo* drug interaction study (Example 4) conducted with a known strong CYP3A4 inhibitor, itraconazole, to evaluate the impact of CYP3A inhibition on venglustat exposure.

Verification of the PBPK model was carried out by comparing predicted and observed plasma concentration-time profiles of venglustat following a single oral dose of 11.2 mg, 18.6 mg, and 112 mg venglustat and following QD oral dose of 3.72 mg, 7.44 mg, and 14.9 mg venglustat for 14 days to healthy subjects. The simulated results of DDI were verified using a clinical drug interaction study (Example 4) with a known strong inhibitor, itraconazole, to assess the contribution of CYP3A4 mediated metabolism in the elimination of venglustat following a single oral dose of 15 mg (measured as free base). The trial designs (dose, dosing regimen, age range, and number of virtual subjects) were replicated as closely as possible to ensure that the characteristics of the virtual subjects were matched to those described in the Clinical Study Reports.

Software tools, model development, and input parameters

PBPK model development and simulations were performed in Simcyp® Population Based Simulator V17 (Simcyp Ltd, part of Certara, Sheffield, UK) running on Windows Server 2012 R2 Standard with Excel 2013.

Physicochemical properties of venglustat, as well as its absorption, distribution, metabolism, and excretion (ADME) parameters, were used as PBPK model inputs, and the sources are summarized in Table 2.

Table 2: Input PK parameters for venglustat in the PBPK model

Compound model	Parameter	Value	Description
Physical-chemical and blood binding parameters	Molecular weight (free base)	389.49	
	LogP	3.79	
	Compound type	Monoprotic Base	
	pKa1	9.00	
	pKa2	Remove	
	Fraction unbound in plasma (f_u)	0.18	Average based on <i>in vitro</i> data
	Blood to plasma ratio	1.3	Average based on <i>in vitro</i> data
	HSA/AGP	HSA selected	
Absorption (model: 1 st order)	f_a	0.978	Predicted from Caco-2 data
	f_g	0.99	Predicted from Caco-2 data
	K_a (h ⁻¹)	1.514	Predicted
	Lag time (h)	0.458	Estimated from population PK model developed using Phase 1 studies including TDU12766, FED12767, and TDR12768 (Example 3)
	P_{app} ($\times 10^{-6}$ cm/s): Caco-2 system (A/B, pH 7.4/7.4)	27 (ref: propranolol at 42)	Measured <i>in vitro</i> Caco-2 study
	Fraction unbound in gut ($f_{u,Gut}$)	1	Assumed
Distribution (model: minimal PBPK with SAC)	V_{ss} (L/kg)	3.12 (30%CV)	$V2/F+V3/F$ estimated from population PK model (supra)
	SAC (L/Kg)	0.67	$V3/F$ estimated from population PK model (supra)
	SAC $CL_{in/out}$ (L/h)	7.63	Estimated from population PK model (supra)
Elimination (enzyme kinetics)	System	Human liver microsomes	$CL_{int-CYP2D6}$ and 3A4 values were back-calculated from CL_{po}/F by population PK model (supra). Measured in <i>in vitro</i> metabolic stability study in HLM, reaction phenotyping study (f_{m_CYP3A} , 0.8; f_{m_CYP2D6} , 0.2; in HLMs), and microsomal binding
	$CL_{int-CYP2D6}$ (μ L/min/mg microsomal protein)	0.464	

	CL _{int-CYP3A4} (μ L/min/mg microsomal protein)	1.86	
	f _{u,mic}	0.45	
	CL _r (L/h)	1.7	30% of estimated total clearance (CL/F, supra) according to the urine excretion of unchanged drug in study TDR12768
Interaction for Pgp (gut)	K _i (μ M)	54	Measured in <i>in vitro</i> MDR1 substrate potential assessment study using a MDCKII-MDR1 cell model

CL_r = Renal clearance; CL_{int-CYP2D6} = intrinsic metabolic clearance assigned to CYP2D6;
 CL_{int-CYP3A4} = intrinsic metabolic clearance assigned to CYP3A4; CYP = Cytochrome P450;
 f_{u,mic} = fraction of unbound drug in the *in vitro* microsomal incubation system; HLM =
 Human liver microsomes; K_i = inhibition constant; LogP = Calculated logarithm of the
 octanol-water partition coefficient; obs = observed; Papp = Apparent permeability
 coefficient; pred = predicted; V_{ss} = Apparent volume of distribution at steady state.

Consistent with the results from an earlier clinical study, food intake had no impact on
 venglustat PK. Thus, the first order absorption parameters (e.g., f_a, K_a) of venglustat under fed
 conditions were kept the same as the ones used in fasting status. The drug distribution of
 venglustat was reflected by a minimal PBPK model with a single adjustable compartment,
 which considered both liver and intestinal metabolism, and lumped other tissues together.
 The transporter impact on venglustat PK was assumed to be minimal.

Model performance was confirmed by predicted to observed venglustat exposure ratios of
 0.93 to 1.2 after single or repeated oral doses and 1.1 to 1.3 for venglustat alone or when co-
 administered with itraconazole. Venglustat exposure following co-administration with
 moderate (fluconazole, and fluvoxamine with CYP2D6 inhibition turned off) and weak
 (cimetidine with CYP2D6 inhibition turned off) CYP3A inhibitors were predicted to be
 1.52-, 1.08-, and 1.08-fold higher compared to venglustat alone, respectively (see Example
 5).

For oral administration, the first order absorption was assumed in all simulations. Values of
 the fraction absorbed (f_a) and first order absorption rate constant (K_a) were from an estimate
 of *in vivo* permeability, P_{eff,man}, which, in turn, was extrapolated from Caco-2 data using
 standard assays. The intestinal availability (F_g) was predicted by the Q_{gut} model, which

represents a nominal blood flow and is a hybrid parameter reflecting drug absorption rate from the gut lumen, removal of drug from the enterocyte by the enterocytic blood supply and the volume of enterocytes. In the absence of any information on active drug uptake into the enterocyte, $f_{u,gut}$ was set at a default value of 1 (assuming that there is insufficient time for plasma protein binding equilibrium or erythrocyte uptake before the drug is removed from the basolateral side of the enterocyte). The calculation of gut intrinsic clearance ($CL_{uG,int}$) was based on the assumption the intrinsic clearance per pmol CYP is the same in both gut and liver.

Unbound fraction in plasma ($f_{u,p}$), blood-to-plasma ratio (B/P) and mean percent unbound to human liver microsome proteins ($f_{u,mic}$) were measured for venglustat using standard assays. The clinical data from completed Phase 1 studies were first modelled using population PK (POPPK) method in order to derive PK parameters for PBPK model inputs (e.g., Distribution parameters, V_{ss} and SAC). The fractional metabolism (f_m) by CYP3A4 and CYP2D6 were based on the *in vitro* intrinsic metabolic clearance data. In order to recover the *in vivo* clearance in PBPK simulations, CYP3A4 and CYP2D6-mediated intrinsic clearance was calculated using the Simcyp[®] built-in retrograde calculator based on f_m and oral clearance (CL/F) from the preliminary POPPK model. Based on earlier studies, the contribution of the renal components to the *in vivo* clearance was estimated to be approximately 30%. The IC_{50} value of venglustat against human MDR1-mediated transport was determined in house using a standard assay.

Clinical PK data for model verification

Concentration-time data of venglustat from the Phase 1 single ascending dose and multiple ascending dose clinical trials (Example 3) were used for venglustat model verification in healthy subjects. The venglustat PBPK model was further verified for PK prediction in the absence and presence of itraconazole, a strong CYP3A inhibitor, in healthy subjects using available data from a clinical DDI study (Example 4). A summary of the clinical study design for studies used for venglustat PBPK model verification is provided in Table 3.

Table 3: *Studies used for venglustat PBPK model verification*

Dose (mg, measured as free base)	N	Male/Female (%)	Age (years)	Dosing regimen
11.2	6	100/0	19-31	Day 1 : Single dose
18.6	6	100/0	24-45	Day 1 : Single dose
112	5	100/0	25-35	Day 1 : Single dose
3.72	9	44.4/55.6	21-41	Repeated dosing, QD for 14 days
7.44	9	55.6/44.4	19-39	Repeated dosing, QD for 14 days
14.9	9	76.7/33.3	23-43	Repeated dosing, QD for 14 days
15	8	100/0	20-43	Treatment Period 1: 15 mg venglustat SD on Day 1; Treatment Period 2: 15 mg venglustat SD on Day 6 Itraconazole 100 mg BID from Day 1 to Day 12

The verification of itraconazole and its primary metabolite PBPK models were performed using their PK data from the study in Example 4.

Simulations were conducted with 10 virtual trials at each dose and dosing regimen. Simcyp®
5 simulates variability in the “Sim-Healthy Volunteers” population using a Monte Carlo
approach. Inter-individual physiological variability (height, weight, age, lymphatic flows,
etc.) and variation in phenotype, if any, is calculated automatically using databases within the
library. The “PK profiles” option was selected for the present analysis. Hence, all calculations
(dynamic modeling) are time- and concentration-dependent. The overlay-to-observations
10 option was used to allow the verification of the PBPK model based on the comparison of the
concentration-time profiles between observations and predictions. In order to derive PK
parameters (e.g., AUC), simulations were performed at least 3 half-lives of venglustat in
healthy subjects, for groups receiving a single dose. For the groups receiving multiple doses,
simulations were performed until the end of the dosing interval of the last dose, as described,
15 e.g., in the clinical studies disclosed herein.

Verification of the venglustat PBPK model in healthy subjects consisted of:

- A. Graphical comparison of mean (5th and 95th percentile) predicted plasma concentration (venglustat) and individual observed plasma concentrations from Phase 1 trials (Examples 3 and 4).
- 5 B. The observed venglustat exposures ($C_{\max}$, AUC [single dose], AUC_{0-24h} [repeated dosing]) in the clinical study were compared to those predicted by Simcyp[®]. Observed and predicted PK parameters with corresponding mean ratios (predicted/observed) were also computed. These ratios should be within a two-fold interval [0.5-2].
- C. The performance of the Simcyp[®] V17 built-in model for CYP3A inhibitor
10 itraconazole (SVItraconazole_Fed Capsule) and its primary metabolite (SV-OH-Itraconazole) model was verified by comparing the model predicted and observed data from clinical studies in healthy subjects (Example 4). The PBPK model performance for the prediction of venglustat-itraconazole interaction was verified using the following methods:
 - 15 • Visual predictive check comparing the model predicted mean and 90% prediction interval of plasma concentration time profiles to that of the individual observed data of venglustat, itraconazole, and OH-itraconazole;
 - Comparing PBPK-predicted PK parameters to observed data of itraconazole and OH-itraconazole (steady state $C_{\max}$, C_{trough} , AUC_{0-12h}) with corresponding mean ratios
20 (predicted/observed);
 - Observed and predicted drug interaction ratios of venglustat PK ($C_{\max}$ ratio, AUC_{last} ratio, and AUC ratio) with corresponding geometric mean ratios (predicted divided by observed) were also computed. The predicted vs. observed values should be within a two-fold interval [0.5-2].
- 25 The final PBPK model was used to predict the effect of CYP3A4 inhibitors on the steady state PK of venglustat in healthy subjects. Each simulation was conducted with 10 virtual trials of 10 subjects, who are co-administered with the inhibitor, aged from 18 to 65 years old, with a male/female ratio of 50/50, following venglustat repeated dosing to reach steady state. The library virtual population, “Sim-Healthy Volunteers”, was implemented for model

application. Study design varied dependent on the inhibitor properties and the assumed clinical scenarios. Simulations were run for long enough to reach steady state PK for venglustat and CYP3A inhibitors in healthy subjects, when co-administered.

For predicting DDI between venglustat and CYP3A inhibitors, 2 scenarios were assessed, i.e., first, assuming that subjects are already on venglustat treatment and need CYP3A inhibitor comedication and second, assuming that subjects are already on CYP3A inhibitor medication before starting venglustat treatment. Simulation study design for each of these scenarios for each perpetrator is described as follows. For the inhibitors, generally the maximum dose and dose regimen most-used in clinic or the highest approved dosage was chosen to maximize the DDI potential.

Each virtual subject received multiple oral doses of venglustat 15 mg QD or 8 mg QD from Day 1. The repeated doses of itraconazole at 100 mg BID was co-administered with venglustat from Day 6 to Day 17 in healthy subjects.

To simulate venglustat exposure when co-administered with strong CYP3A inhibitors (e.g., itraconazole), the following clinical scenario was assumed:

- Each virtual subject received multiple oral doses of venglustat 15 mg QD from Day 1 to Day 5, and then switch to 8 mg QD from Day 6 to Day 17. The repeated doses of itraconazole at 100 mg BID was co-administered with venglustat from Day 6 to Day 17 in healthy subjects.
- Each virtual subject received multiple oral doses of itraconazole at 100 mg BID from Day 1. The repeated doses of venglustat at 15 mg QD or 8 mg QD was co-administered with itraconazole from Day 10 until venglustat achieved steady state.

As a final step, the model described above was compared to a similar model built using an updated version of Simcyp® (V19) having updated library models of SV-Itraconazole_fed Capsule. In V19, besides first-order absorption model as the default itraconazole cmpz file, the user can select advanced dissolution absorption and metabolism (ADAM) option to reflect the factors influencing the rate and extent of oral drug absorption. Based on the assessment shown above, it was concluded that the itraconazole compound library file used in V17 adequately described itraconazole PK. In comparison with V17, the majority of model parameters are kept the same in V19 itraconazole cmpz library files. The slight difference in

the predicted V_{ss} probably resulted from the updated system parameter values, and the addition of inhibition parameters against multiple transporters expressed in gut and liver. To further understand the impact of V19 updates on the prediction results, a partial verification of both itraconazole models (first order absorption and ADAM models) using Example 4 data was conducted. The simulation settings were identical to those shown above.

The predicted venglustat PK parameters for the V19 model, including C_{max} , AUC_{last} , AUC and drug interaction ratios, were generally comparable to the values obtained using the V17 model. However, the predictive accuracy of the V19 itraconazole model with ADMA absorption was not acceptable and so it was not used for further modelling.

10 *Results – single and repeated QD dosing of venglustat*

The observed and predicted venglustat concentrations in the healthy male subjects after a single oral doses of venglustat at 11.2 mg, 18.6 mg, and 112 mg (calculated as free base) using the PBPK model are presented in Figure 3 and Figure 4. The observed venglustat PK parameters in the clinical study were compared to those predicted by the PBPK model and the results are shown in Table 4 below.

Table 4: *Observed (clinical study) and predicted mean PK parameters (CV %) of venglustat in healthy male subjects following single oral administration of venglustat*

Dose (mg) ^a	Parameters		C_{max} (ng/mL)	AUC (ng·h/mL)
11.2	Observed	Mean (N = 6)	53.0	2070
		CV (%)	31.5	29.0
	Predicted	Mean (N = 60)	56.3	2120
		CV (%)	35	32
	Predicted to Observed Ratio		1.1	1.0
18.6	Observed	Mean (N = 6)	84.4	3810
		CV (%)	37.7	28.4
	Predicted	Mean (N = 60)	91.4	3570
		CV (%)	38	32
	Predicted to Observed Ratio		1.1	0.94
112	Observed	Mean (N = 5)	529	20600
		CV (%)	20.7	32.2
	Predicted	Mean (N = 50)	556	22000
		CV (%)	38	30
	Predicted to Observed Ratio		1.1	1.1

^a Shows nominal doses of the free base form; the corresponding malate salt doses were 15 mg, 25 mg and 150 mg in the clinical study.

The observed and predicted venglustat concentrations in the healthy male and female subjects after repeated QD doses of venglustat at 3.72 mg, 7.44 mg, and 14.9 mg using the PBPK model are presented in Figure 5 and Figure 6. The observed venglustat PK parameters in the clinical study were compared to those predicted by the PBPK model in Table 5 below.

Table 5: Observed (clinical study) and predicted mean PK parameters (CV %) of venglustat in healthy subjects following repeated oral administration of venglustat

Dose (mg) ^a	Parameters	Day 1		Day 14		
		C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	
3.72	Observed	Mean (N = 9)	18.5	296	37.0	642
		CV (%)	17.3	18.3	17.2	18.8
	Predicted	Mean (N = 90)	20.3	303	42.3	741
		CV (%)	40	30	28	29
	Predicted to Observed Ratio		1.1	1.0	1.1	1.2
7.44	Observed	Mean (N = 9)	38.5	635	89.7	1550
		CV (%)	19.3	20.8	32.5	30.0
	Predicted	Mean (N = 90)	39.7	593	83.6	1470
		CV (%)	40	30	28	30
	Predicted to Observed Ratio		1.0	0.93	0.93	0.95
14.9	Observed	Mean (N = 9)	68.0	1100	142	2420
		CV (%)	23.1	19.2	28.3	29.2
	Predicted	Mean (N = 90)	78.6	1180	167	2960
		CV (%)	39	28	26	29
	Predicted to Observed Ratio		1.2	1.1	1.2	1.2

^a Shows nominal doses of the free base form; the corresponding malate salt doses were 5 mg, 10 mg, and 20 mg in the clinical study.

As demonstrated by the graphical comparisons shown from Figure 3 to Figure 6, most of the individual observed concentration-time points were within the 5th and 95th percentile of predicted plasma concentrations. The PBPK model was able to adequately predict venglustat exposures on Day 1 with single dose and Day 14 after repeated QD doses of venglustat in healthy subjects. The difference between mean observed and predicted PK parameters was

within 20% with mean predicted/observed ratios in the range of 0.93–1.2, which were within the predefined two-fold interval.

Results – single dose of venglustat in the absence and presence of itraconazole

The simulated plasma concentration-time profiles of venglustat after single dose of 15 mg
5 calculated as free base) on Day 6, in the absence and presence of 100 mg itraconazole co-
administered BID from day 1 to day 12 are shown in Figures 7 and 8, respectively.
Venglustat (15 mg single dose) was administered alone in treatment period 1 (as in Example
4). The observed and simulated PK profiles are shown in Figure 7A and Figure 8A, but
during a restricted time-frame of 120 to 288 hours. Virtual healthy male subjects were
10 generated and randomly assigned to ten different trials of 8 subjects to indicate the variability
between groups. For each simulation, concentration-time profiles representative of the total
virtual population (n = 80) are shown. The predicted mean C_{max}, AUC_{last}, and AUC ratios are
shown in Table 6 below.

Table 6: *Observed (Example 4) and predicted mean PK parameters (CV %) of*
15 *venglustat in healthy male subjects following single oral dose of 15 mg on Day 6 without*
and with co-medication of itraconazole 100 mg BID for 12 days

Parameters		Without interaction			With interaction			Treatment Ratio*		
		C _{max}	AUC _{last}	AUC	C _{max}	AUC _{last}	AUC	C _{max} Ratio	AUC _{last} Ratio	AUC Ratio
Observed (N=8)	Mean	57.5	2330	2400	63.2	4110	4810	1.12	1.79	2.03
	CV (%)	34	38	39	27	31	34	(1.05– 1.20)	(1.61– 1.99)	(1.81– 2.27)
Predicted (N=80)	Mean	71.0	2820	3010	74.1	4390	5320	1.04	1.56	1.76
	CV (%)	36	28	30	36	28	32	(1.04– 1.05)	(1.53– 1.60)	(1.71– 1.80)
Predicted to Observed Ratio		1.2	1.2	1.3	1.2	1.1	1.1	0.93	0.87	0.87

* The C_{max}, AUC_{last}, and AUC ratios for venglustat in the presence and absence of itraconazole are presented as the geometric mean with 90% CI in parentheses.

Simulated concentration-time profiles of itraconazole and its primary metabolite (hydroxyitraconazole) with observed values overlaid are shown in Figures 9 and 10, respectively. The observed PK parameters of itraconazole and hydroxyitraconazole in the clinical study (Example 4) were compared to those predicted by the PBPK model in Table 7 below.

Table 7: *Observed (Example 4) and predicted mean PK parameters (CV %) of itraconazole and hydroxyitraconazole on Day 6 in healthy male subjects following repeated oral administration of itraconazole capsule 100 mg BID with a single dose of venglustat under fed conditions*

PK Parameters on Day 6		Itraconazole		Hydroxyitraconazole			
		C _{max} (ng/mL)	t _{max} * (h)	AUC ₀₋₁₂ (ng.h/mL)	C _{max} (ng/mL)	t _{max} * (h)	AUC ₀₋₁₂ (ng.h/mL)
Observed	Mean (N=8)	656	4.50	5090	951	5.00	9550
	CV (%)	25	(3.00–5.00)	24	20	(4.00–5.02)	19
Predicted	Mean (N=80)	393	3.13	4040	737	4.61	8100
	CV (%)	99	(1.61–4.87)	111	87	(1.67–12.0)	97
Predicted to Observed Ratio		0.60	0.70	0.79	0.77	0.92	0.85

* The observed/predicted t_{max} values are presented as the median with minimum to maximum values in parentheses.

As demonstrated by the graphical comparisons shown from Figures 7 to 10, nearly all of the individual observed concentration-time points were within the 5th and 95th percentile of predicted plasma concentrations. The PBPK model was able to adequately predict venglustat exposures without and with co-medication of itraconazole in healthy male subjects. The ratios of the geometric mean of the observed and predicted treatment ratios (C_{max} ratio, AUC_{last} ratio, AUC ratio) were approximately 0.9. Hence, the model performance was considered acceptable. In addition, the PBPK model accurately captured the PK profiles of itraconazole and hydroxyitraconazole on Day 6 after repeated BID doses in healthy subjects, with the difference between observed and predicted within 2-fold. Together, the evidence collected confirmed the adequacy of the PBPK model for venglustat DDI predictions with CYP3A inhibitors, including itraconazole.

Example 6: Application of the PBPK model to predict steady-state plasma concentrations of venglustat co-administered with CYP3A inhibitors

The verified PBPK model of Example 5 was used to predict venglustat PK with 8 and 15 mg repeated doses in healthy subjects co-administered with other CYP3A inhibitors to guide
5 dose recommendations.

Methods

Simulation of pharmacokinetics (PK) of venglustat was conducted with 10 virtual trials of 10 subjects, co-administered with a CYP3A inhibitor, aged from 18 to 65 years old, with a male/female ratio of 50/50, following repeated dosing of venglustat to reach steady state.
10 Simcyp® built-in “Sim-Healthy Volunteers” was used to generate virtual population. Predicted PK parameters and DDI ratios of venglustat (C_{max} , AUC_{tau} , C_{max} ratio, and AUC_{tau} ratio) for the last dose were calculated.

Predictions were made of steady state plasma concentrations of venglustat following repeated oral dosing of venglustat with: (i) fluconazole, a moderate CYP3A4 inhibitor; (ii)
15 fluvoxamine, a moderate CYP3A4 inhibitor; and (iii) cimetidine, a weak CYP3A inhibitor, in healthy subjects. CYP2D6 inhibition was turned off in the model.

Simcyp® V17 library model for fluconazole (SV-Fluconazole), a moderate CYP3A inhibitor, was used for model application without any change. Model input parameters for fluvoxamine (a moderate CYP3A inhibitor) and cimetidine (a weak CYP3A inhibitor) in the simulations
20 had the default values indicated in the compound library files (SV-Fluvoxamine and SV-Cimetidin, respectively) within the Simcyp Simulator (V17), except for a minor modification of turning off the inhibitory effects on CYP2D6, since both CYP3A and CYP2D6 inhibition had been built in the library models. This allowed for the assessment of the impact of fluvoxamine and cimetidine on venglustat solely via the CYP3A pathway.

25 The fluconazole PBPK model was further verified using clinical data from the literature (Olkola *et al.*, Anesth. Analg. (1996) 82(3):511-516), regarding the effect of fluconazole on the midazolam exposure. The predicted midazolam C_{max} and AUC ratios in healthy subjects following single oral administration of midazolam 7.5 mg on day 1 and on day 6 in the absence and presence of fluconazole are shown in Table 8 below. To compare with the
30 observed AUC ratios, which were derived from reported AUC from time 0 to infinity, two

independent simulations were conducted to generate the corresponding ratios for midazolam on day 1 and day 6.

Table 8: *Observed and predicted PK parameters of midazolam in healthy subjects following single oral dose of 7.5 mg midazolam on day 1 and day 6 without and with co-medication of fluconazole (400 mg SD on day 1 and 200 mg QD from day 2 to day 6)*

Clinical Study for CYP3A Inhibitor Model Verification	CYP3A Substrate	PK Parameters		Treatment Ratio*	
				C _{max} Ratio	AUC Ratio
Fluconazole: (Olkola <i>et al.</i> , 1996)	Midazolam (Day 1)	Observed	Mean (N=12)	2.50	3.51
		Predicted	Mean (N=120)	1.92	3.11
			Trial Range	1.75 – 2.17	2.89 – 3.52
			Predicted to Observed Ratio	0.77	0.89
	Midazolam (Day 6)	Observed	Mean (N=12)	1.74	3.60
		Predicted	Mean (N=120)	2.10	3.75
			Trial Range	1.85 – 2.30	3.10 – 4.08
			Predicted to Observed Ratio	1.2	1.0

* The observed C_{max} and AUC ratios are expressed as arithmetic mean values. Predicted values show arithmetic mean, and trial range from 10 simulated trials matching the clinical study design.

The ratios of predicted to observed PK parameters were approximately 1. The results indicated the good quality of the model for DDI predictions with fluconazole as a moderate CYP3A inhibitor.

These modified PBPK models were verified for the impact of fluvoxamine/cimetidine on sensitive CYP3A substrates based on published clinical data which studied the effect of fluvoxamine on a sensitive CYP3A substrate (midazolam), as well as the effect of cimetidine on a number of sensitive CYP3A substrates (midazolam, nifedipine, and sildenafil) (See, e.g., Lam *et al.*, J. Clin. Pharmacol. (2003) 43(11):1274-1282; Fee *et al.*, Clin. Pharmacol. Ther. (1987) 41(1):80-84; Schwartz *et al.*, Clin. Pharmacol. Ther. (1988) 43(6):673-80; and Wilner *et al.*, Br. J. Clin. Pharmacol. (2002) 53(Suppl 1):31S-36S). The predicted mean C_{max}, and AUC ratios in healthy subjects following single oral dose of midazolam / nifedipine / sildenafil in the absence and presence of a CYP3A inhibitor are shown in Table 9 below.

Table 9: Observed and predicted PK parameters of CYP3A substrates in healthy subjects following single oral dose of 10 mg midazolam without and with co-medication of fluvoxamine (50 mg, BID), and 15 mg midazolam, 20 mg nifedipine, or 50 mg sildenafil without and with co-medication of cimetidine at dose regimes of 400 mg/BID, 300 mg/QD, or 800 mg/QD, respectively

Clinical Study for CYP3A Inhibitor Model Verification	CYP3A Substrate	PK Parameters		Treatment Ratio*	
				C _{max} Ratio	AUC Ratio
Fluvoxamine: (Lam <i>et al.</i> , 2003)	Midazolam	Observed	Mean (N=10)	1.38	1.39
		Predicted	Mean (N=100)	1.25	1.37
			Trial Range	1.17 – 1.32	1.23 – 1.47
			Predicted to Observed Ratio	0.91	0.99
		Cimetidine: (Fee <i>et al.</i> , 1987)	Midazolam	Observed	Mean (N=8)
Predicted	Mean (N=80)			1.32	1.39
	Trial Range			1.30 – 1.36	1.36 – 1.43
	Predicted to Observed Ratio			NA	1.0
Cimetidine: (Schwartz <i>et al.</i> , 1988)	Nifedipine			Observed	Mean (N=11)
		Predicted	Mean (N=110)	1.20	1.32
			Trial Range	1.17 – 1.22	1.29 – 1.34
			Predicted to Observed Ratio	0.75	0.73
		Cimetidine: (Wilner <i>et al.</i> , 2002)	Sildenafil [†]	Observed	Mean (N=10)
Predicted	95% CI			(1.14, 2.09)	(1.21, 2.03)
	Mean (N=100)			1.36	1.41
	95% CI			(1.33, 1.38)	(1.38, 1.43)
Predicted to Observed Ratio	0.88			0.90	

NA = Not Applicable

* Other than the case of Wilner *et al.* (Br. J. Clin. Pharmacol. (2002) 53(Suppl 1):31S-36S), the observed C_{max} and AUC ratios are expressed as arithmetic mean values. Predicted values show mean, and trial range from 10 simulated trials matching the clinical study design.

† The observed and predicted C_{max} or AUC ratios of sildenafil in the presence and absence of cimetidine are presented as the geometric mean with 95% CI in parentheses.

The PBPK model was able to adequately predict the DDI potential of fluvoxamine and cimetidine in healthy subjects. The ratio of predicted to observed PK parameters was approximately 1. Together, the results confirmed the good quality of the model for DDI

predictions with fluvoxamine and cimetidine as the moderate and weak CYP3A inhibitor, respectively.

Impact on venglustat exposure of co-administering other CYP3A4 inhibitors

Plasma PK parameters of venglustat in healthy subjects after repeated dosing at 15 mg or 8 mg administered in the absence and presence of itraconazole (strong CYP3A inhibitor), fluconazole (moderate CYP3A inhibitor), fluvoxamine (moderate CYP3A inhibitor), and cimetidine were simulated and the results are shown in Table 10 below. Virtual subjects (age, 18-65; Female, 50%) were generated and randomly assigned to ten different trials of 10 subjects to indicate the variability between groups. The predicted mean C_{max} and AUC_{tau} ratios of venglustat at steady state in the presence and absence of the corresponding inhibitor were also generated.

Table 10: Steady state venglustat PK parameters in healthy subjects following repeated administration at 15 mg or 8 mg with co-administration of a CYP3A inhibitor

Dosing regimen		Predicted PK parameter mean (5 th -95 th centile) (N=100)		Ratio mean (5 th -95 th percentile) (N=100)	
Venglustat	CYP3A Inhibitor	C_{max} (ng/mL)	AUC_{tau} (ng.h/mL)	C_{max}	AUC_{tau}
15 mg QD for 17 days	Itraconazole (100 mg BID from days 6-17)	259 (132–367)	5170 (2640–7550)	1.51 (1.27–1.77)	1.69 (1.36–2.03)
8 mg QD for 17 days	Itraconazole (100 mg BID from days 6-17)	138 (70.6–196)	2760 (1410–4030)	1.51 (1.27–1.78)	1.69 (1.36–2.03)
15 mg QD for 5 days; 8 mg QD days 6-17	Itraconazole (100 mg BID from days 6-17)	141 (70.9–198)	2810 (1410–4090)	1.52 (1.28–1.80)	1.71 (1.38–2.06)
15 mg QD from days 10-26	Itraconazole (100 mg BID for 26 days)	262 (133–369)	5240 (2640–7640)	1.53 (1.28–1.81)	1.72 (1.37–2.07)
8 mg QD from days 10-26	Itraconazole (100 mg BID for 26 days)	140 (70.9–197)	2790 (1410–4080)	1.53 (1.28–1.81)	1.72 (1.37–2.07)
15 mg QD for 17 days	Fluconazole (400 mg QD on day 6, then 200 mg QD on days 7-17)	233 (151–338)	4560 (2860–6530)	1.37 (1.18–1.57)	1.52 (1.23–1.88)
15 mg QD from days 6-17	Fluconazole (400 mg QD on day 1, then 200 mg QD on days 2-17)	230 (149–334)	4490 (2860–6480)	1.36 (1.17–1.57)	1.51 (1.23–1.88)
15 mg QD for 17 days	Fluvoxamine (100 mg BID from days 6-17)	184 (105–281)	3310 (1660–4910)	1.06 (1.03–1.11)	1.08 (1.03–1.15)

15 mg QD from days 6-17	Fluvoxamine (100 mg BID for 17 days)	183 (105–278)	3280 (1660–4870)	1.06 (1.03–1.11)	1.08 (1.03–1.15)
15 mg QD for 17 days	Cimetidine (400 mg TID from days 6-17)	182 (103–277)	3270 (1630–4770)	1.06 (1.03–1.09)	1.08 (1.04–1.12)
15 mg QD from days 6-17	Cimetidine (400 mg TID for 17 days)	181 (103–276)	3230 (1630–4650)	1.06 (1.03–1.08)	1.08 (1.04–1.12)

NB: The predicted C_{max} and AUC_{tau} at steady state represent mathematic mean values of 100 virtual subjects in 10 trials. The predicted C_{max} and AUC_{tau} ratios represent mathematic mean values (with an inhibitor compared to without an inhibitor) of 100 virtual subjects in 10 trials.

5 Conclusions

The present analysis allowed for the development of a PBPK model for venglustat in healthy adults based on physicochemical, *in vitro* / *in vivo* absorption, distribution, metabolism, and excretion (ADME) data available. This model was fully validated using information from venglustat single and multiple ascending dose clinical studies (Example 3), as well as the clinical DDI study with itraconazole as the strong CYP3A inhibitor (Example 4). The predicted plasma concentration profiles (venglustat, itraconazole and hydroxyitraconazole) agreed with the observed data in the clinical studies. Nearly all the observed individual concentrations fell into the predicted 90% confidence interval, and the predicted versus observed ratios for PK parameters were within 2-fold. The drug interaction ratios were also well captured, which further confirmed the contribution of CYP3A4-mediated metabolism to the overall clearance of venglustat in healthy subjects. Therefore, the venglustat model developed and verified using Simcyp V17 could be used to predict PK of venglustat when co-administered with other CYP3A inhibitors.

In April 2020, Simcyp Ltd released the Simcyp® Population Based Simulator V19, with updated library models of SV-Itraconazole_Fed Capsule. Based on the assessment set out above, it was decided to utilize the itraconazole PBPK model V17 for the final simulations. The library model of SV-Fluconazole was used without any change and further verification with the available clinical data demonstrated its good performance for model application. The modified Simcyp library models of fluvoxamine/cimetidine were verified for the impact on sensitive CYP3A substrates based on published clinical data, as documented above, and the model performance was considered acceptable for model applications.

- Collectively, venglustat PBPK model was developed using Simcyp V17. This model was verified for PK prediction in the absence and presence of a strong CYP3A inhibitor (itraconazole) in healthy adult subjects. Co-administration of venglustat with CYP3A inhibitors is predicted to result in higher exposures, with the magnitude of the effect
- 5 depending to an extent on the potency of the inhibitor. Venglustat steady state AUC_{tau} following co-administration with strong and moderate CYP3A inhibitors were predicted to be 1.69 fold higher with itraconazole, 1.52 fold higher with fluconazole, and 1.08 fold higher with fluvoxamine. The impact of weak CYP3A inhibitor cimetidine on venglustat systemic exposure was considered to be minimal (1.08 fold higher).
- 10 These results indicate that concomitant administration of some (but not all) CYP3A4 inhibitors may require dosage adjustment of venglustat to maximise the safety and efficacy of treatment. The results observed in the model between different inhibitors also suggest that the impact of any given inhibitor on venglustat exposure is not readily predictable, such that choosing the appropriate dose adjustment might not be straightforward without guidance
- 15 from the PBPK model developed herein.

* * * *

- It is to be understood that while the disclosure has been described in conjunction with the above embodiments, that the foregoing description and examples are intended to illustrate
- 20 and not limit the scope of the disclosure. Other aspects, advantages, and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

- In addition, where features or aspects are described in terms of Markush groups, those skilled in the art will recognize that such features or aspects are also thereby described in terms of
- 25 any individual member or subgroup of members of the Markush group.

All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entirety, to the same extent as if each were incorporated by reference individually. In case of conflict, the present specification, including definitions, will control.

CLAIMS

1. A method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of venglustat or a pharmaceutically acceptable salt thereof, wherein said subject is concurrently being administered a strong or moderate inhibitor of CYP3A4.
2. A method for treating a disease or disorder in a subject in need thereof, the method comprising administering to the subject an effective amount of venglustat or a pharmaceutically acceptable salt thereof, wherein said subject is concurrently being administered an inhibitor of CYP3A4, whereby the plasma exposure (e.g., AUC) of venglustat is increased by between about 5% and 25% as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor.
3. The method of claim 2, wherein the venglustat or the pharmaceutically acceptable salt thereof is administered in a dosage of about 12 mg per day or a dosage of about 15 mg per day (calculated as the free base).
4. The method of claim 1, wherein the CYP3A4 inhibitor is a strong inhibitor which increases the plasma exposure of venglustat by between about 60% and 120% as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and wherein the venglustat or pharmaceutically acceptable salt thereof is administered in a dosage of between about 4 mg and 15 mg per day (calculated as the free base).
5. The method of claim 4, wherein the venglustat or the pharmaceutically acceptable salt thereof is administered in a dosage of about 8 mg per day (calculated as the free base).
6. The method of claim 1, wherein the CYP3A4 inhibitor is a moderate inhibitor which increases the plasma exposure of venglustat by between about 40% and 60% as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor, and the venglustat or the pharmaceutically acceptable salt thereof is administered in a dosage of between about 12 mg and 15 mg per day (calculated as the free base).

7. The method of claim 6, wherein the venglustat or the pharmaceutically acceptable salt thereof is administered in a dosage of about 15 mg per day (calculated as the free base).
8. The method of any one of claims 1-7, wherein the venglustat is in the form of venglustat free base, a pharmaceutically acceptable salt of venglustat, or a prodrug of venglustat, optionally venglustat L-malate salt.
9. The method of any one of claims 1-8, wherein the venglustat or the pharmaceutically acceptable salt thereof and the CYP3A4 inhibitor are administered in combination, e.g., in the same pharmaceutical composition.
10. The method of any one of claims 1-9, wherein the venglustat or the pharmaceutically acceptable salt thereof is administered orally and the CYP3A4 inhibitor is administered transmucosally, intravenously, or orally.
11. The method of any one of claims 1-10, wherein the disease or disorder is selected from a lysosomal storage disease (e.g., Gaucher disease or Fabry disease), a proteinopathy (e.g., Alzheimer's disease, Parkinson's disease, or Huntington's disease), a cystic disease (e.g., polycystic kidney disease), and a ciliopathy (e.g., Bardet-Biedl syndrome).
12. The method of any one of claims 1-11, wherein the subject has a co-morbidity selected from a fungal infection, a viral infection, a bacterial infection, a mood disorder, and a cancer.
13. Venglustat or a pharmaceutically acceptable salt thereof (or a combination of venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor, e.g., a composition comprising venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor) for use in a method as defined in any one of claims 1-12.
14. Use of venglustat or a pharmaceutically acceptable salt thereof (or a combination of venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor, e.g., a composition comprising venglustat or a pharmaceutically acceptable salt thereof and a CYP3A4 inhibitor) in the manufacture of a medicament for use in a method as defined in any one of claims 1-12.
15. A method for optimizing (e.g., reducing) the dosage of venglustat in a subject being treated with or intended to be treated with venglustat or a pharmaceutically acceptable salt

thereof, the method comprising administering to the subject a strong or moderate CYP3A4 inhibitor.

16. A method for minimising the drug-drug interaction between venglustat and a moderate or strong CYP3A4 inhibitor in a subject suffering from a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with said CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) adjusting the dosage of the venglustat or the pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25% increase.

17. A method for establishing the correct dosage of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) reducing the dosage of the venglustat or the pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25%.

18. A method for improving a dosage regimen of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof, the method comprising: (i) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (ii) reducing the dosage of the venglustat or the pharmaceutically acceptable salt thereof if the change in plasma exposure is an increase of more than about 25%.

19. A method for managing the risk of venglustat/CYP3A4 inhibitor interaction in a subject having a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, the method comprising: (i) initiating treatment in the subject with venglustat or a pharmaceutically acceptable salt thereof at a standard

indicated dose; (ii) determining the change in plasma exposure of venglustat when venglustat or a pharmaceutically acceptable salt thereof is administered in conjunction with a strong or moderate CYP3A4 inhibitor, as compared to the exposure resulting from administration of venglustat in the same dosage, form, and regimen in the absence of said CYP3A4 inhibitor; and (iii) reducing the dosage if the change in plasma exposure is an increase of more than about 25%.

20. Use of a strong or moderate CYP3A4 inhibitor in a method for: (a) establishing the correct dosage of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof; (b) improving a dosage regimen of venglustat or a pharmaceutically acceptable salt thereof in a subject in need thereof; or (c) managing the risk of venglustat/CYP3A4 inhibitor interaction in a subject having a disease or disorder which is amenable to treatment with venglustat or a pharmaceutically acceptable salt thereof, wherein the subject is being administered or is intended to be administered said CYP3A4 inhibitor.

21. A method for inhibiting CYP3A4 activity in a subject being treated with venglustat or a pharmaceutically acceptable salt thereof, the method comprising concurrently administering the venglustat or the pharmaceutically acceptable salt thereof with a strong or moderate CYP3A4 inhibitor.

22. A method for improving the therapeutic response to venglustat treatment in a subject in need thereof, the method comprising concurrently administering venglustat or a pharmaceutically acceptable salt thereof with a strong or moderate CYP3A4 inhibitor.

23. A pharmaceutical composition (e.g., an oral pharmaceutical dosage form) comprising venglustat or a pharmaceutically acceptable salt thereof, in combination with a strong or moderate CYP3A4 inhibitor, and at least one pharmaceutically acceptable excipient.

24. The composition of claim 23, wherein the composition is formulated for oral administration.

25. The composition of claim 24, wherein the composition is a dosage form selected from a capsule (e.g., a hard capsule) and a tablet (e.g., a chewable tablet, orally disintegrating tablet, dispersible tablet, or a classic tablet or caplet).

26. A composition as defined in any one of claims 23-25, for use in a method as defined in any one of claims 1-22.