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(54) **Title:** METHODS OF TREATING FABRY DISEASE IN PEDIATRIC PATIENTS

(57) **Abstract:** Provided are methods for the treatment of Fabry disease in adolescent patient.

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METHODS OF TREATING FABRY DISEASE IN PEDIATRIC PATIENTS

TECHNICAL FIELD

[0001] Principles and embodiments of the present invention relate generally to the treatment of Fabry disease.

BACKGROUND

[0002] Many human diseases result from mutations that cause changes in the amino acid sequence of a protein which reduce its stability and may prevent it from folding properly. Proteins generally fold in a specific region of the cell known as the endoplasmic reticulum, or ER. The cell has quality control mechanisms that ensure that proteins are folded into their correct three-dimensional shape before they can move from the ER to the appropriate destination in the cell, a process generally referred to as protein trafficking. Misfolded proteins are often eliminated by the quality control mechanisms after initially being retained in the ER. In certain instances, misfolded proteins can accumulate in the ER before being eliminated. The retention of misfolded proteins in the ER interrupts their proper trafficking, and the resulting reduced biological activity can lead to impaired cellular function and ultimately to disease. In addition, the accumulation of misfolded proteins in the ER may lead to various types of stress on cells, which may also contribute to cellular dysfunction and disease.

[0003] Such mutations can lead to lysosomal storage disorders (LSDs), which are characterized by deficiencies of lysosomal enzymes due to mutations in the genes encoding the lysosomal enzymes. The resultant disease causes the pathologic accumulation of substrates of those enzymes, which include lipids, carbohydrates, and polysaccharides. Although there are many different mutant genotypes associated with each LSD, many of the mutations are missense mutations which can lead to the production of a less stable enzyme. These less stable enzymes are sometimes prematurely degraded by the ER-associated degradation pathway. This results in the enzyme deficiency in the lysosome, and the pathologic accumulation of substrate. Such mutant enzymes are sometimes referred to in the pertinent art as "folding mutants" or "conformational mutants."

[0004] Fabry disease, an LSD, is a progressive, X-linked inborn error of glycosphingolipid metabolism caused by a deficiency in the lysosomal enzyme α-galactosidase

A (α-Gal A) as a result of mutations in the α-Gal A gene (GLA). Despite being an X-linked disorder, females can express varying degrees of clinical manifestations.

[0005] Fabry disease is classified by clinical manifestations into three groups: a classic form with generalized vasculopathy, an atypical variant form with clinical manifestations limited to cardiac tissue, and later-onset disease, which includes female carriers with mild to severe forms of the disease. The clinical manifestations include angiokeratoma (small, raised reddish-purple blemishes on the skin), acroparesthesias (burning in hands and feet), hypohidrosis (decreased ability to sweat), and characteristic corneal and lenticular opacities (*The Metabolic and Molecular Bases of Inherited Disease*, 8th Edition 2001, Scriver et al., ed., pp. 3733-3774, McGraw-Hill, New York).

[0006] Fabry is a rare disease with incidence estimated between 1 in 40,000 males to 1 in 117,000 in the general population. Moreover, there are variants of later onset phenotype of Fabry disease that can be under-diagnosed, as they do not present with classical signs and symptoms. This, and newborn screening for Fabry disease, suggests that the actual incidence of Fabry disease can be higher than currently estimated.

[0007] Untreated, life expectancy in Fabry patients is reduced and death usually occurs in the fourth or fifth decade because of vascular disease affecting the kidneys, heart and/or central nervous system. The enzyme deficiency leads to intracellular accumulation of the substrate, globotriaosylceramide (GL-3) in the vascular endothelium and visceral tissues throughout the body. The heart may also become enlarged and the kidneys may become progressively involved. Gradual deterioration of renal function and the development of azotemia, due to glycosphingolipid deposition, usually occur in the third to fifth decades of life, but can occur as early as in the second decade. Renal lesions are found in both hemizygous (male) and heterozygous (female) patients. The affected male's life expectancy is reduced, and death usually occurs in the fourth or fifth decade as a result of vascular disease of the heart, brain, and/or kidneys. Other symptoms include fever and gastrointestinal difficulties, particularly after eating.

[0008] Cardiac disease as a result of Fabry disease occurs in most males and many females. Early cardiac findings include left ventricular enlargement, valvular involvement and conduction abnormalities. Mitral insufficiency is the most frequent valvular lesion typically present in childhood or adolescence. Cerebrovascular manifestations result primarily from multifocal small-vessel involvement and can include thromboses, transient ischemic attacks,

basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, or cerebral hemorrhages. Average age of onset of cerebrovascular manifestations is 33.8 years. Personality change and psychotic behavior can manifest with increasing age.

[0009] Individuals with later-onset Fabry disease can be male or female. Late-onset Fabry disease presents as the atypical variant form, and growing evidence indicates there may be a significant number of "atypical variants" which are unaccounted for in the world. Females, who inherit an X chromosome containing an a-GAL mutation, may exhibit symptoms later in life, significantly increasing the prevalence of this disease. These patients typically first experience disease symptoms in adulthood, and often have disease symptoms focused on a single organ. For example, many males and females with later-onset Fabry disease have enlargement of the left ventricle of the heart. Later-onset Fabry disease may also present in the form of strokes of unknown cause. As the patients advance in age, the cardiac complications of the disease progress, and can lead to death.

[0010] Patients with the milder "cardiac variant" of Fabry diseasenormally have 5-15% of normal a-GAL activity, and present with left ventricular hypertrophy or a cardiomyopathy. These cardiac variant patients remain essentially asymptomatic when their classically affected counterparts are severely compromised. Cardiac variants were found in 1 1% of adult male patients with unexplained left ventricular hypertrophic cardiomyopathy, suggesting that Fabry disease may be more frequent than previously estimated (*Nakao et al.*, N. Engl. J. Med. 1995; 333: 288-293).

[0011] There have been several approaches to treatment of Fabry disease. One approved therapy for treating Fabry disease is enzyme replacement therapy (ERT), which typically involves intravenous, infusion of a purified form of the corresponding wild-type protein (Fabrazyme®, Genzyme Corp.). ERT has several drawbacks, however. One of the main complications with enzyme replacement therapy is rapid degradation of the infused protein, which leads to the need for numerous, costly high dose infusions. ERT has several additional caveats, such as difficulties with large-scale generation, purification, and storage of properly folded protein; obtaining glycosylated native protein; generation of an anti-protein immune response; and inability of protein to cross the blood-brain barrier to mitigate central nervous system pathologies (i.e., low bioavailability). In addition, replacement enzyme cannot

penetrate the heart or kidney in sufficient amounts to reduce substrate accumulation in the renal podocytes or cardiac myocytes, which figure prominently in Fabry pathology.

[0012] Additionally, ERT typically involves intravenous, infusion of a purified form of the corresponding wild-type protein. Two α-Gal A products are currently available for the treatment of Fabry disease: agalsidase alfa (Replagal®, Shire Human Genetic Therapies) and agalsidase beta (Fabrazyme®; Sanofi Genzyme Corporation). While ERT is effective in many settings, the treatment also has limitations. ERT has not been demonstrated to decrease the risk of stroke, cardiac muscle responds slowly, and GL-3 elimination from some of the cell types of the kidneys is limited. Some patients also develop immune reactions to ERT.

[0013] Another approach to treating some enzyme deficiencies involves the use of small molecule inhibitors to reduce production of the natural substrate of deficient enzyme proteins, thereby ameliorating the pathology. This "substrate reduction" approach has been specifically described for a class of about 40 related enzyme disorders called lysosomal storage disorders that include glycosphingolipid storage disorders. The small molecule inhibitors proposed for use as therapy are specific for inhibiting the enzymes involved in synthesis of glycolipids, reducing the amount of cellular glycolipid that needs to be broken down by the deficient enzyme.

[0014] A third approach to treating Fabry disease has been treatment with what are called pharmacological chaperones (PCs). Such PCs include small molecule inhibitors of α-Gal A, which can bind to the α-Gal A to increase the stability of both mutant enzyme and the corresponding wild type.

[0015] Accordingly, there remains a need for therapies for the treatment of Fabry disease.

SUMMARY

[0016] Various aspects of the present invention relate to the treatment of Fabry disease.

[0017] One aspect of the present invention pertains to a method of treatment of Fabry disease in a human patient in need thereof. In one or more embodiments, the method comprises administering to the patient a formulation. In some embodiments, the formulation comprises a therapeutically effective dose of migalastat or a salt thereof. In some embodiments, the patient is a pediatric patient. In some embodiments, the patient has an age in a range of from about 2

year to about <18 year. In some embodiments, the patient has a weight in a range of from about <15 kg to about ≥50 kg. In some embodiments, the therapeutically effective dose of migalastat or a salt thereof is in a range of from about 15 mg to about 150 mg every other day. In some embodiments, the therapeutically effective dose of migalastat hydrochloride is in a range of from about 25 mg to about 150 mg every other day. In some embodiments, the therapeutically effective dose of migalastat FBE is in a range of from about 15 mg to about 123 mg every other day.

[0018] In one or more embodiments, the patient has an age in a range of from 12 to <18. In some embodiments, the patient has a weight of about ≥25 kg. In some embodiments, the therapeutically effective dose of migalastat hydrochloride is in a range of from about 80 mg to about 150 mg every other day. In one or more embodiments, the patient has a weight of about ≥45 kg. In some embodiments, the therapeutically effective dose of migalastat hydrochloride is about 150 mg every other day. In some embodiments, the therapeutically effective dose of migalastat FBE is about 123 mg every other day.

[0019] In one or more embodiments, the patient has an age in a range of from about 6 year to about <12 year. In some embodiments, the patient has a weight of about ≥25 kg. In some embodiments, the therapeutically effective dose of migalastat hydrochloride is in a range of from about 80 mg to about 150 mg every other day.

[0020] In one or more embodiments, the patient has an age in a range of from about 2 year to about <6 year. In some embodiments, the patient has a weight of about <35 kg. In some embodiments, the therapeutically effective dose of migalastat hydrochloride is in a range of from about 40 mg to about 80 mg every other day.

[0021] In one or more embodiments, the patient has an eGFR of about ≥60 mL/min/1.73 m^2.

[0022] In one or more embodiments, the migalastat or salt thereof enhances or prolongs α-galactosidase A activity.

[0023] In one or more embodiments, the formulation comprises an oral dosage form. In some embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[0024] In one or more embodiments, the patient is male.

[0025] In one or more embodiments, the patient is female.

[0026] In one or more embodiments, the patient is an ERT-naïve patient.

[0027] In one or more embodiments, the patient is an ERT-experienced patient, who has stopped ERT for at least 14 days.

[0028] In one or more embodiments, the patient has a HEK assay amenable mutation in α-galactosidase A. In one or more embodiments, the mutation is disclosed in a pharmacological reference table. In one or more embodiments, the pharmacological reference table is provided in a product label for a migalastat product approved for the treatment of Fabry disease. In one or more embodiments, the pharmacological reference table is provided in a product label for GALAFOLD®. In one or more embodiments, the pharmacological reference table is provided at a website. In one or more embodiments, the website is one or more of www.galafoldamenabilitytable.com or www.fabrygenevariantsearch.com.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] Further features of the present invention will become apparent from the following written description and the accompanying figures, in which:

[0030] FIGS. 1A-E show the full DNA sequence of the human wild-type GLA gene (SEQ ID NO: 1);

[0031] FIG. 2 shows the wild-type α-Gal A protein (SEQ ID NO: 2); and

[0032] FIG. 3 shows the nucleic acid sequence encoding the wild-type α-Gal A protein (SEQ ID NO: 3).

DETAILED DESCRIPTION

[0033] Before describing several exemplary embodiments of the invention, it is to be understood that the invention is not limited to the details of construction or process steps set forth in the following description. The invention is capable of other embodiments and of being practiced or being carried out in various ways.

[0034] Various aspects of the present invention pertain to the administration of pharmacological chaperones such as migalastat for the treatment of Fabry disease in pediatric and adolescent patients.

Definitions

[0035] The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compositions and methods of the invention and how to make and use them.

[0036] The term "Fabry disease" refers to an X-linked inborn error of glycosphingolipid catabolism due to deficient lysosomal α-Gal A activity. This defect causes accumulation of the substrate globotriaosylceramide ("GL-3", also known as Gb3 or ceramide trihexoside) and related glycosphingolipids in vascular endothelial lysosomes of the heart, kidneys, skin, and other tissues. Another substrate of the enzyme is plasma globotriaosylsphingosine ("plasma lyso-Gb_3").

[0037] The term "atypical Fabry disease" refers to patients with primarily cardiac manifestations of the α-Gal A deficiency, namely progressive GL-3 accumulation in myocardial cells that leads to significant enlargement of the heart, particularly the left ventricle.

[0038] A "carrier" is a female who has one X chromosome with a defective α-Gal A gene and one X chromosome with the normal gene and in whom X chromosome inactivation of the normal allele is present in one or more cell types. A carrier is often diagnosed with Fabry disease.

[0039] A "patient" refers to a subject who has been diagnosed with or is suspected of having a particular disease. The patient may be human or animal.

[0040] A "Fabry patient" refers to an individual who has been diagnosed with or suspected of having Fabry disease and has a mutated α-Gal A as defined further below. Characteristic markers of Fabry disease can occur in male hemizygotes and female carriers with the same prevalence, although females typically are less severely affected.

[0041] Human α-galactosidase A (α-Gal A) refers to an enzyme encoded by the human GLA gene. The full DNA sequence of α-Gal A, including introns and exons, is available in GenBank Accession No. X14448.1 and shown in FIG. 1A-E (SEQ ID NO: 1). The human α-Gal A enzyme consists of 429 amino acids and is available in GenBank Accession Nos. X14448.1 and U78027.1 and shown in FIG. 2 (SEQ ID NO: 2). The nucleic acid sequence that

only includes the coding regions (i.e. exons) of SEQ ID NO: 1 is shown in FIG. 3 (SEQ ID NO: 3).

[0042] The term "mutant protein" includes a protein which has a mutation in the gene encoding the protein which results in the inability of the protein to achieve a stable conformation under the conditions normally present in the endoplasmic reticulum (ER). The failure to achieve a stable conformation results in a substantial amount of the enzyme being degraded, rather than being transported to the lysosome. Such a mutation is sometimes called a "conformational mutant." Such mutations include, but are not limited to, missense mutations, and in-frame small deletions and insertions.

[0043] As used herein in one embodiment, the term "mutant α-Gal A" includes an α-Gal A which has a mutation in the gene encoding α-Gal A which results in the inability of the enzyme to achieve a stable conformation under the conditions normally present in the ER. The failure to achieve a stable conformation results in a substantial amount of the enzyme being degraded, rather than being transported to the lysosome.

[0044] As used herein, the term "pharmacological chaperone" ("PC") or "specific pharmacological chaperone" ("SPC") refers to any molecule including a small molecule, protein, peptide, nucleic acid, carbohydrate, etc. that specifically binds to a protein and has one or more of the following effects: (i) enhances the formation of a stable molecular conformation of the protein; (ii) induces trafficking of the protein from the ER to another cellular location, preferably a native cellular location, *i.e.*, prevents ER-associated degradation of the protein; (iii) prevents aggregation of misfolded proteins; and/or (iv) restores or enhances at least partial wild-type function and/or activity to the protein. A compound that specifically binds to *e.g.*, α-Gal A, means that it binds to and exerts a chaperone effect on the enzyme and not a generic group of related or unrelated enzymes. More specifically, this term does not refer to endogenous chaperones, such as BiP, or to non-specific agents which have demonstrated non-specific chaperone activity against various proteins, such as glycerol, DMSO or deuterated water, *i.e.*, chemical chaperones. In one or more embodiments of the present invention, the PC may be a reversible competitive inhibitor. In one embodiment, the PC is migalastat or a salt thereof. In another embodiment, the PC is migalastat free base (*e.g.*, 123 mg of migalastat free base). In yet another embodiment, the PC is a salt of migalastat (*e.g.*, 150 mg of migalastat HCl).

[0045] A "competitive inhibitor" of an enzyme can refer to a compound which structurally resembles the chemical structure and molecular geometry of the enzyme substrate to bind the enzyme in approximately the same location as the substrate. Thus, the inhibitor competes for the same active site as the substrate molecule, thus increasing the Km. Competitive inhibition is usually reversible if sufficient substrate molecules are available to displace the inhibitor, *i.e.*, competitive inhibitors can bind reversibly. Therefore, the amount of enzyme inhibition depends upon the inhibitor concentration, substrate concentration, and the relative affinities of the inhibitor and substrate for the active site.

[0046] As used herein, the term "specifically binds" refers to the interaction of a pharmacological chaperone with a protein such as α-Gal A, specifically, an interaction with amino acid residues of the protein that directly participate in contacting the pharmacological chaperone. A pharmacological chaperone specifically binds a target protein, *e.g.*, α-Gal A, to exert a chaperone effect on the protein and not a generic group of related or unrelated proteins. The amino acid residues of a protein that interact with any given pharmacological chaperone may or may not be within the protein's "active site." Specific binding can be evaluated through routine binding assays or through structural studies, *e.g.*, co-crystallization, NMR, and the like. The active site for α-Gal A is the substrate binding site.

[0047] "Deficient α-Gal A activity" refers to α-Gal A activity in cells from a patient which is below the normal range as compared (using the same methods) to the activity in normal individuals not having or suspected of having Fabry or any other disease (especially a blood disease).

[0048] As used herein, the terms "enhance α-Gal A activity" or "increase α-Gal A activity" refer to increasing the amount of α-Gal A that adopts a stable conformation in a cell contacted with a pharmacological chaperone specific for the α-Gal A, relative to the amount in a cell (preferably of the same cell-type or the same cell, *e.g.*, at an earlier time) not contacted with the pharmacological chaperone specific for the α-Gal A. This term also refers to increasing the trafficking of α-Gal A to the lysosome in a cell contacted with a pharmacological chaperone specific for the α-Gal A, relative to the trafficking of α-Gal A not contacted with the pharmacological chaperone specific for the protein. These terms refer to both wild-type and mutant α-Gal A. In one embodiment, the increase in the amount of α-Gal A in the cell is measured by measuring the hydrolysis of an artificial substrate in lysates from

cells that have been treated with the PC. An increase in hydrolysis is indicative of increased α-Gal A activity.

[0049] The term "α-Gal A activity" refers to the normal physiological function of a wild-type α-Gal A in a cell. For example, α-Gal A activity includes hydrolysis of GL-3.

[0050] A "responder" is an individual diagnosed with or suspected of having a lysosomal storage disorder (LSD), such, for example Fabry disease, whose cells exhibit sufficiently increased α-Gal A activity, respectively, and/or amelioration of symptoms or enhancement in surrogate markers, in response to contact with a PC. Non-limiting examples of enhancements in surrogate markers for Fabry are lyso-GB3 and those disclosed in US Patent Application Publication No. U.S. 2010/0113517, which is hereby incorporated by reference in its entirety.

[0051] Non-limiting examples of improvements in surrogate markers for Fabry disease disclosed in U.S. 2010/0113517 include increases in α-Gal A levels or activity in cells (*e.g.*, fibroblasts) and tissue; reductions in of GL-3 accumulation; decreased plasma concentrations of homocysteine and vascular cell adhesion molecule-1 (VCAM-1); decreased GL-3 accumulation within myocardial cells and valvular fibrocytes; reduction in plasma lyso-Gb_3; reduction in cardiac hypertrophy (especially of the left ventricle), amelioration of valvular insufficiency, and arrhythmias; amelioration of proteinuria; decreased urinary concentrations of lipids such as CTH, lactosylceramide, ceramide, and increased urinary concentrations of glucosylceramide and sphingomyelin; the absence of laminated inclusion bodies (Zebra bodies) in glomerular epithelial cells; improvements in renal function; mitigation of hypohidrosis; the absence of angiokeratomas; and improvements in hearing abnormalities such as high frequency sensorineural hearing loss progressive hearing loss, sudden deafness, or tinnitus. Improvements in neurological symptoms include prevention of transient ischemic attack (TIA) or stroke; and amelioration of neuropathic pain manifesting itself as acroparaesthesia (burning or tingling in extremities). Another type of clinical marker that can be assessed for Fabry disease is the prevalence of deleterious cardiovascular manifestations. Common cardiac-related signs and symptoms of Fabry disease include left ventricular hypertrophy, valvular disease (especially mitral valve prolapse and/or regurgitation), premature coronary artery disease, angina, myocardial infarction, conduction abnormalities, arrhythmias, congestive heart failure.

[0052] The dose that achieves one or more of the aforementioned responses is a "therapeutically effective dose."

[0053] The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a human. In some embodiments, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans. The term "carrier" in reference to a pharmaceutical carrier refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, 18th Edition, or other editions.

[0054] As used herein, the term "isolated" means that the referenced material is removed from the environment in which it is normally found. Thus, an isolated biological material can be free of cellular components, *i.e.*, components of the cells in which the material is found or produced. In the case of nucleic acid molecules, an isolated nucleic acid includes a PCR product, an mRNA band on a gel, a cDNA, or a restriction fragment. In another embodiment, an isolated nucleic acid is preferably excised from the chromosome in which it may be found, and more preferably is no longer joined to non-regulatory, non-coding regions, or to other genes, located upstream or downstream of the gene contained by the isolated nucleic acid molecule when found in the chromosome. In yet another embodiment, the isolated nucleic acid lacks one or more introns. Isolated nucleic acids include sequences inserted into plasmids, cosmids, artificial chromosomes, and the like. Thus, in a specific embodiment, a recombinant nucleic acid is an isolated nucleic acid. An isolated protein may be associated with other proteins or nucleic acids, or both, with which it associates in the cell, or with cellular membranes if it is a membrane-associated protein. An isolated organelle, cell, or tissue is removed from the anatomical site in which it is found in an organism. An isolated material may be, but need not be, purified.

[0055] The term "enzyme replacement therapy" or "ERT" refers to the introduction of a non-native, purified enzyme into an individual having a deficiency in such enzyme. The

administered protein can be obtained from natural sources or by recombinant expression (as described in greater detail below). The term also refers to the introduction of a purified enzyme in an individual otherwise requiring or benefiting from administration of a purified enzyme, *e.g.*, suffering from enzyme insufficiency. The introduced enzyme may be a purified, recombinant enzyme produced *in vitro*, or protein purified from isolated tissue or fluid, such as, *e.g.*, placenta or animal milk, or from plants.

[0056] The term "ERT-naïve patient" refers to a Fabry patient that has never received ERT or has not received ERT for at least 6 months prior to initiating migalastat therapy.

[0057] The term "ERT-experienced patient" refers to a Fabry patient that was receiving ERT immediately prior to initiating migalastat therapy. In some embodiments, the ERT-experienced patient has received at least 12 months of ERT immediately prior to initiating migalastat therapy.

[0058] As used herein, the term "free base equivalent" or "FBE" refers to the amount of migalastat present in the migalastat or salt thereof. In other words, the term "FBE" means either an amount of migalastat free base, or the equivalent amount of migalastat free base that is provided by a salt of migalastat. For example, due to the weight of the hydrochloride salt, 150 mg of migalastat hydrochloride only provides as much migalastat as 123 mg of the free base form of migalastat. Other salts are expected to have different conversion factors, depending on the molecular weight of the salt.

[0059] The term "migalastat" encompasses migalastat free base or a pharmaceutically acceptable salt thereof (*e.g.*, migalastat HCl), unless specifically indicated to the contrary.

[0060] The terms "mutation" and "variant" (*e.g.*, as in "amenable mutation or variant") refer to a change in the nucleotide sequence of a gene or a chromosome. The two terms referred herein are typically used together – *e.g.*, as in "mutation or variant"– referring to the change in nucleotide sequence stated in the previous sentence. If only one of the two terms is recited for some reason, the missing term was intended to be included and one should understand as such. Furthermore, the terms "amenable mutation" and "amenable variant" refer to a mutation or variant that is amenable to PC therapy, *e*.g., a mutation that is amenable to migalastat therapy. A particular type of amenable mutation or variant is a "HEK assay amenable mutation or variant", which is a mutation or variant that is determined to be amenable to migalastat therapy according to the criteria in the *in vitro* HEK assay described

herein and in U.S. Patent No. 8,592,362, which is hereby incorporated by reference in its entirety.

[0061] The terms "about" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Typical, exemplary degrees of error are within 20 percent (%), preferably within 10%, and more preferably within 5% of a given value or range of values. Alternatively, and particularly in biological systems, the terms "about" and "approximately" may mean values that are within an order of magnitude, preferably within 10- or 5-fold, and more preferably within 2-fold of a given value. Numerical quantities given herein are approximate unless stated otherwise, meaning that the term "about" or "approximately" can be inferred when not expressly stated.

Fabry Disease

[0062] Fabry disease is a rare, progressive and devastating X-linked lysosomal storage disorder (LSD). Mutations in the GLA gene result in a deficiency of the lysosomal enzyme, α-Gal A, which is required for glycosphingolipid metabolism. Beginning early in life, the reduction in α-Gal A activity results in an accumulation of glycosphingolipids, including GL-3 and plasma lyso-Gb3, and leads to the symptoms and life-limiting sequelae of Fabry disease, including pain, gastrointestinal symptoms, renal failure, cardiomyopathy, cerebrovascular events, and early mortality. Early initiation of therapy and lifelong treatment provide an opportunity to slow disease progression and prolong life expectancy.

[0063] Fabry disease encompasses a spectrum of disease severity and age of onset, although it has traditionally been divided into 2 main phenotypes, "classic" and "late-onset". The classic phenotype has been ascribed primarily to males with undetectable to low α-Gal A activity and earlier onset of renal, cardiac and/or cerebrovascular manifestations. The late-onset phenotype has been ascribed primarily to males with higher residual α-Gal A activity and later onset of these disease manifestations. Heterozygous female carriers typically express the late-onset phenotype but depending on the pattern of X-chromosome inactivation may also display the classic phenotype.

[0064] More than 1,000 Fabry disease-causing GLA mutations have been identified. The GLA mutation includes but not limited to missense, nonsense, and splicing mutations, in addition to small deletions and insertions, and larger gene rearrangements. Approximately 60%

are missense mutations, resulting in single amino acid substitutions in the α-Gal A enzyme. Missense GLA mutations often result in the production of abnormally folded and unstable forms of α-Gal A and the majority are associated with the classic phenotype. Normal cellular quality control mechanisms in the ER block the transit of these abnormal proteins to lysosomes and target them for premature degradation and elimination. Many missense mutant forms are targets for migalastat, an α-Gal A-specific pharmacological chaperone.

[0065] The clinical manifestations of Fabry disease span a broad spectrum of severity and roughly correlate with a patient's residual α-Gal A levels. The majority of currently treated patients are referred to as classic Fabry patients, most of whom are males. These patients experience disease of various organs, including the kidneys, heart and brain, with disease symptoms first appearing in adolescence and typically progressing in severity until death in the fourth or fifth decade of life. A number of recent studies suggest that there are a large number of undiagnosed males and females that have a range of Fabry disease symptoms, such as impaired cardiac or renal function and strokes, that usually first appear in adulthood. Individuals with this type of Fabry disease, referred to as later-onset Fabry disease, tend to have higher residual α-Gal A levels than classic Fabry patients. Individuals with later-onset Fabry disease typically first experience disease symptoms in adulthood, and often have disease symptoms focused on a single organ, such as enlargement of the left ventricle or progressive kidney failure. In addition, later-onset Fabry disease may also present in the form of strokes of unknown cause.

[0066] Because Fabry disease is rare, involves multiple organs, has a wide age range of onset, and is heterogeneous, proper diagnosis is a challenge. For example, Fabry patients have progressive kidney impairment, and untreated patients exhibit end-stage renal impairment by the fifth decade of life. Deficiency in α-Gal A activity leads to accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in many cell types including cells in the kidney. Gb3 accumulates in podocytes, epithelial cells and the tubular cells of the distal tubule and loop of Henle. Impairment in kidney function can manifest as proteinuria and reduced glomerular filtration rate.

[0067] Furthermore, awareness is low among health care professionals and misdiagnoses are frequent. Diagnosis of Fabry disease is most often confirmed on the basis of decreased α-Gal A activity in plasma or peripheral leukocytes (WBCs) once a patient is symptomatic, coupled with mutational analysis. In females, diagnosis is even more challenging

since the enzymatic identification of carrier females is less reliable due to random X-chromosomal inactivation in some cells of carriers. For example, some obligate carriers (daughters of classically affected males) have α-Gal A enzyme activities ranging from normal to very low activities. Since carriers can have normal α-Gal A enzyme activity in leukocytes, only the identification of an α-Gal A mutation by genetic testing provides precise carrier identification and/or diagnosis.

[0068] In one or more embodiments, mutant forms of α-Gal A are considered to be amenable to migalastat are defined as showing a relative increase (+10 μM migalastat) of ≥1.20-fold and an absolute increase (+ 10 μM migalastat) of ≥ 3.0% wild-type (WT) when the mutant form of α-Gal A is expressed in HEK-293 cells (referred to as the "HEK assay") according to Good Laboratory Practice (GLP)-validated *in vitro* assay (GLP HEK or Migalastat Amenability Assay). Such mutations are also referred to herein as "HEK assay amenable" mutations.

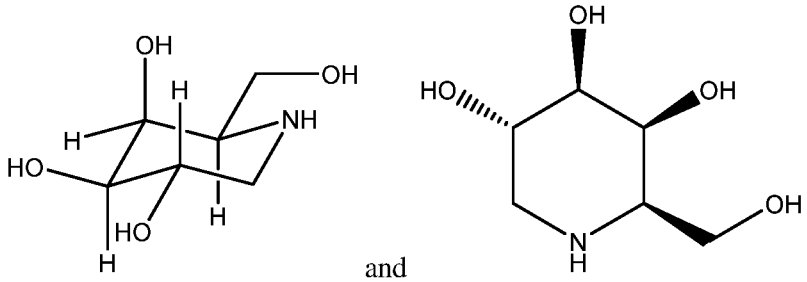
[0069] Previous screening methods have been provided that assess enzyme enhancement prior to the initiation of treatment. For example, an assay using HEK-293 cells has been utilized in clinical trials to predict whether a given mutation will be responsive to pharmacological chaperone (*e.g.*, migalastat) treatment. In this assay, cDNA constructs are created. The corresponding α-Gal A mutant forms are transiently expressed in HEK-293 cells. Cells are then incubated ± migalastat (17 nM to 1 mM) for 4 to 5 days. After, α-Gal A levels are measured in cell lysates using a synthetic fluorogenic substrate (4-MU-α-Gal) or by western blot. This has been done for known disease-causing missense or small in-frame insertion/deletion mutations. Mutations that have previously been identified as responsive to a PC (*e.g.*, migalastat) using these methods are listed in U.S. Patent No. 8,592,362, which is hereby incorporated by reference in its entirety.

Pharmacological Chaperones

[0070] The binding of small molecule inhibitors of enzymes associated with LSDs can increase the stability of both mutant enzyme and the corresponding wild-type enzyme (see U.S. Pat. Nos. 6,274,597; 6,583,158; 6,589,964; 6,599,919; 6,916,829, and 7,141,582 all incorporated herein by reference). In particular, administration of small molecule derivatives of glucose and galactose, which are specific, selective competitive inhibitors for several target

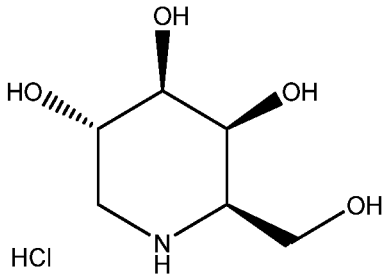
lysosomal enzymes, effectively increased the stability of the enzymes in cells *in vitro* and, thus, increased trafficking of the enzymes to the lysosome. Thus, by increasing the amount of enzyme in the lysosome, hydrolysis of the enzyme substrates is expected to increase. The original theory behind this strategy was as follows: since the mutant enzyme protein is unstable in the ER (Ishii *et al.*, *Biochem. Biophys. Res. Comm.* 1996; 220: 812-815), the enzyme protein is retarded in the normal transport pathway (ER→Golgi apparatus→endosomes→lysosome) and prematurely degraded. Therefore, a compound which binds to and increases the stability of a mutant enzyme, may serve as a "chaperone" for the enzyme and increase the amount that can exit the ER and move to the lysosomes. In addition, because the folding and trafficking of some wild-type proteins is incomplete, with up to 70% of some wild-type proteins being degraded in some instances prior to reaching their final cellular location, the chaperones can be used to stabilize wild-type enzymes and increase the amount of enzyme which can exit the ER and be trafficked to lysosomes.

[0071] In one or more embodiments, the pharmacological chaperone comprises migalastat or a salt thereof. The compound migalastat, also known as 1-deoxygalactonojirimycin (1-DGJ) or (2R,3S,4R,5S)-2-(hydroxymethyl) piperdine-3,4,5-triol is a compound having the following chemical formula:



Migalastat free base

[0072] As discussed herein, pharmaceutically acceptable salts of migalastat may also be used in the present invention. When a salt of migalastat is used, the dosage of the salt will be adjusted so that the dose of migalastat received by the patient is equivalent to the amount which would have been received had the migalastat free base been used. One example of a pharmaceutically acceptable salt of migalastat is migalastat HCl:



Migalastat HCl

[0073] Migalastat is a low molecular weight iminosugar and is an analogue of the terminal galactose of GL-3. *In vitro* and *in vivo* pharmacologic studies have demonstrated that migalastat acts as a pharmacological chaperone, selectively and reversibly binding, with high affinity, to the active site of wild-type α-Gal A and specific mutant forms of α-Gal A, the genotypes of which are referred to as HEK assay amenable mutations. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum facilitating their proper trafficking to lysosomes where dissociation of migalastat allows α-Gal A to reduce the level of GL-3 and other substrates. Approximately 30-50% of patients with Fabry disease have HEK assay amenable mutations; the majority of which are associated with the classic phenotype of the disease.

[0074] HEK assay amenable mutations include at least those mutations listed in a pharmacological reference table (*e.g.*, the ones recited in the U.S. or International Product labels for a migalastat product such as GALAFOLD®). As used herein, "pharmacological reference table" refers to any publicly accessible written or electronic record, included in either the product label within the packaging of a migalastat product (*e.g.*, GALAFOLD®) or in a website accessible by health care providers, that conveys whether a particular mutation or variant is responsive to migalastat (*e.g.*, GALAFOLD®) PC therapy, and is not necessarily limited to written records presented in tabular form. In one embodiment of the present invention, a "pharmacological reference table" thus refers to any depository of information that includes one or more amenable mutations or variants. An exemplary pharmacological reference table for HEK assay amenable mutations can be found in the summary of product characteristics and/or prescribing information for GALAFOLD® in various countries in which GALAFOLD® is approved for use, or at a website such as www.galafoldamenabilitytable.com

or www.fabrygenevariantsearch.com, each of which is hereby incorporated by reference in its entirety.

[0075] Although the vast majority of a-GAL mutations are missense mutations, with most being outside the catalytic site, it difficult to predict which mutations result in an unstable enzyme that could be "rescued" by a pharmacological chaperone (PC) which stabilizes the enzyme, and which ones cannot be stabilized using a PC.

[0076] An exemplary pharmacological reference table for HEK assay amenable mutations is provided in Table 1 below. In one or more embodiments, if a double mutation is present on the same chromosome (males and females), that patient is considered HEK assay amenable if the double mutation is present in one entry in Table 1 (*e.g.*, D55V/Q57L). In some embodiments, if a double mutation is present on different chromosomes (only in females) that patient is considered HEK assay amenable if either one of the individual mutations is present in Table 1.

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.7C>G	c.C7G	L3V
c.8T>C	c.T8C	L3P
c.[11G>T; 620A>C]	c.G11T/A620C	R4M/Y207S
c.13A>G	c.A13G	N5D
c.15C>G	c.C15G	N5K
c.16C>A	c.C16A	P6T
c.16C>T	c.C16T	P6S
c.17C>A	c.C17A	P6Q
c.17C>G	c.C17G	P6R
c.17C>T	c.C17T	P6L
c.19G>A	c.G19A	E7K
c.20A>T	c.A20T	E7V
c.21A>T	c.A21T	E7D
c.22C>A	c.C22A	L8I
c.23T>A	c.T23A	L8Q
c.23T>C	c.T23C	L8P
c.25C>T	c.C25T	H9Y
c.26A>G	c.A26G	H9R
c.26A>T	c.A26T	H9L
c.27T>A	c.T27A	H9Q
c.28C>A	c.C28A	L10M
c.28C>G	c.C28G	L10V
c.29T>A	c.T29A	L10Q

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.29T>C	c.T29C	L10P
c.29T>G	c.T29G	L10R
c.31G>A	c.G31A	G11S
c.31G>C	c.G31C	G11R
c.31G>T	c.G31T	G11C
c.32G>A	c.G32A	G11D
c.32G>T	c.G32T	G11V
c.34T>A	c.T34A	C12S
c.34T>C	c.T34C	C12R
c.34T>G	c.T34G	C12G
c.35G>A	c.G35A	C12Y
c.37G>A	c.G37A	A13T
c.37G>C	c.G37C	A13P
c.38C>A	c.C38A	A13E
c.38C>G	c.C38G	A13G
c.40C>G	c.C40G	L14V
c.40C>T	c.C40T	L14F
c.41T>A	c.T41A	L14H
c.43G>A	c.G43A	A15T
c.44C>G	c.C44G	A15G
c.49C>A	c.C49A	R17S
c.49C>G	c.C49G	R17G
c.49C>T	c.C49T	R17C
c.50G>A	c.G50A	R17H
c.50G>C	c.G50C	R17P
c.52T>A	c.T52A	F18I
c.53T>G	c.T53G	F18C
c.54C>G	c.C54G	F18L
c.58G>C	c.G58C	A20P
c.59C>A	c.C59A	A20D
c.59C>G	c.C59G	A20G
c.62T>A	c.T62A	L21H
c.64G>A	c.G64A	V22I
c.64G>C	c.G64C	V22L
c.64G>T	c.G64T	V22F
c.65T>C	c.T65C	V22A
c.65T>G	c.T65G	V22G
c.67T>A	c.T67A	S23T
c.67T>C	c.T67C	S23P
c.70T>C or c.70T>A	c.T70C or c.T70A	W24R
c.70T>G	c.T70G	W24G
c.71G>C	c.G71C	W24S
c.72G>C or c.72G>T	c.G72C or c.G72T	W24C
c.73G>C	c.G73C	D25H

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.77T>A	c.T77A	I26N
c.79C>A	c.C79A	P27T
c.79C>G	c.C79G	P27A
c.79C>T	c.C79T	P27S
c.80C>T	c.C80T	P27L
c.82G>C	c.G82C	G28R
c.82G>T	c.G82T	G28W
c.83G>A	c.G83A	G28E
c.85G>C	c.G85C	A29P
c.86C>A	c.C86A	A29D
c.86C>G	c.C86G	A29G
c.86C>T	c.C86T	A29V
c.88A>G	c.A88G	R30G
c.94C>A	c.C94A	L32M
c.94C>G	c.C94G	L32V
c.95T>A	c.T95A	L32Q
c.95T>C	c.T95C	L32P
c.95T>G	c.T95G	L32R
c.97G>C	c.G97C	D33H
c.97G>T	c.G97T	D33Y
c.98A>C	c.A98C	D33A
c.98A>G	c.A98G	D33G
c.98A>T	c.A98T	D33V
c.99C>G	c.C99G	D33E
c.100A>C	c.A100C	N34H
c.100A>G	c.A100G	N34D
c.101A>C	c.A101C	N34T
c.101A>G	c.A101G	N34S
c.102T>G or c.102T>A	c.T102G or c.T102A	N34K
c.103G>C or c.103G>A	c.G103C or c.G103A	G35R
c.104G>A	c.G104A	G35E
c.104G>C	c.G104C	G35A
c.104G>T	c.G104T	G35V
c.106T>A	c.T106A	L36M
c.106T>G	c.T106G	L36V
c.107T>C	c.T107C	L36S
c.107T>G	c.T107G	L36W
c.108G>C or c.108G>T	c.G108C or c.G108T	L36F
c.109G>A	c.G109A	A37T
c.109G>T	c.G109T	A37S
c.110C>A	c.C110A	A37E
c.110C>G	c.C110G	A37G
c.110C>T	c.C110T	A37V
c.112A>G	c.A112G	R38G

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.112A>T	c.A112T	R38W
c.113G>T	c.G113T	R38M
c.114G>C	c.G114C	R38S
c.115A>G	c.A115G	T39A
c.115A>T	c.A115T	T39S
c.116C>A	c.C116A	T39K
c.116C>G	c.C116G	T39R
c.116C>T	c.C116T	T39M
c.121A>G	c.A121G	T41A
c.122C>A	c.C122A	T41N
c.122C>G	c.C122G	T41S
c.122C>T	c.C122T	T41I
c.124A>C or c.124A>T	c.A124C or c.A124T	M42L
c.124A>G	c.A124G	M42V
c.125T>A	c.T125A	M42K
c.125T>C	c.T125C	M42T
c.125T>G	c.T125G	M42R
c.126G>A or c.126G>C or c.126G>T	c.G126A or c.G126C or c.G126T	M42I
c.128G>C	c.G128C	G43A
c.133C>A	c.C133A	L45M
c.133C>G	c.C133G	L45V
c.136C>A	c.C136A	H46N
c.136C>G	c.C136G	H46D
c.137A>C	c.A137C	H46P
c.138C>G	c.C138G	H46Q
c.142G>C	c.G142C	E48Q
c.143A>C	c.A143C	E48A
c.149T>A	c.T149A	F50Y
c.151A>G	c.A151G	M51V
c.152T>A	c.T152A	M51K
c.152T>C	c.T152C	M51T
c.152T>G	c.T152G	M51R
c.153G>A or c.153G>T or c.153G>C	c.G153A or c.G153T or c.G153C	M51I
c.157A>C	c.A157C	N53H
c.[157A>C; 158A>T]	c.A157C/A158T	N53L
c.157A>G	c.A157G	N53D
c.157A>T	c.A157T	N53Y
c.158A>C	c.A158C	N53T
c.158A>G	c.A158G	N53S
c.158A>T	c.A158T	N53I
c.159C>G or c.159C>A	c.C159G or c.C159A	N53K
c.160C>G	c.C160G	L54V

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.160C>T	c.C160T	L54F
c.161T>A	c.T161A	L54H
c.161T>C	c.T161C	L54P
c.161T>G	c.T161G	L54R
c.163G>C	c.G163C	D55H
c.163G>T	c.G163T	D55Y
c.164A>C	c.A164C	D55A
c.164A>G	c.A164G	D55G
c.164A>T	c.A164T	D55V
c.[164A>T; 170A>T]	c.A164T/A170T	D55V/Q57L
c.165C>G	c.C165G	D55E
c.167G>A	c.G167A	C56Y
c.167G>T	c.G167T	C56F
c.168C>G	c.C168G	C56W
c.170A>G	c.A170G	Q57R
c.170A>T	c.A170T	Q57L
c.172G>A	c.G172A	E58K
c.175G>A	c.G175A	E59K
c.175G>C	c.G175C	E59Q
c.176A>C	c.A176C	E59A
c.176A>G	c.A176G	E59G
c.176A>T	c.A176T	E59V
c.177G>C	c.G177C	E59D
c.178C>A	c.C178A	P60T
c.178C>G	c.C178G	P60A
c.178C>T	c.C178T	P60S
c.179C>A	c.C179A	P60Q
c.179C>G	c.C179G	P60R
c.179C>T	c.C179T	P60L
c.182A>T	c.A182T	D61V
c.183T>A	c.T183A	D61E
c.184_185insTAG	c.184_185insTAG	S62delinsLA
c.184T>C	c.T184C	S62P
c.184T>G	c.T184G	S62A
c.185C>A	c.C185A	S62Y
c.185C>G	c.C185G	S62C
c.185C>T	c.C185T	S62F
c.190A>C	c.A190C	I64L
c.190A>G	c.A190G	I64V
c.193A>G	c.A193G	S65G
c.193A>T	c.A193T	S65C
c.195T>A	c.T195A	S65R
c.196G>A	c.G196A	E66K
c.197A>G	c.A197G	E66G

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.197A>T	c.A197T	E66V
c.198G>C	c.G198C	E66D
c.199A>C	c.A199C	K67Q
c.199A>G	c.A199G	K67E
c.200A>C	c.A200C	K67T
c.200A>T	c.A200T	K67M
c.201G>C	c.G201C	K67N
c.202C>A	c.C202A	L68I
c.205T>A	c.T205A	F69I
c.206T>A	c.T206A	F69Y
c.207C>A or c.207C>G	c.C207A or c.C207G	F69L
c.208A>T	c.A208T	M70L
c.209T>A	c.T209A	M70K
c.209T>G	c.T209G	M70R
c.210G>C	c.G210C	M70I
c.211G>C	c.G211C	E71Q
c.212A>C	c.A212C	E71A
c.212A>G	c.A212G	E71G
c.212A>T	c.A212T	E71V
c.213G>C	c.G213C	E71D
c.214A>G	c.A214G	M72V
c.214A>T	c.A214T	M72L
c.215T>C	c.T215C	M72T
c.216G>A or c.216G>T or c.216G>C	c.G216A or c.G216T or c.G216C	M72I
c.217G>A	c.G217A	A73T
c.217G>T	c.G217T	A73S
c.218C>T	c.C218T	A73V
c.220G>A	c.G220A	E74K
c.221A>G	c.A221G	E74G
c.221A>T	c.A221T	E74V
c.222G>C	c.G222C	E74D
c.223C>T	c.C223T	L75F
c.224T>C	c.T224C	L75P
c.226A>G	c.A226G	M76V
c.227T>C	c.T227C	M76T
c.229G>A	c.G229A	V77I
c.229G>C	c.G229C	V77L
c.232T>C	c.T232C	S78P
c.233C>T	c.C233T	S78L
c.235G>A	c.G235A	E79K
c.235G>C	c.G235C	E79Q
c.236A>C	c.A236C	E79A
c.236A>G	c.A236G	E79G

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.236A>T	c.A236T	E79V
c.237A>T	c.A237T	E79D
c.238G>A	c.G238A	G80S
c.238G>T	c.G238T	G80C
c.239G>A	c.G239A	G80D
c.239G>C	c.G239C	G80A
c.239G>T	c.G239T	G80V
c.242G>T	c.G242T	W81L
c.244A>G	c.A244G	K82E
c.245A>C	c.A245C	K82T
c.245A>G	c.A245G	K82R
c.245A>T	c.A245T	K82M
c.246G>C	c.G246C	K82N
c.247G>A	c.G247A	D83N
c.248A>C	c.A248C	D83A
c.248A>G	c.A248G	D83G
c.248A>T	c.A248T	D83V
c.249T>A	c.T249A	D83E
c.250G>A	c.G250A	A84T
c.250G>C	c.G250C	A84P
c.250G>T	c.G250T	A84S
c.251C>A	c.C251A	A84E
c.251C>G	c.C251G	A84G
c.251C>T	c.C251T	A84V
c.253G>A	c.G253A	G85S
c.[253G>A; 254G>A]	c.G253A/G254A	G85N
c.[253G>A; 254G>T; 255T>G]	c.G253A/G254T/T255G	G85M
c.253G>C	c.G253C	G85R
c.253G>T	c.G253T	G85C
c.254G>A	c.G254A	G85D
c.254G>C	c.G254C	G85A
c.257A>T	c.A257T	Y86F
c.260A>G	c.A260G	E87G
c.261G>C or c.261G>T	c.G261C or c.G261T	E87D
c.262T>A	c.T262A	Y88N
c.262T>C	c.T262C	Y88H
c.263A>C	c.A263C	Y88S
c.263A>G	c.A263G	Y88C
c.265C>G	c.C265G	L89V
c.265C>T	c.C265T	L89F
c.271A>C	c.A271C	I91L
c.271A>T	c.A271T	I91F
c.272T>C	c.T272C	I91T

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.272T>G	c.T272G	I91S
c.273T>G	c.T273G	I91M
c.286A>G	c.A286G	M96V
c.286A>T	c.A286T	M96L
c.287T>C	c.T287C	M96T
c.288G>A or c.288G>T or c.288G>C	c.G288A or c.G288T or c.G288C	M96I
c.289G>A	c.G289A	A97T
c.289G>C	c.G289C	A97P
c.289G>T	c.G289T	A97S
c.290C>A	c.C290A	A97D
c.290C>T	c.C290T	A97V
c.293C>A	c.C293A	P98H
c.293C>G	c.C293G	P98R
c.293C>T	c.C293T	P98L
c.295C>G	c.C295G	Q99E
c.296A>C	c.A296C	Q99P
c.296A>G	c.A296G	Q99R
c.296A>T	c.A296T	Q99L
c.301G>C	c.G301C	D101H
c.302A>C	c.A302C	D101A
c.302A>G	c.A302G	D101G
c.302A>T	c.A302T	D101V
c.303T>A	c.T303A	D101E
c.304T>A	c.T304A	S102T
c.304T>C	c.T304C	S102P
c.304T>G	c.T304G	S102A
c.305C>T	c.C305T	S102L
c.310G>A	c.G310A	G104S
c.311G>A	c.G311A	G104D
c.311G>C	c.G311C	G104A
c.311G>T	c.G311T	G104V
c.313A>G	c.A313G	R105G
c.314G>A	c.G314A	R105K
c.314G>C	c.G314C	R105T
c.314G>T	c.G314T	R105I
c.316C>A	c.C316A	L106I
c.316C>G	c.C316G	L106V
c.316C>T	c.C316T	L106F
c.317T>A	c.T317A	L106H
c.317T>C	c.T317C	L106P
c.319C>A	c.C319A	Q107K
c.319C>G	c.C319G	Q107E
c.320A>G	c.A320G	Q107R

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.321G>C	c.G321C	Q107H
c.322G>A	c.G322A	A108T
c.323C>A	c.C323A	A108E
c.323C>T	c.C323T	A108V
c.325G>A	c.G325A	D109N
c.325G>C	c.G325C	D109H
c.325G>T	c.G325T	D109Y
c.326A>C	c.A326C	D109A
c.326A>G	c.A326G	D109G
c.327C>G	c.C327G	D109E
c.328C>A	c.C328A	P110T
c.334C>G	c.C334G	R112G
c.335G>A	c.G335A	R112H
c.335G>T	c.G335T	R112L
c.337T>A	c.T337A	F113I
c.337T>C or c.339T>A or c.339T>G	c.T337C or c.T339A or c.T339G	F113L
c.337T>G	c.T337G	F113V
c.338T>A	c.T338A	F113Y
c.341C>T	c.C341T	P114L
c.343C>A	c.C343A	H115N
c.343C>G	c.C343G	H115D
c.346G>C	c.G346C	G116R
c.350T>C	c.T350C	I117T
c.351T>G	c.T351G	I117M
c.352C>T	c.C352T	R118C
c.361G>A	c.G361A	A121T
c.362C>T	c.C362T	A121V
c.367T>A	c.T367A	Y123N
c.367T>G	c.T367G	Y123D
c.368A>C	c.A368C	Y123S
c.368A>G	c.A368G	Y123C
c.368A>T	c.A368T	Y123F
c.370G>A	c.G370A	V124I
c.371T>G	c.T371G	V124G
c.373C>A	c.C373A	H125N
c.373C>G	c.C373G	H125D
c.373C>T	c.C373T	H125Y
c.374A>G	c.A374G	H125R
c.374A>T	c.A374T	H125L
c.376A>G	c.A376G	S126G
c.376A>T	c.A376T	S126C
c.377G>T	c.G377T	S126I
c.379A>G	c.A379G	K127E

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.383G>A	c.G383A	G128E
c.383G>C	c.G383C	G128A
c.385C>G	c.C385G	L129V
c.388A>C	c.A388C	K130Q
c.389A>T	c.A389T	K130M
c.390G>C	c.G390C	K130N
c.391C>G	c.C391G	L131V
c.397A>C	c.A397C	I133L
c.397A>G	c.A397G	I133V
c.397A>T	c.A397T	I133F
c.398T>C	c.T398C	I133T
c.399T>G	c.T399G	I133M
c.[399T>G; 434T>C]	c.T399G/T434C	I133M/F145S
c.403G>A	c.G403A	A135T
c.403G>T	c.G403T	A135S
c.404C>A	c.C404A	A135E
c.404C>G	c.C404G	A135G
c.404C>T	c.C404T	A135V
c.406G>A	c.G406A	D136N
c.407A>C	c.A407C	D136A
c.407A>T	c.A407T	D136V
c.408T>A or c.408T>G	c.T408A or c.T408G	D136E
c.409G>A	c.G409A	V137I
c.409G>C	c.G409C	V137L
c.410T>A	c.T410A	V137D
c.410T>C	c.T410C	V137A
c.410T>G	c.T410G	V137G
c.413G>C	c.G413C	G138A
c.415A>C	c.A415C	N139H
c.415A>T	c.A415T	N139Y
c.416A>G	c.A416G	N139S
c.416A>T	c.A416T	N139I
c.417T>A	c.T417A	N139K
c.418A>C	c.A418C	K140Q
c.418A>G	c.A418G	K140E
c.419A>C	c.A419C	K140T
c.419A>G	c.A419G	K140R
c.419A>T	c.A419T	K140I
c.420A>T	c.A420T	K140N
c.421A>T	c.A421T	T141S
c.427G>A	c.G427A	A143T
c.428C>A	c.C428A	A143E
c.428C>G	c.C428G	A143G
c.428C>T	c.C428T	A143V

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.430G>A	c.G430A	G144S
c.430G>C	c.G430C	G144R
c.430G>T	c.G430T	G144C
c.431G>A	c.G431A	G144D
c.431G>C	c.G431C	G144A
c.431G>T	c.G431T	G144V
c.433T>G	c.T433G	F145V
c.434T>A	c.T434A	F145Y
c.434T>C	c.T434C	F145S
c.434T>G	c.T434G	F145C
c.435C>G	c.C435G	F145L
c.436C>A	c.C436A	P146T
c.436C>G	c.C436G	P146A
c.436C>T	c.C436T	P146S
c.437C>A	c.C437A	P146H
c.437C>G	c.C437G	P146R
c.437C>T	c.C437T	P146L
c.440G>C	c.G440C	G147A
c.442A>G	c.A442G	S148G
c.442A>T	c.A442T	S148C
c.443G>C	c.G443C	S148T
c.446T>G	c.T446G	F149C
c.449G>A	c.G449A	G150E
c.449G>T	c.G449T	G150V
c.451T>G	c.T451G	Y151D
c.452A>C	c.A452C	Y151S
c.452A>G	c.A452G	Y151C
c.454T>A	c.T454A	Y152N
c.454T>C	c.T454C	Y152H
c.454T>G	c.T454G	Y152D
c.455A>C	c.A455C	Y152S
c.455A>G	c.A455G	Y152C
c.455A>T	c.A455T	Y152F
c.457G>A	c.G457A	D153N
c.457G>C	c.G457C	D153H
c.457G>T	c.G457T	D153Y
c.458A>C	c.A458C	D153A
c.458A>T	c.A458T	D153V
c.465T>A or c.465T>G	c.T465A or c.T465G	D155E
c.466G>A	c.G466A	A156T
c.466G>T	c.G466T	A156S
c.467C>G	c.C467G	A156G
c.467C>T	c.C467T	A156V
c.469C>A	c.C469A	Q157K

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.469C>G	c.C469G	Q157E
c.470A>C	c.A470C	Q157P
c.470A>T	c.A470T	Q157L
c.471G>C or c.471G>T	c.G471C or c.G471T	Q157H
c.472A>G	c.A472G	T158A
c.472A>T	c.A472T	T158S
c.473C>A	c.C473A	T158N
c.473C>T	c.C473T	T158I
c.475T>A	c.T475A	F159I
c.475T>G	c.T475G	F159V
c.476T>A	c.T476A	F159Y
c.476T>G	c.T476G	F159C
c.477T>A	c.T477A	F159L
c.478G>A	c.G478A	A160T
c.478G>T	c.G478T	A160S
c.479C>A	c.C479A	A160D
c.479C>G	c.C479G	A160G
c.479C>T	c.C479T	A160V
c.481G>A	c.G481A	D161N
c.481G>C	c.G481C	D161H
c.481G>T	c.G481T	D161Y
c.482A>T	c.A482T	D161V
c.484T>G	c.T484G	W162G
c.485G>C	c.G485C	W162S
c.490G>A	c.G490A	V164I
c.490G>T	c.G490T	V164L
c.491T>C	c.T491C	V164A
c.493G>A	c.G493A	D165N
c.493G>C	c.G493C	D165H
c.494A>C	c.A494C	D165A
c.494A>G	c.A494G	D165G
c.495T>A	c.T495A	D165E
c.496_497delinsTC	c.496_497delinsTC	L166S
c.496C>A	c.C496A	L166M
c.496C>G	c.C496G	L166V
c.[496C>G; 497T>G]	c.C496G/T497G	L166G
c.497T>A	c.T497A	L166Q
c.499C>A	c.C499A	L167I
c.499C>G	c.C499G	L167V
c.505T>A	c.T505A	F169I
c.505T>G	c.T505G	F169V
c.506T>A	c.T506A	F169Y
c.506T>C	c.T506C	F169S
c.506T>G	c.T506G	F169C

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.507T>A	c.T507A	F169L
c.511G>A	c.G511A	G171S
c.512G>C	c.G512C	G171A
c.512G>T	c.G512T	G171V
c.517T>C	c.T517C	Y173H
c.518A>C	c.A518C	Y173S
c.518A>G	c.A518G	Y173C
c.518A>T	c.A518T	Y173F
c.520T>C	c.T520C	C174R
c.520T>G	c.T520G	C174G
c.523G>C	c.G523C	D175H
c.523G>T	c.G523T	D175Y
c.524A>G	c.A524G	D175G
c.524A>T	c.A524T	D175V
c.525C>G or c.525C>A	c.C525G or c.C525A	D175E
c.526A>T	c.A526T	S176C
c.528T>A	c.T528A	S176R
c.529T>A	c.T529A	L177M
c.529T>G	c.T529G	L177V
c.530T>C	c.T530C	L177S
c.530T>G	c.T530G	L177W
c.531G>C	c.G531C	L177F
c.532G>A	c.G532A	E178K
c.532G>C	c.G532C	E178Q
c.533A>C	c.A533C	E178A
c.533A>G	c.A533G	E178G
c.538T>A	c.T538A	L180M
c.538T>G	c.T538G	L180V
c.539T>C	c.T539C	L180S
c.539T>G	c.T539G	L180W
c.540G>C or c.540G>T	c.G540C or c.G540T	L180F
c.541G>A	c.G541A	A181T
c.541G>C	c.G541C	A181P
c.542C>T	c.C542T	A181V
c.544G>T	c.G544T	D182Y
c.545A>C	c.A545C	D182A
c.545A>G	c.A545G	D182G
c.545A>T	c.A545T	D182V
c.546T>A	c.T546A	D182E
c.548G>A	c.G548A	G183D
c.548G>C	c.G548C	G183A
c.550T>A	c.T550A	Y184N
c.550T>C	c.T550C	Y184H
c.551A>C	c.A551C	Y184S

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.551A>G	c.A551G	Y184C
c.551A>T	c.A551T	Y184F
c.553A>C	c.A553C	K185Q
c.553A>G	c.A553G	K185E
c.554A>C	c.A554C	K185T
c.554A>T	c.A554T	K185M
c.555G>C	c.G555C	K185N
c.556C>A	c.C556A	H186N
c.556C>G	c.C556G	H186D
c.556C>T	c.C556T	H186Y
c.557A>T	c.A557T	H186L
c.558C>G	c.C558G	H186Q
c.559_564dup	c.559_564dup	p.M187_S188dup
c.559A>T	c.A559T	M187L
c.559A>G	c.A559G	M187V
c.560T>C	c.T560C	M187T
c.561G>T or c.561G>A or c.561G>C	c.G561T or c.G561A or c.G561C	M187I
c.562T>A	c.T562A	S188T
c.562T>C	c.T562C	S188P
c.562T>G	c.T562G	S188A
c.563C>A	c.C563A	S188Y
c.563C>G	c.C563G	S188C
c.563C>T	c.C563T	S188F
c.565T>G	c.T565G	L189V
c.566T>C	c.T566C	L189S
c.567G>C or c.567G>T	c.G567C or c.G567T	L189F
c.568G>A	c.G568A	A190T
c.568G>T	c.G568T	A190S
c.569C>A	c.C569A	A190D
c.569C>G	c.C569G	A190G
c.569C>T	c.C569T	A190V
c.571C>A	c.C571A	L191M
c.571C>G	c.C571G	L191V
c.572T>A	c.T572A	L191Q
c.574A>C	c.A574C	N192H
c.574A>G	c.A574G	N192D
c.575A>C	c.A575C	N192T
c.575A>G	c.A575G	N192S
c.576T>A	c.T576A	N192K
c.577A>G	c.A577G	R193G
c.577A>T	c.A577T	R193W
c.578G>C	c.G578C	R193T
c.578G>T	c.G578T	R193M

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.580A>C	c.A580C	T194P
c.580A>G	c.A580G	T194A
c.580A>T or c.581C>G	c.A580T or c.C581G	T194S
c.581C>A	c.C581A	T194N
c.581C>T	c.C581T	T194I
c.583G>A	c.G583A	G195S
c.583G>C	c.G583C	G195R
c.583G>T	c.G583T	G195C
c.584G>T	c.G584T	G195V
c.586A>G	c.A586G	R196G
c.587G>A	c.G587A	R196K
c.587G>C	c.G587C	R196T
c.587G>T	c.G587T	R196I
c.589A>G	c.A589G	S197G
c.589A>T	c.A589T	S197C
c.590G>A	c.G590A	S197N
c.590G>C	c.G590C	S197T
c.590G>T	c.G590T	S197I
c.593T>C	c.T593C	I198T
c.593T>G	c.T593G	I198S
c.594T>G	c.T594G	I198M
c.595G>A	c.G595A	V199M
c.595G>C	c.G595C	V199L
c.596T>A	c.T596A	V199E
c.596T>C	c.T596C	V199A
c.596T>G	c.T596G	V199G
c.598T>A	c.T598A	Y200N
c.599A>C	c.A599C	Y200S
c.599A>G	c.A599G	Y200C
c.601T>A	c.T601A	S201T
c.601T>G	c.T601G	S201A
c.602C>A	c.C602A	S201Y
c.602C>G	c.C602G	S201C
c.602C>T	c.C602T	S201F
c.607G>C	c.G607C	E203Q
c.608A>C	c.A608C	E203A
c.608A>G	c.A608G	E203G
c.608A>T	c.A608T	E203V
c.609G>C or c.609G>T	c.G609C or c.G609T	E203D
c.610T>G	c.T610G	W204G
c.611G>C	c.G611C	W204S
c.611G>T	c.G611T	W204L
c.613C>A	c.C613A	P205T
c.613C>T	c.C613T	P205S

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.614C>T	c.C614T	P205L
c.616C>A	c.C616A	L206I
c.616C>G	c.C616G	L206V
c.616C>T	c.C616T	L206F
c.617T>A	c.T617A	L206H
c.617T>G	c.T617G	L206R
c.619T>C	c.T619C	Y207H
c.620A>C	c.A620C	Y207S
c.620A>T	c.A620T	Y207F
c.623T>A	c.T623A	M208K
c.623T>G	c.T623G	M208R
c.625T>A	c.T625A	W209R
c.625T>G	c.T625G	W209G
c.627G>C	c.G627C	W209C
c.628C>A	c.C628A	P210T
c.628C>T	c.C628T	P210S
c.629C>A	c.C629A	P210H
c.629C>T	c.C629T	P210L
c.631T>C	c.T631C	F211L
c.631T>G	c.T631G	F211V
c.632T>A	c.T632A	F211Y
c.632T>C	c.T632C	F211S
c.632T>G	c.T632G	F211C
c.635A>C	c.A635C	Q212P
c.636A>T	c.A636T	Q212H
c.637A>C	c.A637C	K213Q
c.637A>G	c.A637G	K213E
c.638A>G	c.A638G	K213R
c.638A>T	c.A638T	K213M
c.640C>A	c.C640A	P214T
c.640C>G	c.C640G	P214A
c.640C>T	c.C640T	P214S
c.641C>A	c.C641A	P214H
c.641C>G	c.C641G	P214R
c.641C>T	c.C641T	P214L
c.643A>C	c.A643C	N215H
c.643A>G	c.A643G	N215D
c.643A>T	c.A643T	N215Y
c.644A>C	c.A644C	N215T
c.644A>G	c.A644G	N215S
c.[644A>G; 937G>T]	c.A644G/G937T	N215S/D313Y
c.644A>T	c.A644T	N215I
c.645T>A	c.T645A	N215K
c.646T>A	c.T646A	Y216N

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.646T>C	c.T646C	Y216H
c.646T>G	c.T646G	Y216D
c.647A>C	c.A647C	Y216S
c.647A>G	c.A647G	Y216C
c.647A>T	c.A647T	Y216F
c.649A>C	c.A649C	T217P
c.649A>G	c.A649G	T217A
c.649A>T	c.A649T	T217S
c.650C>A	c.C650A	T217K
c.650C>G	c.C650G	T217R
c.650C>T	c.C650T	T217I
c.652G>A	c.G652A	E218K
c.652G>C	c.G652C	E218Q
c.653A>C	c.A653C	E218A
c.653A>G	c.A653G	E218G
c.653A>T	c.A653T	E218V
c.654A>T	c.A654T	E218D
c.655A>C	c.A655C	I219L
c.655A>T	c.A655T	I219F
c.656T>A	c.T656A	I219N
c.656T>C	c.T656C	I219T
c.656T>G	c.T656G	I219S
c.657C>G	c.C657G	I219M
c.659G>A	c.G659A	R220Q
c.659G>C	c.G659C	R220P
c.659G>T	c.G659T	R220L
c.661C>A	c.C661A	Q221K
c.661C>G	c.C661G	Q221E
c.662A>C	c.A662C	Q221P
c.662A>G	c.A662G	Q221R
c.662A>T	c.A662T	Q221L
c.663G>C	c.G663C	Q221H
c.664T>A	c.T664A	Y222N
c.664T>C	c.T664C	Y222H
c.664T>G	c.T664G	Y222D
c.665A>C	c.A665C	Y222S
c.665A>G	c.A665G	Y222C
c.670A>C	c.A670C	N224H
c.671A>C	c.A671C	N224T
c.671A>G	c.A671G	N224S
c.673C>G	c.C673G	H225D
c.679C>G	c.C679G	R227G
c.682A>C	c.A682C	N228H
c.682A>G	c.A682G	N228D

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.683A>C	c.A683C	N228T
c.683A>G	c.A683G	N228S
c.683A>T	c.A683T	N228I
c.685T>A	c.T685A	F229I
c.686T>A	c.T686A	F229Y
c.686T>C	c.T686C	F229S
c.687T>A or c.687T>G	c.T687A or c.T687G	F229L
c.688G>C	c.G688C	A230P
c.689C>A	c.C689A	A230D
c.689C>G	c.C689G	A230G
c.689C>T	c.C689T	A230V
c.694A>C	c.A694C	I232L
c.694A>G	c.A694G	I232V
c.695T>C	c.T695C	I232T
c.696T>G	c.T696G	I232M
c.698A>C	c.A698C	D233A
c.698A>G	c.A698G	D233G
c.698A>T	c.A698T	D233V
c.699T>A	c.T699A	D233E
c.703T>A	c.T703A	S235T
c.703T>G	c.T703G	S235A
c.710A>T	c.A710T	K237I
c.712A>G	c.A712G	S238G
c.712A>T	c.A712T	S238C
c.713G>A	c.G713A	S238N
c.713G>C	c.G713C	S238T
c.713G>T	c.G713T	S238I
c.715A>T	c.A715T	I239L
c.716T>C	c.T716C	I239T
c.717A>G	c.A717G	I239M
c.718A>G	c.A718G	K240E
c.719A>G	c.A719G	K240R
c.719A>T	c.A719T	K240M
c.720G>C or c.720G>T	c.G720C or c.G720T	K240N
c.721A>T	c.A721T	S241C
c.722G>C	c.G722C	S241T
c.722G>T	c.G722T	S241I
c.724A>C	c.A724C	I242L
c.724A>G	c.A724G	I242V
c.724A>T	c.A724T	I242F
c.725T>A	c.T725A	I242N
c.725T>C	c.T725C	I242T
c.725T>G	c.T725G	I242S
c.726C>G	c.C726G	I242M

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.727T>A	c.T727A	L243M
c.727T>G	c.T727G	L243V
c.728T>C	c.T728C	L243S
c.728T>G	c.T728G	L243W
c.729G>C or c.729G>T	c.G729C or c.G729T	L243F
c.730G>A	c.G730A	D244N
c.730G>C	c.G730C	D244H
c.730G>T	c.G730T	D244Y
c.731A>C	c.A731C	D244A
c.731A>G	c.A731G	D244G
c.731A>T	c.A731T	D244V
c.732C>G	c.C732G	D244E
c.733T>G	c.T733G	W245G
c.735G>C	c.G735C	W245C
c.736A>G	c.A736G	T246A
c.737C>A	c.C737A	T246K
c.737C>G	c.C737G	T246R
c.737C>T	c.C737T	T246I
c.739T>A	c.T739A	S247T
c.739T>G	c.T739G	S247A
c.740C>A	c.C740A	S247Y
c.740C>G	c.C740G	S247C
c.740C>T	c.C740T	S247F
c.742T>G	c.T742G	F248V
c.743T>A	c.T743A	F248Y
c.743T>G	c.T743G	F248C
c.744T>A	c.T744A	F248L
c.745A>C	c.A745C	N249H
c.745A>G	c.A745G	N249D
c.745A>T	c.A745T	N249Y
c.746A>C	c.A746C	N249T
c.746A>G	c.A746G	N249S
c.746A>T	c.A746T	N249I
c.747C>G or c.747C>A	c.C747G or c.C747A	N249K
c.748C>A	c.C748A	Q250K
c.748C>G	c.C748G	Q250E
c.749A>C	c.A749C	Q250P
c.749A>G	c.A749G	Q250R
c.749A>T	c.A749T	Q250L
c.750G>C	c.G750C	Q250H
c.751G>A	c.G751A	E251K
c.751G>C	c.G751C	E251Q
c.752A>G	c.A752G	E251G
c.752A>T	c.A752T	E251V

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.754A>G	c.A754G	R252G
c.757A>G	c.A757G	I253V
c.757A>T	c.A757T	I253F
c.758T>A	c.T758A	I253N
c.758T>C	c.T758C	I253T
c.758T>G	c.T758G	I253S
c.760-762delGTT or c.761-763del	c.760_762delGTT or c.761_763del	p.V254del
c.760G>T	c.G760T	V254F
c.761T>A	c.T761A	V254D
c.761T>C	c.T761C	V254A
c.761T>G	c.T761G	V254G
c.763G>A	c.G763A	D255N
c.763G>C	c.G763C	D255H
c.763G>T	c.G763T	D255Y
c.764A>C	c.A764C	D255A
c.764A>T	c.A764T	D255V
c.765T>A	c.T765A	D255E
c.766G>C	c.G766C	V256L
c.767T>A	c.T767A	V256D
c.767T>G	c.T767G	V256G
c.769G>A	c.G769A	A257T
c.769G>C	c.G769C	A257P
c.769G>T	c.G769T	A257S
c.770C>G	c.C770G	A257G
c.770C>T	c.C770T	A257V
c.772G>C or c.772G>A	c.G772C or c.G772A	G258R
c.773G>A	c.G773A	G258E
c.773G>T	c.G773T	G258V
c.775C>A	c.C775A	P259T
c.775C>G	c.C775G	P259A
c.775C>T	c.C775T	P259S
c.776C>A	c.C776A	P259Q
c.776C>G	c.C776G	P259R
c.776C>T	c.C776T	P259L
c.778G>T	c.G778T	G260W
c.779G>A	c.G779A	G260E
c.779G>C	c.G779C	G260A
c.781G>A	c.G781A	G261S
c.781G>C	c.G781C	G261R
c.781G>T	c.G781T	G261C
c.782G>C	c.G782C	G261A
c.787A>C	c.A787C	N263H
c.788A>C	c.A788C	N263T

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.788A>G	c.A788G	N263S
c.790G>A	c.G790A	D264N
c.790G>C	c.G790C	D264H
c.790G>T	c.G790T	D264Y
c.793C>G	c.C793G	P265A
c.794C>A	c.C794A	P265Q
c.794C>T	c.C794T	P265L
c.799A>G	c.A799G	M267V
c.799A>T	c.A799T	M267L
c.800T>C	c.T800C	M267T
c.802T>A	c.T802A	L268I
c.804A>T	c.A804T	L268F
c.805G>A	c.G805A	V269M
c.805G>C	c.G805C	V269L
c.806T>C	c.T806C	V269A
c.808A>C	c.A808C	I270L
c.808A>G	c.A808G	I270V
c.809T>C	c.T809C	I270T
c.809T>G	c.T809G	I270S
c.810T>G	c.T810G	I270M
c.811G>A	c.G811A	G271S
c.[811G>A; 937G>T]	c.G811A/G937T	G271S/D313Y
c.812G>A	c.G812A	G271D
c.812G>C	c.G812C	G271A
c.814A>G	c.A814G	N272D
c.818T>A	c.T818A	F273Y
c.823C>A	c.C823A	L275I
c.823C>G	c.C823G	L275V
c.827G>A	c.G827A	S276N
c.827G>C	c.G827C	S276T
c.829T>G	c.T829G	W277G
c.830G>T	c.G830T	W277L
c.831G>T or c.831G>C	c.G831T or c.G831C	W277C
c.832A>T	c.A832T	N278Y
c.833A>T	c.A833T	N278I
c.835C>G	c.C835G	Q279E
c.838C>A	c.C838A	Q280K
c.839A>G	c.A839G	Q280R
c.839A>T	c.A839T	Q280L
c.840A>T or c.840A>C	c.A840T or c.A840C	Q280H
c.841G>C	c.G841C	V281L
c.842T>A	c.T842A	V281E
c.842T>C	c.T842C	V281A
c.842T>G	c.T842G	V281G

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.844A>G	c.A844G	T282A
c.844A>T	c.A844T	T282S
c.845C>T	c.C845T	T282I
c.847C>G	c.C847G	Q283E
c.848A>T	c.A848T	Q283L
c.849G>C	c.G849C	Q283H
c.850A>G	c.A850G	M284V
c.850A>T	c.A850T	M284L
c.851T>C	c.T851C	M284T
c.852G>C	c.G852C	M284I
c.853G>A	c.G853A	A285T
c.854C>G	c.C854G	A285G
c.854C>T	c.C854T	A285V
c.856C>G	c.C856G	L286V
c.856C>T	c.C856T	L286F
c.857T>A	c.T857A	L286H
c.860G>T	c.G860T	W287L
c.862G>C	c.G862C	A288P
c.862G>T	c.G862T	A288S
c.863C>G	c.C863G	A288G
c.863C>T	c.C863T	A288V
c.865A>C	c.A865C	I289L
c.865A>G	c.A865G	I289V
c.866T>C	c.T866C	I289T
c.866T>G	c.T866G	I289S
c.868A>C or c.868A>T	c.A868C or c.A868T	M290L
c.868A>G	c.A868G	M290V
c.869T>C	c.T869C	M290T
c.870G>A or c.870G>C or c.870G>T	c.G870A or c.G870C or c.G870T	M290I
c.871G>A	c.G871A	A291T
c.871G>T	c.G871T	A291S
c.872C>G	c.C872G	A291G
c.874G>T	c.G874T	A292S
c.875C>G	c.C875G	A292G
c.877C>A	c.C877A	P293T
c.880T>A	c.T880A	L294I
c.880T>G	c.T880G	L294V
c.881T>C	c.T881C	L294S
c.882A>T	c.A882T	L294F
c.883T>A	c.T883A	F295I
c.883T>G	c.T883G	F295V
c.884T>A	c.T884A	F295Y
c.884T>C	c.T884C	F295S

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.884T>G	c.T884G	F295C
c.886A>G	c.A886G	M296V
c.886A>T or c.886A>C	c.A886T or c.A886C	M296L
c.887T>C	c.T887C	M296T
c.888G>A or c.888G>T or c.888G>C	c.G888A or c.G888T or c.G888C	M296I
c.889T>A	c.T889A	S297T
c.892A>G	c.A892G	N298D
c.893A>C	c.A893C	N298T
c.893A>G	c.A893G	N298S
c.893A>T	c.A893T	N298I
c.895G>A	c.G895A	D299N
c.895G>C	c.G895C	D299H
c.897C>G or c.897C>A	c.C897G or c.C897A	D299E
c.898C>A	c.C898A	L300I
c.898C>G	c.C898G	L300V
c.898C>T	c.C898T	L300F
c.899T>C	c.T899C	L300P
c.901C>G	c.C901G	R301G
c.902G>A	c.G902A	R301Q
c.902G>C	c.G902C	R301P
c.902G>T	c.G902T	R301L
c.904C>A	c.C904A	H302N
c.904C>G	c.C904G	H302D
c.904C>T	c.C904T	H302Y
c.905A>T	c.A905T	H302L
c.907A>G	c.A907G	I303V
c.907A>T	c.A907T	I303F
c.908T>A	c.T908A	I303N
c.908T>C	c.T908C	I303T
c.908T>G	c.T908G	I303S
c.911G>A	c.G911A	S304N
c.911G>C	c.G911C	S304T
c.911G>T	c.G911T	S304I
c.916C>G	c.C916G	Q306E
c.917A>C	c.A917C	Q306P
c.917A>T	c.A917T	Q306L
c.919G>A	c.G919A	A307T
c.919G>C	c.G919C	A307P
c.919G>T	c.G919T	A307S
c.920C>A	c.C920A	A307D
c.920C>G	c.C920G	A307G
c.920C>T	c.C920T	A307V
c.922A>C	c.A922C	K308Q

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.922A>G	c.A922G	K308E
c.923A>G	c.A923G	K308R
c.923A>T	c.A923T	K308I
c.924A>T or c.924A>C	c.A924T or c.A924C	K308N
c.925G>A	c.G925A	A309T
c.925G>C	c.G925C	A309P
c.926C>A	c.C926A	A309D
c.926C>T	c.C926T	A309V
c.928C>A	c.C928A	L310I
c.928C>G	c.C928G	L310V
c.928C>T	c.C928T	L310F
c.931C>A	c.C931A	L311I
c.931C>G	c.C931G	L311V
c.934C>A	c.C934A	Q312K
c.934C>G	c.C934G	Q312E
c.935A>G	c.A935G	Q312R
c.935A>T	c.A935T	Q312L
c.936G>T or c.936G>C	c.G936T or c.G936C	Q312H
c.937G>T	c.G937T	D313Y
c.[937G>T; 1232G>A]	c.G937T/G1232A	D313Y/G411D
c.938A>G	c.A938G	D313G
c.938A>T	c.A938T	D313V
c.939T>A	c.T939A	D313E
c.940A>G	c.A940G	K314E
c.941A>C	c.A941C	K314T
c.941A>T	c.A941T	K314M
c.942G>C	c.G942C	K314N
c.943G>A	c.G943A	D315N
c.943G>C	c.G943C	D315H
c.943G>T	c.G943T	D315Y
c.944A>C	c.A944C	D315A
c.944A>G	c.A944G	D315G
c.944A>T	c.A944T	D315V
c.946G>A	c.G946A	V316I
c.946G>C	c.G946C	V316L
c.947T>C	c.T947C	V316A
c.947T>G	c.T947G	V316G
c.949A>C	c.A949C	I317L
c.949A>G	c.A949G	I317V
c.950T>C	c.T950C	I317T
c.951T>G	c.T951G	I317M
c.952G>A	c.G952A	A318T
c.952G>C	c.G952C	A318P
c.953C>A	c.C953A	A318D

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.953C>T	c.C953T	A318V
c.955A>T	c.A955T	I319F
c.956T>C	c.T956C	I319T
c.957C>G	c.C957G	I319M
c.958A>C	c.A958C	N320H
c.959A>C	c.A959C	N320T
c.959A>G	c.A959G	N320S
c.959A>T	c.A959T	N320I
c.961C>A	c.C961A	Q321K
c.962A>G	c.A962G	Q321R
c.962A>T	c.A962T	Q321L
c.963G>C or c.963G>T	c.G963C or c.G963T	Q321H
c.964G>A	c.G964A	D322N
c.964G>C	c.G964C	D322H
c.965A>C	c.A965C	D322A
c.965A>T	c.A965T	D322V
c.966C>A or c.966C>G	c.C966A or c.C966G	D322E
c.967C>A	c.C967A	P323T
c.968C>G	c.C968G	P323R
c.970T>G	c.T970G	L324V
c.971T>G	c.T971G	L324W
c.973G>A	c.G973A	G325S
c.973G>C	c.G973C	G325R
c.973G>T	c.G973T	G325C
c.974G>C	c.G974C	G325A
c.974G>T	c.G974T	G325V
c.976A>C	c.A976C	K326Q
c.976A>G	c.A976G	K326E
c.977A>C	c.A977C	K326T
c.977A>G	c.A977G	K326R
c.977A>T	c.A977T	K326M
c.978G>C or c.978G>T	c.G978C or c.G978T	K326N
c.979C>G	c.C979G	Q327E
c.980A>C	c.A980C	Q327P
c.980A>T	c.A980T	Q327L
c.981A>T	c.A981T	Q327H
c.983G>C	c.G983C	G328A
c.985T>A	c.T985A	Y329N
c.985T>C	c.T985C	Y329H
c.985T>G	c.T985G	Y329D
c.986A>G	c.A986G	Y329C
c.986A>T	c.A986T	Y329F
c.988C>A	c.C988A	Q330K
c.988C>G	c.C988G	Q330E

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.989A>C	c.A989C	Q330P
c.989A>G	c.A989G	Q330R
c.990G>C	c.G990C	Q330H
c.991C>G	c.C991G	L331V
c.992T>A	c.T992A	L331H
c.992T>C	c.T992C	L331P
c.992T>G	c.T992G	L331R
c.994A>G	c.A994G	R332G
c.995G>C	c.G995C	R332T
c.995G>T	c.G995T	R332I
c.996A>T	c.A996T	R332S
c.997C>G	c.C997G	Q333E
c.998A>C	c.A998C	Q333P
c.998A>T	c.A998T	Q333L
c.1000G>C	c.G1000C	G334R
c.1001G>A	c.G1001A	G334E
c.1001G>T	c.G1001T	G334V
c.1003G>T	c.G1003T	D335Y
c.1004A>C	c.A1004C	D335A
c.1004A>G	c.A1004G	D335G
c.1004A>T	c.A1004T	D335V
c.1005C>G	c.C1005G	D335E
c.1006A>G	c.A1006G	N336D
c.1006A>T	c.A1006T	N336Y
c.1007A>C	c.A1007C	N336T
c.1007A>G	c.A1007G	N336S
c.1007A>T	c.A1007T	N336I
c.1009T>G	c.T1009G	F337V
c.1010T>A	c.T1010A	F337Y
c.1010T>C	c.T1010C	F337S
c.1010T>G	c.T1010G	F337C
c.1011T>A	c.T1011A	F337L
c.1012G>A	c.G1012A	E338K
c.1013A>C	c.A1013C	E338A
c.1013A>G	c.A1013G	E338G
c.1013A>T	c.A1013T	E338V
c.1014A>T	c.A1014T	E338D
c.1015G>A	c.G1015A	V339M
c.1016T>A	c.T1016A	V339E
c.1016T>C	c.T1016C	V339A
c.1021G>C	c.G1021C	E341Q
c.1022A>C	c.A1022C	E341A
c.1027C>A	c.C1027A	P343T
c.1027C>G	c.C1027G	P343A

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.1027C>T	c.C1027T	P343S
c.1028C>T	c.C1028T	P343L
c.1030C>G	c.C1030G	L344V
c.1030C>T	c.C1030T	L344F
c.1031T>G	c.T1031G	L344R
c.1033T>C	c.T1033C	S345P
c.1036G>T	c.G1036T	G346C
c.1037G>A	c.G1037A	G346D
c.1037G>C	c.G1037C	G346A
c.1037G>T	c.G1037T	G346V
c.1039T>A	c.T1039A	L347I
c.1043C>A	c.C1043A	A348D
c.1046G>C	c.G1046C	W349S
c.1046G>T	c.G1046T	W349L
c.1047G>C	c.G1047C	W349C
c.1048G>A	c.G1048A	A350T
c.1048G>T	c.G1048T	A350S
c.1049C>G	c.C1049G	A350G
c.1049C>T	c.C1049T	A350V
c.1052T>A	c.T1052A	V351E
c.1052T>C	c.T1052C	V351A
c.1054G>A	c.G1054A	A352T
c.1054G>T	c.G1054T	A352S
c.1055C>G	c.C1055G	A352G
c.1055C>T	c.C1055T	A352V
c.1057A>T	c.A1057T	M353L
c.1058T>A	c.T1058A	M353K
c.1058T>C	c.T1058C	M353T
c.1061T>A	c.T1061A	I354K
c.1061T>G	c.T1061G	I354R
c.1063A>C	c.A1063C	N355H
c.1063A>G	c.A1063G	N355D
c.1063A>T	c.A1063T	N355Y
c.1064A>G	c.A1064G	N355S
c.1066C>G	c.C1066G	R356G
c.1066C>T	c.C1066T	R356W
c.1067G>A	c.G1067A	R356Q
c.1067G>C	c.G1067C	R356P
c.1067G>T	c.G1067T	R356L
c.1069C>G	c.C1069G	Q357E
c.1072G>C	c.G1072C	E358Q
c.1073A>C	c.A1073C	E358A
c.1073A>G	c.A1073G	E358G
c.1074G>T or c.1074G>C	c.G1074T or c.G1074C	E358D

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.1075A>C	c.A1075C	I359L
c.1075A>G	c.A1075G	I359V
c.1075A>T	c.A1075T	I359F
c.1076T>A	c.T1076A	I359N
c.1076T>C	c.T1076C	I359T
c.1076T>G	c.T1076G	I359S
c.1078G>A	c.G1078A	G360S
c.1078G>C	c.G1078C	G360R
c.1078G>T	c.G1078T	G360C
c.1079G>A	c.G1079A	G360D
c.1079G>C	c.G1079C	G360A
c.1082G>A	c.G1082A	G361E
c.1082G>C	c.G1082C	G361A
c.1084C>A	c.C1084A	P362T
c.1084C>G	c.C1084G	P362A
c.1084C>T	c.C1084T	P362S
c.1085C>A	c.C1085A	P362H
c.1085C>G	c.C1085G	P362R
c.1085C>T	c.C1085T	P362L
c.1087C>A	c.C1087A	R363S
c.1087C>G	c.C1087G	R363G
c.1087C>T	c.C1087T	R363C
c.1088G>A	c.G1088A	R363H
c.1088G>T	c.G1088T	R363L
c.1090T>C	c.T1090C	S364P
c.1091C>G	c.C1091G	S364C
c.1093T>A	c.T1093A	Y365N
c.1093T>G	c.T1093G	Y365D
c.1094A>C	c.A1094C	Y365S
c.1094A>T	c.A1094T	Y365F
c.1096A>C	c.A1096C	T366P
c.1096A>T	c.A1096T	T366S
c.1097C>A	c.C1097A	T366N
c.1097C>T	c.C1097T	T366I
c.1099A>C	c.A1099C	I367L
c.1099A>T	c.A1099T	I367F
c.1101C>G	c.C1101G	I367M
c.1102G>A	c.G1102A	A368T
c.1102G>C	c.G1102C	A368P
c.1103C>G	c.C1103G	A368G
c.1105G>A	c.G1105A	V369I
c.1105G>C	c.G1105C	V369L
c.1105G>T	c.G1105T	V369F
c.1106T>C	c.T1106C	V369A

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.1106T>G	c.T1106G	V369G
c.1108G>A	c.G1108A	A370T
c.1108G>C	c.G1108C	A370P
c.1109C>A	c.C1109A	A370D
c.1109C>G	c.C1109G	A370G
c.1109C>T	c.C1109T	A370V
c.1111T>A	c.T1111A	S371T
c.1112C>G	c.C1112G	S371C
c.1117G>A	c.G1117A	G373S
c.1117G>T	c.G1117T	G373C
c.1118G>C	c.G1118C	G373A
c.1120A>G	c.A1120G	K374E
c.1121A>C	c.A1121C	K374T
c.1121A>G	c.A1121G	K374R
c.1121A>T	c.A1121T	K374I
c.1123G>C	c.G1123C	G375R
c.1124G>A	c.G1124A	G375E
c.1124G>C	c.G1124C	G375A
c.1126G>A	c.G1126A	V376M
c.1126G>C	c.G1126C	V376L
c.1127T>A	c.T1127A	V376E
c.1127T>G	c.T1127G	V376G
c.1129G>A	c.G1129A	A377T
c.1129G>C	c.G1129C	A377P
c.1129G>T	c.G1129T	A377S
c.1130C>G	c.C1130G	A377G
c.1135A>G	c.A1135G	N379D
c.1136A>C	c.A1136C	N379T
c.1136A>T	c.A1136T	N379I
c.1137T>A	c.T1137A	N379K
c.1138C>A	c.C1138A	P380T
c.1138C>G	c.C1138G	P380A
c.1139C>A	c.C1139A	P380H
c.1139C>G	c.C1139G	P380R
c.1139C>T	c.C1139T	P380L
c.1142C>A	c.C1142A	A381D
c.1147T>A	c.T1147A	F383I
c.1148T>A	c.T1148A	F383Y
c.1148T>G	c.T1148G	F383C
c.1150A>T	c.A1150T	I384F
c.1151T>C	c.T1151C	I384T
c.1152C>G	c.C1152G	I384M
c.1153A>G	c.A1153G	T385A
c.1154C>T	c.C1154T	T385I

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.1156C>A	c.C1156A	Q386K
c.1157A>T	c.A1157T	Q386L
c.1158G>C	c.G1158C	Q386H
c.1159C>A	c.C1159A	L387I
c.1159C>T	c.C1159T	L387F
c.1160T>A	c.T1160A	L387H
c.1160T>G	c.T1160G	L387R
c.1162C>A	c.C1162A	L388I
c.1162C>G	c.C1162G	L388V
c.1162C>T	c.C1162T	L388F
c.1163T>A	c.T1163A	L388H
c.1163T>G	c.T1163G	L388R
c.1168G>A	c.G1168A	V390M
c.1171A>C	c.A1171C	K391Q
c.1171A>G	c.A1171G	K391E
c.1172A>C	c.A1172C	K391T
c.1172A>G	c.A1172G	K391R
c.1172A>T	c.A1172T	K391I
c.1173A>T	c.A1173T	K391N
c.1174A>G	c.A1174G	R392G
c.1174A>T	c.A1174T	R392W
c.1175G>A	c.G1175A	R392K
c.1175G>C	c.G1175C	R392T
c.1175G>T	c.G1175T	R392M
c.1177A>C	c.A1177C	K393Q
c.1177A>G	c.A1177G	K393E
c.1178A>C	c.A1178C	K393T
c.1179G>C	c.G1179C	K393N
c.1180C>A	c.C1180A	L394I
c.1181T>A	c.T1181A	L394Q
c.1181T>C	c.T1181C	L394P
c.1181T>G	c.T1181G	L394R
c.1183G>C	c.G1183C	G395R
c.1184G>A	c.G1184A	G395E
c.1184G>C	c.G1184C	G395A
c.1186T>A	c.T1186A	F396I
c.1186T>G	c.T1186G	F396V
c.1187T>G	c.T1187G	F396C
c.1188C>G	c.C1188G	F396L
c.1189T>A	c.T1189A	Y397N
c.1189T>C	c.T1189C	Y397H
c.1190A>C	c.A1190C	Y397S
c.1190A>G	c.A1190G	Y397C
c.1190A>T	c.A1190T	Y397F

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.1192G>A	c.G1192A	E398K
c.1192G>C	c.G1192C	E398Q
c.1193A>G	c.A1193G	E398G
c.1195T>A	c.T1195A	W399R
c.1195T>G	c.T1195G	W399G
c.1198A>C	c.A1198C	T400P
c.1198A>G	c.A1198G	T400A
c.1198A>T	c.A1198T	T400S
c.1199C>A	c.C1199A	T400N
c.1199C>T	c.C1199T	T400I
c.1201T>A	c.T1201A	S401T
c.1201T>G	c.T1201G	S401A
c.1202_1203insGACTTC	c.1202_1203insGACTTC	p.T400_S401dup
c.1202C>T	c.C1202T	S401L
c.1204A>G	c.A1204G	R402G
c.1204A>T	c.A1204T	R402W
c.1205G>C	c.G1205C	R402T
c.1205G>T	c.G1205T	R402M
c.1206G>C	c.G1206C	R402S
c.1207T>G	c.T1207G	L403V
c.1208T>C	c.T1208C	L403S
c.1209A>T	c.A1209T	L403F
c.1210A>G	c.A1210G	R404G
c.1211G>A	c.G1211A	R404K
c.1211G>C	c.G1211C	R404T
c.1211G>T	c.G1211T	R404I
c.1212A>T	c.A1212T	R404S
c.1213A>G	c.A1213G	S405G
c.1216C>G	c.C1216G	H406D
c.1217A>T	c.A1217T	H406L
c.1218C>G	c.C1218G	H406Q
c.1219A>T	c.A1219T	I407L
c.1220T>C	c.T1220C	I407T
c.1221A>G	c.A1221G	I407M
c.1222A>C	c.A1222C	N408H
c.1222A>G	c.A1222G	N408D
c.1222A>T	c.A1222T	N408Y
c.1223A>C	c.A1223C	N408T
c.1225C>A	c.C1225A	P409T
c.1225C>G	c.C1225G	P409A
c.1225C>T	c.C1225T	P409S
c.1226C>T	c.C1226T	P409L
c.1228A>G	c.A1228G	T410A
c.1228A>T	c.A1228T	T410S

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.1229C>T	c.C1229T	T410I
c.1231G>A	c.G1231A	G411S
c.1231G>T	c.G1231T	G411C
c.1232G>A	c.G1232A	G411D
c.1232G>C	c.G1232C	G411A
c.1232G>T	c.G1232T	G411V
c.1234A>C	c.A1234C	T412P
c.1234A>G	c.A1234G	T412A
c.1234A>T	c.A1234T	T412S
c.1235C>A	c.C1235A	T412N
c.1235C>T	c.C1235T	T412I
c.1237G>A	c.G1237A	V413I
c.1237G>T	c.G1237T	V413F
c.1238T>G	c.T1238G	V413G
c.1240T>G	c.T1240G	L414V
c.1242G>C	c.G1242C	L414F
c.1243C>A	c.C1243A	L415I
c.1244T>A	c.T1244A	L415H
c.1246C>G	c.C1246G	Q416E
c.1247A>T	c.A1247T	Q416L
c.1248G>C	c.G1248C	Q416H
c.1249C>A	c.C1249A	L417I
c.1252G>A	c.G1252A	E418K
c.1252G>C	c.G1252C	E418Q
c.1253A>C	c.A1253C	E418A
c.1253A>G	c.A1253G	E418G
c.1254A>T	c.A1254T	E418D
c.1255A>G	c.A1255G	N419D
c.1255A>T	c.A1255T	N419Y
c.1256A>C	c.A1256C	N419T
c.1256A>G	c.A1256G	N419S
c.1256A>T	c.A1256T	N419I
c.1258A>C	c.A1258C	T420P
c.1258A>T	c.A1258T	T420S
c.1259C>A	c.C1259A	T420K
c.1259C>G	c.C1259G	T420R
c.1261A>G	c.A1261G	M421V
c.1261A>T	c.A1261T	M421L
c.1262T>A	c.T1262A	M421K
c.1262T>C	c.T1262C	M421T
c.1262T>G	c.T1262G	M421R
c.1263G>C	c.G1263C	M421I
c.1265A>C	c.A1265C	Q422P
c.1267A>T	c.A1267T	M423L

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.1268T>A	c.T1268A	M423K
c.1268T>C	c.T1268C	M423T
c.1269G>C	c.G1269C	M423I
c.1271C>T	c.C1271T	S424L
c.1275A>C	c.A1275C	L425F
c.1279G>A	c.G1279A	D427N
c.1286T>G	c.T1286G	L429R

Dosing, Formulation and Administration

[0077] In one or more embodiments, the Fabry patient is administered migalastat or salt thereof at a frequency of once every other day (also referred to as "QOD"). In various embodiments, the doses described herein pertain to migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt. In some embodiments, these doses pertain to the free base of migalastat. In alternate embodiments, these doses pertain to a salt of migalastat. In further embodiments, the salt of migalastat is migalastat hydrochloride. The administration of migalastat or a salt of migalastat is referred to herein as "migalastat therapy".

[0078] Accordingly, in one or more embodiments, the Fabry patient is administered migalastat of salt thereof in a range of from about 15 mg to about 300 mg, from about 15 mg to about 250 mg, from about 15 mg to about 200 mg, from about 15 mg to about 150 mg or from about 15 mg to about 123 mg at a frequency of once every other day, once every three days, once every four days, once every five days, once every six days or once every seven days. In one or more embodiments, the migalastat or salt thereof is administered at a frequency of once every other day (also referred to as "QOD" or "Q48H"), every four days (also referred to as "Q4D" or "Q96H") or every seven days (also referred to as "Q7D" or "Q168H"). In some embodiments, dosing intervals may include any dosing interval with more than 48 hours between doses. For example, dosing intervals may include dosing every 72, 96, 120, 144, or 168 hours.

[0079] In one or more embodiments, the Fabry patient is administered migalastat FBE in a range of from about 15 mg to about 300 mg, from about 15 mg to about 250 mg, from

about 15 mg to about 200 mg, from about 15 mg to about 150 mg, from about 15 mg to about 123 mg, from about 15 mg to about 100 mg, from about 15 mg to about 50 mg, from about 50 mg to about 300 mg, from about 50 mg to about 250 mg, from about 50 mg to about 200 mg, from about 50 mg to about 150 mg, from about 50 mg to about 123 mg, from about 50 mg to about 100 mg, from about 100 mg to about 300 mg, from about 100 mg to about 250 mg, from about 100 mg to about 200 mg, from about 100 mg to about 150 mg, from about 100 mg to about 123 mg, from about 150 mg to about 300 mg, from about 150 mg to about 250 mg, from about 150 mg to about 200 mg, from about 200 mg to about 300 mg, from about 200 mg to about 250 mg or from about 250 mg to about 300 mg at a frequency of once every other day, once every three days, once every four days, once every five days, once every six days or once every seven days.

[0080] In one or more embodiments, the Fabry patient is administered migalastat FBE of about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 123 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg or about 300 mg at a frequency of once every other day, once every three days, once every four days, once every five days, once every six days or once every seven days.

[0081] Again, it is noted that 150 mg of migalastat hydrochloride is equivalent to 123 mg of the free base form of migalastat. Thus, in one or more embodiments, the dose is 150 mg of migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt, administered at a frequency of once every other day, once every three days, once every four days, once every five days, once every six days or once every seven days. In further embodiments, the dose is 150 mg of migalastat hydrochloride administered at a frequency of once every other day. In other embodiments, the dose is 123 mg of the migalastat free base administered at a frequency of once every other day.

[0082] In one or more embodiments, the Fabry patient is administered migalastat hydrochloride in a range of from about 15 mg to about 300 mg, from about 15 mg to about 250 mg, from about 15 mg to about 200 mg, from about 15 mg to about 150 mg, from about 15 mg to about 123 mg, from about 15 mg to about 100 mg, from about 15 mg to about 50 mg, from about 50 mg to about 300 mg, from about 50 mg to about 250 mg, from about 50 mg to about 200 mg, from about 50 mg to about 150 mg, from about 50 mg to about 123 mg, from about 50 mg to about 100 mg, from about 100 mg to about 300 mg, from about 100 mg to about 250 mg, from about 100 mg to about 200 mg, from about 100 mg to about 150 mg, from about 100 mg to about 123 mg, from about 150 mg to about 300 mg, from about 150 mg to about 250 mg, from about 150 mg to about 200 mg, from about 200 mg to about 300 mg, from about 200 mg to about 250 mg or from about 250 mg to about 300 mg at a frequency of once every other day, once every three days, once every four days, once every five days, once every six days or once every seven days.

[0083] In one or more embodiments, the Fabry patient is administered migalastat hydrochloride of about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 42 mg, about 45 mg, about 50 mg, about 55 mg, about 57 mg, about 60 mg, about 65 mg, about 67 mg, about 70 mg, about 75 mg, about 77 mg, about 79 mg, about 80 mg, about 85 mg, about 90 mg, about 94 mg, about 95 mg, about 97 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 128 mg, about 130 mg, about 135 mg, about 140 mg, about 144 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg or about 300 mg at a frequency of once every other day, once every three days, once every four days, once every five days, once every six days or once every seven days.

[0084] In some embodiments, the patient weighs in a range of from about 10 kg to about ≥50 kg, from about 10 kg to about ≤50 kg, from about 10 kg to about ≤45 kg, from about 10 kg to about ≤40 kg, from about 10 kg to about ≤35 kg, from about 10 kg to about ≤30 kg, from about 10 kg to about ≤25 kg, from about 10 kg to about ≤20 kg, from about 10 kg to about ≤15 kg, from about 15 kg to about ≥50 kg, from about 15 kg to about ≤50 kg, from about

15 kg to about ≤45 kg, from about 15 kg to about ≤40 kg, from about 15 kg to about ≤35 kg, from about 15 kg to about ≤30 kg, from about 15 kg to about ≤25 kg, from about 20 kg to about ≥50 kg, from about 20 kg to about ≤50 kg, from about 20 kg to about ≤45 kg, from about 20 kg to about ≤40 kg, from about 20 kg to about ≤35 kg, from about 20 kg to about ≤30 kg, from about 20 kg to about ≤25 kg, from about 25 kg to about ≥50 kg, from about 25 kg to about ≤50 kg, from about 25 kg to about ≤45 kg, from about 25 kg to about ≤40 kg, from about 25 kg to about ≤35 kg, from about 25 kg to about ≤30 kg, from about 30 kg to about ≥50 kg, from about 30 kg to about ≤50 kg, from about 30 kg to about ≤45 kg, from about 30 kg to about ≤40 kg, from about 30 kg to about ≤35 kg, from about 35 kg to about ≥50 kg, from about 35 kg to about ≤50 kg, from about 35 kg to about ≤45 kg, from about 35 kg to about ≤40 kg, from about 40 kg to about ≥50 kg, from about 40 kg to about ≤50 kg, from about 40 kg to about ≤45 kg, from about 45 kg to about ≥50 kg or from about 45 kg to about ≤50 kg.

[0085] Administration of migalastat or salt thereof according to the present invention may be in a formulation suitable for any route of administration, but is preferably administered in an oral dosage form such as a tablet, capsule or solution. For example, the patient is orally administered capsules each containing 25 mg, 40 mg, 50 mg, 60 mg, 75 mg, 80 mg, 100 mg or 150 mg migalastat hydrochloride (i.e. 1-deoxygalactonojirimycin hydrochloride) or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt. In another example, the patient is orally administered capsules each containing 150 mg migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt.

[0086] In various embodiments, the doses described herein pertain to migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt. In some embodiments, these doses pertain to the free base of migalastat. In alternate embodiments, these doses pertain to a salt of migalastat. In further embodiments, the salt of migalastat is migalastat hydrochloride. The administration of migalastat or a salt of migalastat is referred to herein as "migalastat therapy".

[0087] The administration of migalastat or salt thereof may be for a certain period of time. In one or more embodiments, the migalastat or salt thereof is administered for a duration of at least 28 days, such as at least 30, 60 or 90 days or at least 4, 6, 8, 12, 16, 26 or 52 weeks or at least 1,2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 30 or 36 months or at least 1, 2, 3, 4 or 5 years. In some embodiments, the migalastat therapy is of at least about 4 weeks. In various

embodiments, the migalastat therapy is a long-term migalastat therapy of at least about 2, 3, 4 or 5 years.

[0088] In some embodiments, the PC (*e.g.*, migalastat or salt thereof) is administered orally. In one or more embodiments, the PC (*e.g.*, migalastat or salt thereof) is administered by injection. The PC may be accompanied by a pharmaceutically acceptable carrier, which may depend on the method of administration.

[0089] In one or more embodiments, the PC (*e.g.*, migalastat or salt thereof) is administered as monotherapy, and can be in a form suitable for any route of administration, including *e.g.*, orally in the form tablets or capsules or liquid, or in sterile aqueous solution for injection. In other embodiments, the PC is provided in a dry lyophilized powder to be added to the formulation of the replacement enzyme during or immediately after reconstitution to prevent enzyme aggregation *in vitro* prior to administration.

[0090] When the PC (*e.g.*, migalastat or salt thereof) is formulated for oral administration, the tablets or capsules can be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or another suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p- hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active chaperone compound.

[0091] The pharmaceutical formulations of the PC (*e.g.*, migalastat or salt thereof) suitable for parenteral/injectable use generally include sterile aqueous solutions (where water soluble), or dispersions and sterile powders for the extemporaneous preparation of sterile

injectable solutions or dispersion. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, benzyl alcohol, sorbic acid, and the like. In many cases, it will be reasonable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monosterate and gelatin.

[0092] Sterile injectable solutions are prepared by incorporating the purified enzyme (if any) and the PC (*e.g.*, migalastat or salt thereof) in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter or terminal sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

[0093] The formulation can contain an excipient. Pharmaceutically acceptable excipients which may be included in the formulation are buffers such as citrate buffer, phosphate buffer, acetate buffer, bicarbonate buffer, amino acids, urea, alcohols, ascorbic acid, and phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrollidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (*e.g.*, PEG-4000, PEG-6000); glycerol; glycine or other amino acids; and lipids. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers. Phosphate buffer is a preferred embodiment.

[0094] The route of administration of the chaperone compound may be oral or parenteral, including intravenous, subcutaneous, intra-arterial, intraperitoneal, ophthalmic, intramuscular, buccal, rectal, vaginal, intraorbital, intracerebral, intradermal, intracranial, intraspinal, intraventricular, intrathecal, intracisternal, intracapsular, intrapulmonary, intranasal, transmucosal, transdermal, or via inhalation.

[0095] Administration of the above-described parenteral formulations of the chaperone compound may be by periodic injections of a bolus of the preparation, or may be administered by intravenous or intraperitoneal administration from a reservoir which is external (*e.g.*, an i.v. bag) or internal (*e.g.*, a bioerodable implant).

[0096] Embodiments relating to pharmaceutical formulations and administration may be combined with any of the other embodiments of the invention, for example embodiments relating to methods of treating patients with Fabry disease, methods of treating ERT-naïve Fabry patients, methods of treating ERT-experienced Fabry patients, methods of reducing the risk of CBV events, methods of reducing the risk of composite clinical outcomes, methods of assessing symptoms or outcomes of a patient or groups of patients, methods of evaluating a treatment therapy, methods of enhancing α-Gal A in a patient diagnosed with or suspected of having Fabry disease, use of a pharmacological chaperone for α-Gal A for the manufacture of a medicament for treating a patient diagnosed with Fabry disease or to a pharmacological chaperone for α-Gal A for use in treating a patient diagnosed with Fabry disease as well as embodiments relating to amenable mutations, the PCs and suitable dosages thereof.

[0097] In one or more embodiments, the PC (*e.g.*, migalastat or salt thereof) is administered in combination with ERT. ERT increases the amount of protein by exogenously introducing wild-type or biologically functional enzyme by way of infusion. This therapy has been developed for many genetic disorders, including LSDs such as Fabry disease, as referenced above. After the infusion, the exogenous enzyme is expected to be taken up by tissues through non-specific or receptor-specific mechanism. In general, the uptake efficiency is not high, and the circulation time of the exogenous protein is short. In addition, the exogenous protein is unstable and subject to rapid intracellular degradation as well as having the potential for adverse immunological reactions with subsequent treatments. In one or more embodiments, the chaperone is administered at the same time as replacement enzyme (*e.g.*, replacement α-Gal A). In some embodiments, the chaperone is co-formulated with the replacement enzyme (*e.g.*, replacement α-Gal A).

[0098] In one or more embodiments, a patient is switched from ERT to migalastat therapy. In some embodiments, a patient on ERT is identified, the patient's ERT is discontinued, and the patient begins receiving migalastat therapy. The migalastat therapy can be in accordance with any of the methods described herein. In various embodiments, the patient has some degree of renal impairment, such as mild, moderate or severe renal impairment.

Administration of Migalastat

[0099] In some embodiments, migalastat or salt thereof is administered to an adult patient. In some embodiments, age of the adult patient is ≥18 years. In some embodiments, migalastat or salt thereof is administered to an adolescent patient. In some embodiments, age of the adolescent patient is in a range of from 12 years to <18 years, from 13 years to <18 years, from 14 years to <18 years, from 15 years to <18 years, from 16 years to <18 years, from 17 years to <18 years, from 12 years to ≤17 years, from 13 years to ≤17 years, from 14 years to ≤17 years, from 15 years to ≤17 years, from 16 years to ≤17 years, from 12 years to ≤16 years, from 13 years to ≤16 years, from 14 years to ≤16 years, from 15 years to ≤16 years, from 12 years to ≤15 years, from 13 years to ≤15 years, from 14 years to ≤15 years, from 12 years to ≤14 years, from 13 years to ≤14 years, or from 12 years to ≤13 years.

[00100] In some embodiments, migalastat or salt thereof is administered to the patient having a weight a range of from <15 kg to ≥45 kg, from 15 kg to <25 kg, from 25 kg to <35 kg, or from 35 kg to <45 kg. In some embodiments, migalastat or salt thereof is administered to the patient having a weight <15 kg. In some embodiments, migalastat or salt thereof is administered to the patient having a weight ≥45 kg.

[00101] In some embodiments, about 25 mg of migalastat or salt thereof is administered to the patient having a weight of <15 kg. In some embodiments, about 50 mg of migalastat or salt thereof is administered to the patient having a weight in a range of from 15 kg to <25 kg. In some embodiments, about 75 mg of migalastat or salt thereof is administered to the patient having a weight in a range of from 25 kg to <35 kg. In some embodiments, about 75 mg of migalastat or salt thereof is administered to the patient having a weight in a range of from 35 kg to <50 kg.

[00102] In some embodiments, the migalastat or salt thereof is administered at a first frequency for a first time period, and then administered at a second frequency for a second

time period. The first frequency is greater (i.e., more frequent) than the second frequency. The first frequency and the second frequency may be any dosing interval disclosed herein. In some embodiments, the first frequency is every other day and the second frequency is every three days, every four days, every five days, every six days or every seven days. In some embodiments, the first frequency is every four days and the second frequency is every five days, every six days, or every seven days.

[00103] In some embodiments, the migalastat or salt thereof is administered at a first frequency for a first time period, then administered at a second frequency for a second time period, and then administered at a third frequency for a third time period. The first frequency is greater (i.e., more frequent) than the second frequency, and the second frequency is greater than the third frequency. For example, in some embodiments, the migalastat or salt thereof is administered at a first frequency of once every other day for a first time period, then the migalastat or salt thereof is administered at a second frequency of once every four days for a second time period, and then the migalastat or salt thereof is administered at a third frequency of once every seven days for a third time period.

Monitoring Lyso-Gb3 and Migalastat Levels

[00104] Lyso-Gb3 (globotriaosylsphingosine) can be monitored to determine whether substrate is being cleared from the body of a Fabry patient. Higher levels of lyso-Gb3 correlate with higher levels of substrate. If a patient is being successfully treated, then lyso-Gb3 levels are expected to drop. One dosing regimen for Fabry disease is administering to the patient about 20 mg to about 300 mg FBE of migalastat or salt thereof at a frequency of once every other day.

[00105] In some embodiments, the method further comprises measuring migalastat levels. In one or more embodiments, migalastat concentration (*e.g.*, ng/mL) is measured. In some embodiments, the total area under the curve ($AUC_{0-\infty}$) is measured. In one or more embodiments, the lowest concentration the migalastat reaches before the next dose (C_{trough}) is measured.

[00106] Migalastat levels can be measured via methods known in the art. For example, if measuring migalastat from tissue samples, tissue aliquots may be homogenized (7 µL water per 1 mg tissue) using a homogenizer (*e.g.*, FastPrep-24 from MP Biomedical, Irvine, CA). Microcentrifuge tubes containing 100 µl of the tissue homogenate or 50 µl of plasma may then

be spiked with 500 ng/mL 13C d2-AT1001 HCl internal standard (manufactured by MDS Pharma Services). A 600 µl volume of 5 mM HCl in 95/5 MeOH:H_2O can then be added and the tubes vortexed for 2 minutes, followed by centrifugation at 21000 x g for 10 minutes at room temperature. The supernatants may then be collected into a clean, 96-well plate, diluted with 5 mM HCl in dH_2O and applied to a 96-well solid phase extraction (SPE) plate (Waters Corp., Milford MA). After several wash steps and elution into a clean, 96-well plate, the extracts may be dried down under N_2 and reconstituted with mobile phase A. Migalastat levels can then be determined by liquid chromatography – tandem mass spectroscopy (LC-MS/MS) (*e.g.*, LC: Shimadzu; MS/MS: ABSciex API 5500 MS/MS). The liquid chromatography can be conducted using an ACN:water:formate binary mobile phase system (mobile phase A: 5 mM ammonium formate, 0.5% formic acid in 95:5 ACN:water; mobile phase B: 5 mM ammonium formate, 0.5% formic acid in 5:47.5:47.5 ACN:MeOH:water) with a flow rate of 0.7 mL/minute on an Halo HILIC column (150x4.6 mm, 2.7 µm) (Advanced Materials Technology, Inc.). MS/MS analysis may be carried out under APCi positive ion mode. The same procedure may be followed for migalastat determination in plasma except without homogenization. The following precursor ion→product ion transitions may be monitored: mass/charge (m/z) 164.1→m/z 80.1 for migalastat and m/z 167.1→m/z 83.1 for the internal standard. A 12-point calibration curve and quality control samples may be prepared. The ratio of the area under the curve for migalastat to that of the internal standard is then determined and final concentrations of migalastat in each sample calculated using the linear least squares fit equation applied to the calibration curve. To derive approximate molar concentrations, one gram of tissue may be estimated as one mL of volume.

[00107] In some embodiments, samples may be taken at 0, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and/or 168 hours after administration. In some embodiments, the migalastat concentration 48 hours after administration is measured. In some embodiments, the administration of the second time period is begun after more than about 5, 10, 15, 20, 25, 40, 50, 60, 70, 80, 90, 100, 125, 150, 175 or 200 ng/mL of migalastat is measured 48 hours after administration of the migalastat during the first time period is measured.

[00108] In some embodiments, Lyso-Gb3 can be measured via methods known in the art using validated assays. As with migalastat, lyso-Gb3 levels may be determined using liquid chromatography – tandem mass spectroscopy (LC-MS/MS) (*e.g.*, LC: Shimadzu; MS/MS: ABSciex API 5500 MS/MS). For example, one process of measuring plasma lyso-Gb3 is

described in Hamler, Rick, *et al.* "Accurate quantitation of plasma globotriaosylsphingosine (lyso-Gb3) in normal individuals and Fabry disease patients by liquid chromatography–tandem mass spectrometry (LC–MS/MS)." *Molecular Genetics and Metabolism*, Volume 114.2 (2015):S51. In one or more embodiments, lyso-Gb3 is measured in samples from a patient's urine.

Dose Adjustment

[00109] In some embodiments, the dosing frequency of migalastat or salt thereof is adjusted in response to a change in the patient's eGFR. In exemplary embodiments, when the patient's eGFR is reduced below 60 mL/min/1.73 m^2, below 45 mL/min/1.73 m^2, below 30 mL/min/1.73 m^2 or below 15 mL/min/1.73 m^2, the dosing frequency can be reduced. In some embodiments, the patient is not administered migalastat or salt thereof, when the patient's eGFR is reduced below 60 mL/min/1.73 m^2, below 45 mL/min/1.73 m^2, below 30 mL/min/1.73 m^2 or below 15 mL/min/1.73 m^2.

[00110] Migalastat concentration can be measured from plasma samples at various times to monitor clearance from the body. A clinically relevant increase in C_{trough} suggests significant accumulation of plasma migalastat concentration. If the migalastat is not cleared from the body enough prior to the next dose administration, then the levels of migalastat can build up, possibly leading to an inhibitory effect. Thus, in one or more embodiments, a change in the dosing frequency occurs after a 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 or 3.0-fold increase in C_{trough} compared to normal renal function C_{trough}.

[00111] In one or more embodiments, a change in the dosing frequency occurs after a 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9 or 3.0-fold increase in $AUC_{0-\infty}$ compared to normal renal function $AUC_{0-\infty}$.

[00112] In some embodiments, the method further comprises measuring lyso-Gb3 in one or more plasma samples from the patient. A first baseline lyso-Gb3 level may be determined during the first time period. As used herein, "baseline lyso-Gb3 level" refers to the lowest plasma lyso-Gb3 value measured during a given time period or dosing regimen. Thus, if the lyso-Gb3 levels go up significantly from the baseline lyso-Gb3 levels, this may indicate kidney disease progression and/or improper clearance of migalastat. Thus, in further embodiments, the administration of the second time period is begun after an increase (*e.g.*, of at least about

20, 25, 30, 33, 35, 40, 45 or 50% and/or 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5 or 3 nM) above the first baseline lyso-Gb3 level is measured. A 33% and/or 2 nM increase from baseline in plasma lyso-Gb3 has been deemed clinically relevant based upon Phase 3 data in Fabry patients signaling either inhibition-induced migalastat exposure from decline in renal function and/or progression of disease condition. Lyso-Gb3 levels may be measured at varying frequencies (*e.g.*, about once every 2, 3, 4 or 5 months). It is thought that it takes about 3 months for a baseline lyso-Gb3 level to be established once a dosing regimen has been started.

[00113] In some embodiments, the administration of the second time period may begin after an increase above the first baseline lyso-Gb3 level is at least about 30, or 33% and/or 2nM and/or more than about 50 ng/mL of migalastat is measured 48 hours after administration of the migalastat during the first time period is measured. In some embodiments, the administration of the second time period may begin after an increase above the first baseline lyso-Gb3 level is at least about 30, or 33% and/or 2nM and/or more than about 50 ng/mL of migalastat is measured 48 hours after administration of the migalastat during the first time period is measured, or there is a greater than 1.5-fold increase in $AUC_{0-\infty}$ and/or C_{trough} compared to normal renal function during the first time period.

EXAMPLES

Example 1: Dosing Regimens for the Treatment of ERT-Experienced and ERT-Naïve Fabry Patients Using Migalastat Hydrochloride

[00114] This example describes Phase 2 and Phase 3 studies of migalastat therapy in ERT-experienced and ERT-naïve Fabry patients.

Study Designs

[00115] These analyses included data from 4 Phase 2 and 4 Phase 3 clinical trials with the data cutoff of February 10, 2017 as shown in Figure X1 below.

[00116] FAB-CL-202 (NCT00283959), FAB-CL-203 (NCT00283933), and FAB-CL-204 (NCT00304512) were phase 2, open-label, noncomparative studies that evaluated the

safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of migalastat (dose range: 50-250 mg) in patients with Fabry disease.

[00117] FAB-CL-205 (NCT0052607) was a phase 2, long-term, open-label extension (OLE) study for patients completing phase 2 clinical trials, including FAB-CL-202, FAB-CL-203, and FAB-CL-204. The study included a period with migalastat 150 mg every other day (QOD), then a dose-escalation period, followed by 150 mg QOD.

[00118] FACETS (AT1001-011, NCT00925301) was a phase 3, placebo-controlled study designed to evaluate the efficacy, safety, and PD of 6 months of migalastat 150 mg QOD versus placebo, followed by an 18-month open label extension (OLE) of migalastat in ERT-naive patients with Fabry disease and migalastat-amenable GLA variants.

[00119] ATTRACT (AT1001-012, NCT01218659) was a phase 3, open-label, active-controlled study to compare the efficacy and safety of 18 months of migalastat 150 mg QOD versus ERT, followed by a 12-month OLE of migalastat, in ERT-treated patients with migalastat-amenable GLA variants.

[00120] AT1001-041 (NCT01458119) was a long-term OLE study evaluating the long-term safety and efficacy of migalastat in patients completing FAB-CL-205, AT1001-011, or AT1001-012

[00121] AT1001-042 (NCT02194985) is an ongoing, long-term OLE study evaluating the long-term safety and efficacy of migalastat in patients who participated in AT1001-012 or AT1001-041.

Analyses

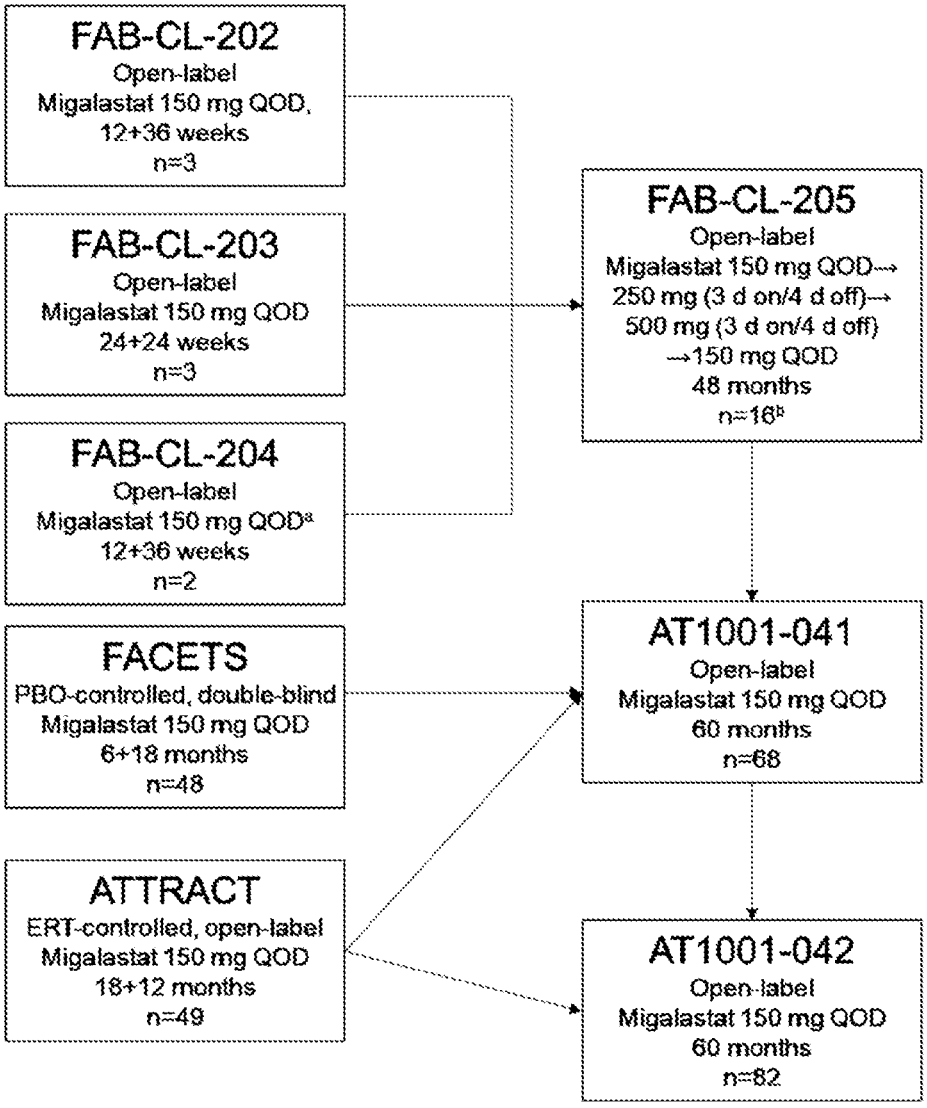
[00122] The analysis evaluates CBV events reported as treatment-emergent adverse events (TEAEs) during migalastat 150 mg QOD treatment in patients with amenable mutations in phase 2 and phase 3 clinical trials.

[00123] CBV events were identified by searching medical history and TEAE listings with stroke-related terms, including brain stem ischemia, cerebral infarction, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, embolic stroke, and TIA.

[00124] Only amenable patients who received at least 1 dose of migalastat 150 mg QOD were included in this analysis.

[00125] Amenability was based on results from a good laboratory practice (GLP)-validated, in vitro migalastat amenability assay.

Clinical Studies Included in the Analysis



PBO=placebo; QOD=every other day

Patient numbers indicate amenable patients who received at least one dose of 150 mg QOD in each study.

[a]FAB-CL-204 also included patients who received migalastat 50 or 250 mg QOD.

[b]FAB-CL-205 also enrolled patients who completed FAB-CL-201 (dose escalation study of migalastat 25, 50, 100, and 250 mg), as well as additional amenable patients from FAB-CL-

204 who received migalastat 50 or 250 mg QOD during FAB-CL-204. The patient number listed for FAB-CL-205 includes all amenable patients who received at least 1 dose of migalastat 150 mg QOD in FAB-CL-205.

[c]AT1001-041 was discontinued early and patients in AT1001-041 had the option to be transferred into Study AT1001-042.

FAB-CL-202, FAB-CL-203, FAB-CL-204 and FAB-CL-205 are Phase 2 clinical studies; FACETS, ATTRACT, AT1001-41 AND AT1001-042 are Phase 3 clinical studies

Results

Migalastat 150 mg QOD Total Exposure

[00126] The total mean (SD) duration of exposure to migalastat 150 mg QOD was 4.0 (2.0) years (N=114).

[00127] The duration of exposure to migalastat 150 mg QOD ranged from 0.1 to 8.3 years, with a median of 4.4 years.

Demographics and Baseline Characteristics

[00128] The mean (SD) age of all amenable patients receiving at least 1 dose of migalastat 150 mg QOD was 46.2 (13.1) years (range: 16 to 72 years) (Table 2). The majority were white, and 57.0% were female. The mean (SD) time since diagnosis of Fabry disease was 9.8 (10.1) years (range: 1 to 44 years).

[00129] **Table 2. Demographics and Baseline Characteristics: All Amenable Patients Receiving Migalastat 150 mg QOD**

Parameter	FAB-CL 202, 203, 204, and 205 (n=17)	FACETS (n=48)	ATTRACT (n=49)	Total (N=114)
Age, year				
Mean (SD)	43.1 (13.4)	43.4 (11.2)	50.0 (14.0)	46.2 (13.1)
Median (range)	42.0 (18, 65)	46.0 (16, 68)	54.0 (18, 72)	46.5
Age group, n (%)				
<18 years old	0	1 (2.1)	0	1 (0.9)

18 to <65 years old	15 (88.2)	46 (95.8)	42 (85.7)	103 (90.4)
≥65 years old	2 (11.8)	1 (2.1)	7 (14.3)	10 (8.8)
Sex, n (%)				
Female	5 (29.4)	30 (62.5)	30 (61.2)	65 (57.0)
Male	12 (70.6)	18 (37.5)	19 (38.8)	49 (43.0)
Years diagnosed with Fabry disease				
Mean (SD)	7.2 (7.5)	7.6 (7.8)[a]	12.9 (12.1)	9.8 (10.1)
Median (range)	5.0 (2, 34)	5.0 (1, 25)	7.0 (3, 44)	6.0 (1, 44)

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor block; RI=renin inhibitor; SD=standard deviation.

[a]Fabry disease diagnosis date was not recorded for 1 patient in FACETS.

Medical History of CBV Events

[00130] Sixteen of 114 patients (14%) had experienced CBV events prior to migalastat treatment (Table 3). One patient from Study AT1001-012 had reported 2 CBV events in medical history.

[00131] In 5/16 patients, the CBV events were considered a current condition at study entry as reported in medical history. One patient from AT1001-011 had ongoing cerebral ischemia; another had ongoing brain stem infarction. Two patients from AT1001-012 had ongoing TIA, one had an ongoing cerebrovascular accident, specifically left middle cerebral artery stroke

[00132] The mean (SD) age at the time of first CBV event was 43.6 (14.4) years.

[00133] **Table 3. Medical History of CBV Events.**

	FAB-CL 202, 203, 204, and 205 (n=17)	**FACETS (n=48)**	**ATTRACT (n=49)**	**Total (N=114)**
Brain stem ischemia	0	0	0	0

Cerebral infarction	0	1 (2%)	0	1 (1%)
Cerebral hemorrhage	0	0	0	0
Cerebral ischemia	0	1 (2%)	1 (2%)	2 (2%)
Cerebrovascular accident	0	2 (4%)	3 (6%)	5 (4%)
Embolic stroke	0	0	0	0
Transient ischemic attack	2 (12%)	2 (4%)	5 (10%)	9 (8%)
Any CBV event history[a]	**2 (12%)**	**6 (12%)**	**8 (16%)**	**16 (14%)**

[a]The last row shows number of unique patients with CBV events. The 1 patient with >1 CBV event was only counted once.

Occurrence of CBV Events During Migalastat 150 mg QOD Treatment

[00134] Eleven CBV events were reported during treatment with migalastat 150 mg QOD in 8 patients (7%) (Table 4). Seven CBV events were categorized as serious adverse events (SAE); however, most (82%) events were mild or moderate in severity (Table 5). Two CBV events led to treatment discontinuation (Table 5). None of the 11 CBV events were considered related to treatment

[00135] Six out of the 8 patients had experienced CBV prior to receiving migalastat treatment; thus only 2/114 (2%) patients had a first CBV event while on migalastat (Table 5).

The mean (SD) age of patients at first event during migalastat treatment was 50.6 (14.6) years (Table 5). The mean (SD) time on migalastat 150 mg QOD at first event onset was 1.1 (1.1) years.

[00136] Among the 16 patients with pre-migalastat CBV event, 10 (63%) did not experience new CBV event during migalastat treatment.

[00137] **Table 4. CBV Events During Treatment With Migalastat 150 mg QOD by Trial**

	FAB-CL 202, 203, 204, and 205 (n=17)	**FACETS (n=48)**	**ATTRACT (n=49)**	**Total (N=114)**
Brain stem ischemia	0	1 (2%)	0	1 (1%)
Cerebral infarction	1 (6%)	0	0	1 (1%)
Cerebral hemorrhage	0	1 (2%)	0	1 (1%)
Cerebral ischemia	1 (6%)	0	0	1 (1%)
Cerebrovascular accident	1 (6%)	0	0	1 (1%)
Embolic stroke	0	0	0	0
Transient ischemic attack	1 (6%)	1 (2%)	2 (4%)	4 (4%)
Any CBV event[a]	**3 (18%)**	**3 (6%)**	**2 (4%)**	**8 (7%)**

[a]The last row shows number of unique patients with CBV events. Patients with >1 CBV event were only counted once.

Patient	**Sex**	**Mutation**	**CBV Event**	**Event**	**Age at**	**Time on**	**Serious**	**Severity**	**Resolved**	**Treatment**	**History**

No.				duration (day)	event onset (year)	migalastat 150 mg QOD at onset (day)				discontinued	of CBV event
1	F	M284T	TIA (right eye)	3	38	589	Yes	Mild	Yes	No	CBV accident
2	M	I253T	Cerebral hemorrhage	Ongoing[b]	63	289	Yes	Severe	No	Yes	None
3	M	I253T	Brain stem ischemia (left pontine region)	47	66	1413	Yes	Moderate	Yes with sequela	No	Cerebral ischemia
4	M	G35R	TIA	7	59	24	Yes	Moderate	Yes	No	TIA
5	F	L32P	TIA	1	56	559	No	Mild	Yes	No	TIA
			TIA	1	56	624	No	Moderate	Yes	No	
6	M	P259R	CBV accident	220	21	90	Yes	Severe	Yes with sequela	Yes	None
7	F	R112H	TIA	3	39	21	Yes	Moderate	Yes	No	TIA
			TIA	2	41	666	Yes	Moderate	Yes	No	
8	F	P205T	Cerebral infarction (right middle artery)	Ongoing[c]	60	371	No	Moderate	No	No	TIA
			Abnormal MRI finding (old ischemic change of right frontal lobe)	Ongoing[c]	60	182	No	Moderate	No	No	

[00138] Table 5. CBV Events During Treatment With Migalastat 150 mg QOD by Patient.

Patient No.	Baseline Parameters[a]					
	Time since diagnosis (year)	Blood Pressure (mm Hg)	Urine Protein (mg/24 hr)	$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	LVMi (g/m^2)	ACEI/ARB/RI use
1	14.5	120/80	399	81.8	88.7	No
2	0.3	NA	1900	53.8	142.8	No
3	4.6	120/80	331	86.8	176.2	Yes
4	10	110/67	182	84.9	154.9	Yes
5	2.2	112/64	231	73.2	68.6	Yes
6	8.3	110/70	66	137.4	NA	No
7	5.8	113/73	163	120.0	NA	No
8	1.9	129/69	NA	NA[d]	NA	No

LVMi=left ventricular mass index; MRI=magnetic resonance imaging; NA=not applicable; TIA=transient ischemic attack.

[a]Baseline was the start of migalastat 150 mg QOD.

[b]Ongoing at the time of discontinuation in FACETS.

[c]Ongoing at the end of FAB-CL-204.

[d]This patient had an $eGFR_{MDRD}$ of 76.4 mL/min/1.73 m^2.

[00139] As can be seen from the tables above, overall incidence of CBV events was low during migalastat treatment. During an average of 4 years of migalastat, 8/114 (7%) patients had experienced CBV events, predominantly occurring in patients with a history of CBV events.

Example 2: Simulation of PK/PD Parameters in Adolescents

PK/PD Modelling

[00140] A population pharmacokinetics (popPK) model previously developed from healthy adult volunteers and adult patients with Fabry disease after oral migalastat administration. After pooling plasma concentration-time data from Phase I, II, and III studies of AT1001 administered orally in adults using a range of doses from 25 mg to 675 mg and regimens under fasting conditions. The conclusions made based on AT1001 study includes:

- A two-compartment population pharmacokinetic model with linear time-dependent absorption characterizes the pharmacokinetics of migalastat in plasma after oral administration.

- Renal function is the most important determinant of variability in migalastat exposure, with an average 3-fold range occurring for eGFR values between 30 and 120 mL/min/1.73 m^2.
- Subject weight is the second-largest determinant of variability in migalastat exposure, with an average < 2-fold difference for body weights between 50 and 170 kg.
- The dose rationale for adults (123 mg every other day (QOD)) was supported by the evaluation of several dose levels and regimens in the 4 Phase II studies (50, 150, and 250 mg QOD; 50 mg once daily; 25, 100, and 250 mg twice daily; and 250 and 500 mg x3 days and off 4 days).
- The present population PK model was considered appropriate for adults; however, it does not have an allometric component with standard exponents (e.g. 0.75 for CLT/F), making pediatric predictions less feasible. Thus, the adult population PK model requires some adjustments to allow extrapolation of migalastat PK to the pediatric age sub-groups of 2 to <6, 6 to <12 and 12 to <18 years.
- The population PK model of migalastat showed that subject weight (WT) and/or renal function (estimated glomerular filtration rate, eGFR) at baseline significantly impacted the apparent oral plasma clearance (CLT/F) and apparent oral volume of distribution of the central compartment (V_2/F). In contrast, other covariates such as sex, age, drug formulation (solution or suspension vs 25 mg capsule vs 150 mg capsule) were not statistically/clinically significant. Since renal function gradually increases from birth and reaches adult levels by the second year of life (Rubin 1949), there are no expected age-dependent changes in eGFR in the pediatric population 2 years and older than adults. Additionally, pediatric patients with Fabry disease usually have a normal renal function or may experience renal hyperfiltration (Hopkin 2008); therefore, weight-based dosing regimens, assuming that pediatrics have a normal renal function, were planned for the simulations in pediatric Fabry patients.

[00141] NONMEM program was used to develop the population PK model of migalastat in adults using first-order conditional estimation with interaction (FOCE-I).

Simulations were conducted using NONMEM to obtain plasma concentration-time; all graphical analyses were performed using R; noncompartmental analysis and pharmacokinetic parameters summaries were conducted using Phoenix WinNonlin. Bootstrapping and visual predictive checks (VPC)s were conducted using Perl-speaks-NONMEM (PsN) R packages of popED and mrgsolve were used in the optimal sampling strategy.

[00142] The population PK model was optimized by one or more of re-examine absorption models, adding allometric scaling components to CLT/F and Q/F with an allometric exponent equal to 0.75 and to V_2/F and V_3/F with an allometric exponent equal to 1.0, and evaluating whether the allometric exponent should be on total CLT/F or on the non-renal clearance only.

[00143] The original linear time-dependent absorption model was chosen among the different absorption models because the conditional weighted residual (CWRES) over time plots were substantially improved, with much less bias and fluctuation throughout the profile. Because the time varying K_a model allows K_a to continuously increase, an upper limit of time-dependent absorption coefficient K_a was set up at 24 hours post-dose to provide reasonable K_a values in simulation/predictions; this was considered to be a minimal change to the original model as the drug is considered to be fairly fully absorbed within 7-10 hours, regardless of the model chosen.

[00144] The overall purpose of the model development was to come up with a model for pediatric extrapolation. The theoretical power model indices of 0.75 (for CL and Q), and 1 (for V2 and V3) were applied and evaluated. The diagnostic plots suggested that allometric scaling was only appropriate for those < 70 kg.

[00145] The final equations for CLT/F, Q/F, V2/F and V3/F were presented as follows:

- WTCO = WT/70 when WT $\leq$ 70; WTCO = 1 when WT > 70, where WTCO was the allometric weight coefficient with allometric scaling for subjects with weight $\leq$ 70 kg.
- $CL_T/F = tvCL * (RF)^{CLEGFR} * \mathbf{W}TCO^{0.75} * (1 + CLHVT)^{1-FBRY} *$ exp(ETA of IIV on CL/F)
- $V_2/F = tvV_2 * \mathbf{W}TCO^{1} * (1 + V_2HVT)^{1-FBRY} *$ exp(ETA of IIV on V_2/F)
- $Q/F = TVQ * \mathbf{W}TCO^{0.75}$ and $V_3/F = TVV3 * \mathbf{W}TCO^{1}$, where TVQ and TVV3 were the typical value of Q/F or V_3/F, respectively.

[00146] Considering that renal function is comparable between pediatric patients 2 years and up and adults, the model was modified to apply the allometric exponent to only the non-renal clearance component. The model that successfully converged suggested only a very small portion of CLT/F was accounted for by non-renal clearance; therefore, the allometric scaling applied to this very small non-renal clearance did not really impact the overall CL_T/F. The diagnostic plots also suggested that applying the allometric exponent to overall CL_T/F for subjects < 70kg was better than applying it to the non-renal clearance. Moreover, pediatric CL_T/F values extrapolated from the non-renal model were higher than the overall CL_T/F approach, resulting in higher pediatric doses for achieving equivalent exposures with adults which was a less conservative approach. Therefore, the overall CL_T/F scaling approach is more conservative and was chosen for the final model, which is shown in Table 6.

[00147] **Table 6. Parameter estimates from the Final Optimized popPK model of migalastat (with and without bootstrap).**

Parameter	NONMEM		Bootstrap	
	Estimate (%RSE); [95% CI]	IIV (%CV)	Estimate (%RSE); [95% CI]	IIV (%CV)
Typical EGFR-related estimate for those with Fabry disease, with EGFR = 90 mL/min/1.73 m^2, and with body weight ≥ 70 kg	18.6 (16.3%); [12.6, 24.6]	28.8%	18.5 (16.0%); [14.0, 25.4]	28.5%
Typical EGFR-related estimate for those with Fabry disease, with EGFR > 120 mL/min/1.73 m^2, and with body weight ≥ 70 kg	20.9 (17.4%); [13.8, 28.0]		20.6 (17.3%); [15.4, 28.8]	
EGFR-related exponential index on CL/F	0.922 (5.64%); [0.820, 1.02]		0.925 (5.25%); [0.832, 1.02]	
Typical total CL/F (L/h) for those with Fabry disease, with EGFR = 90 mL/min/1.73 m^2, and with body weight ≥ 70 kg [a]	14.8		14.9	
Typical total CL/F (L/h) for those with Fabry disease, with EGFR = 120 mL/min/1.73 m^2, and with body weight ≥ 70 kg [b]	16.5		16.4	
Typical V_2/F (L) for those with Fabry disease, with body weight ≥ 70 kg	70.1 (5.29%); [62.8, 77.4]	34.5%	69.7 (4.8%); [63.8, 76.8]	33.9%
Typical Q/F (L/h) for those with body weight ≥ 70 kg	1.00 (5.17%); [0.899, 1.10]	-	1.01 (4.59%); [0.928, 1.11]	-
Typical V_3/F (L) for those with	27.5 (11.7%);	-	27.5 (11.9%);	-

body weight ≥ 70 kg	[21.2, 33.8]		[22.7, 35.2]	
K_a (intercept) (h^{-1})	0.256 (9.41%); [0.209, 0.303]	60.4%	0.256 (8.60%); [0.211, 0.298]	59.9%
K_a (slope)	0.284 (9.12%); [0.233, 0.335]	60.7%	0.282 (7.45%); [0.244, 0.326]	60.6%
Lag time (h)	0.175 (4.65%); [0.159, 0.191]	-	0.176 (4.52%); [0.160, 0.190]	-
WT-related exponential index on CL/F and Q/F for those with body wight < 70 kg	Fixed to 0.75	-	Fixed to 0.75	-
WT-related exponential index on V_2/F and V_3/F for those with body wight < 70 kg	Fixed to 1	-	Fixed to 1	-
Fractional Change in V_2/F in subjects without Fabry disease (decrease in V_2/F)	-0.306 (12.8%); [-0.383, -0.229]	-	-0.305 (12.3%); [-0.372, -0.227]	-
Fractional Change in total CL/F in subjects without Fabry disease (decrease in total CL/F)	0.150 (24.9%); [-0.223, -0.077]	-	-0.151 (23.5%); [-0.233, -0.081]	-
Residual Error (%)	26.2%; [23.2%, 29.0%]	-	26.3%; [24.5%, 27.8%]	-
Residual Error (ng/mL)	2.55; [NA, 3.76]	-	2.47; [1.25, 3.51]	-

a. Derived total CL/F parameter from typical EGFR-related estimate and EGFR-related exponential index; total CL/F=THETA(1)^THETA(9), where THETA(1) is the typical EGFR-related estimate and THETA(9) is the estimate of exponential index for patients with Fabry disease, EGFR = 90 mL/min/1.73 m^2, and with body weight ≥ 70 kg.

b. Derived total CL/F parameter from typical EGFR-related estimate and EGFR-related exponential index; total CL/F=THETA(13)^THETA(9), where THETA(13) is the typical EGFR-related estimate and THETA(9) is the estimate of exponential index for patients with Fabry disease, EGFR > 120 mL/min/1.73 m^2, and with body weight ≥ 70 kg.

[00148] The estimated parameters from bootstrap (see Table 6) were nearly identical to those estimated from the original dataset. All parameters were estimated with adequate precision. The NONMEM estimates (which assume each parameter has a normal distribution) were nearly identical to the nonparametric bootstrap estimates (which do not assume that each parameter has a normal distribution).

[00149] Model performance comparison was made for the adult population. Simulations were performed using a simulated adult dataset following 150 mg of migalastat salt QOD

doses with both model parameters and the steady-state AUC_{tau} and C_{max} were compared. The results showed in Table 7 were comparable between the original model and the optimized/updated model, indicating a good model performance.

[00150] Table 7. Comparison between the original model and optimized model with simulation results for adults receiving 150 mg of migalastat salt QOD dose.

Model	C_{max} (nm/mL)	AUC_{tau}
	Geometric Mean (CV% of Geometric Mean)	
Original Model (N=100)	1120 (34.5%)	7200 (32.5%)
Optimized Model (N=100)	1120 (36.3%)	7580 (32.0%)

[00151] Clinical trial simulations were then conducted to predict the exposure in pediatric patients receiving the initial various weight-based dosing regimens (comparable to about a 3 mg/kg dose). The dose regimens that were used for the simulations are listed in Table 8.

[00152] Table 8. Dose Regimen for Pediatric Patients.

Weight (kg)	Dose (mg)	Frequency
< 15	25	QOD
15 to <25	50	QOD
25 to <35	75	QOD
35 to <50	100	QOD
≥50	150	QOD

[00153] The doses were targeted to achieve a similar AUC_{tau} at steady-state (and not C_{max} or C_{min}) in pediatric sub-groups to that in adults with normal renal function receiving 150 mg of migalastat salt every other day (QOD).

[00154] The pediatric simulations assumed the following: (1) 100 subjects per group for 4 groups including 3 pediatric groups with Fabry disease (2 to <6, 6 to <12 and 12 to <18 years) and 1 adult group (Fabry disease with normal renal function), assuming 50% males and 50% females in each group; (2) All children (and adults) had a normal renal function; (3) Age for pediatric subjects was sampled from a uniform distribution within the age limit of each group; (4) Weight for pediatric subjects was sampled from the normal distribution using the

World Health Organization (WHO) weight chart for age for those less than 5.08 yrs., and from the Centers for Disease Control and Prevention (CDC) weight chart for those between 5.08 and 17.99 year old; and (5) The weight of the adult group was sampled from a random normal distribution (mean=75, standard deviation (SD)=15).

[00155] The results of the simulations, which are shown in Table 9, showed that the C_{max} values were comparable among groups, whereas the AUC_{tau} (0-48 hrs) was about 25% lower in age group 2 to <6 year old (5570 vs 7580 h*ng/ml), and about 10% lower in age group 6 to <12 year old (6850 vs 7580 h*ng/ml).

[00156] **Table 9. Pediatric Study Design with Empirical Dose Scheme PK Parameters.**

Groups	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	CL/F (L/h)	QOD Dose (mg)	T_{max} (hrs)
	Geometric Mean (CV% of Geomean) [95% CI] of Geometric Mean Parameter			Frequency	Median (Min, Max)
2 to <6 Years N=100	1030 (38.6%) [490, 2150]	5570 (37.9%) [2700, 11500]	5.56 (37%) [2.73, 11.3]	25 mg (N=40) 50 mg (N=60)	2 (1-4)
6 to <12 Years N=100	1100 (37.4%) [536, 2250]	6850 (34.0%) [3550, 13200]	8.52 (38.3%) [4.09, 17.8]	50 mg (N=36) 75 mg (N=37) 100 mg (N=22) 150 mg (N=5)	3 (1-4)
12 to <18 Years N=100	1190 (40.1%) [553, 2560]	7530 (37.5%) [3670, 15500]	14.1 (39.4%) [6.64, 29.9]	75 mg (N=2) 100 mg (N=32) 150 mg (N=66)	2 (1-4)
Adults N=100	1120 (36.3%) [556, 2250]	7580 (32.0%) [4090, 14100]	16.2 (32.0%) [8.70, 30.0]	150 mg (N=100)	3 (2-5)

[00157] A weight range analysis with a 5 kg increment on the simulated data was applied, which are shown in Table 10. Using the AUC_{tau} geometric mean value of adult group with normal renal function receiving 150 mg QOD dose as the target (7580 h*ng/ml), dose

adjustment was performed for subjects in each weight group considering dose proportionality with the equation 1:

[00158] $Dose_{adj,i} = Dose_{org,i} * AUC_{tau,a} / AUC_{tau,i}$ .....Equation 1

where $Dose_{adj,i}$ is the adjusted dose for each weight group for achieving equivalent AUC exposure with adults, $Dose_{org,i}$ is the original dose used for each weight group, $AUC_{tau,a}$ is the adult group geometric mean value of 7580 h*ng/ml, and $AUC_{tau,i}$ is the geometric mean value for each weight group. Additionally, the adjusted doses were rounded to the nearest practical dose level to ensure simplicity in formulation preparation.

[00159] **Table 10. Pediatric Dose Adjustment Per 5 kg Weight Range.**

Weight Range (kg)	Geometric Mean AUC_{tau} (h*ng/mL)	Number of Subjects	Original Dose (mg)	Adjusted Dose Calculated (mg)	Adjusted Dose Round (mg)
10-15	4481	40	25	42	40
15-20	6658	52	50	57	60
20-25	5673	43	50	67	60
25-30	7413	21	75	77	80
30-35	7230	19	75	79	80
35-40	8040	18	100	94	100
40-45	7817	18	100	97	100
45-50	5904	18	100	128	150
50+	7907	71	150	144	150

[00160] The resulted adjusted dosing scheme for pediatric groups are summarized in Table 11.

[00161] **Table 11. Summary of Adjusted Dosing Scheme for Pediatric Groups**

Weight (kg)	Dose (mg)	Frequency
<15	40	QOD
15 to <25	60	QOD
25 to <35	80	QOD
35 to <45	100	QOD

≥45	150	QOD

[00162] Based on the dose adjustment analysis and the new revised dosing scheme, simulations were re-run for the 3 pediatric groups (pediatric group age 2 to <6, 6 to <12 and 12 to <18 years), with all other assumptions and settings unchanged, the results of which are shown in Table 12.

[00163] Table 12. Predicted migalastat in pediatrics based on proposed weight-based dosing scheme.

Groups	**C_{max} (ng/mL)**	**AUC_{tau} (h*ng/mL)**	**CL/F (L/h)**	**QOD Dose (mg)**	**T_{max} (hrs)**
	Geometric Mean (CV% of Geomean) [95% CI] of Geometric Mean Parameter			**Frequency**	**Median (Min, Max)**
2 to <6 Years N=100	1400 (36.8%) [691, 2840]	7540 (35.7%) [3790, 15000]	5.66 (32.1%) [3.04, 10.5]	40 mg (N=37) 60 mg (N=59) 80 mg (N=4)	2 (1-4)
6 to <12 Years N=100	1230 (36.9%) [606, 2500]	7660 (33.1%) [4040, 14500]	8.96 (38.6%) [4.28, 18.8]	80 mg (N=21) 80 mg (N=48) 100 mg (N=21) 150 mg (N=10)	3 (1-4)
12 to <18 Years N=100	1250 (36.6%) [616, 2520]	7870 (32.1%) [4230, 14600]	14.1 (38.2%) [6.77, 29.3]	80 mg (N=3) 100 mg (N=20) 150 mg (N=77)	2 (1-4)
Adults N=100	1120 (36.3%) [556, 2250]	7580 (32.0%) [4090, 14100]	16.2 (32.0%) [8.70, 30.0]	150 mg (N=100)	3 (2-5)

[00164] population PK data in adults and adolescents weighing ≥ 45 kg receiving the 150 mg migalastat HCL capsule q.o.d. are presented in Table 13.

[00165] Table 13. Simulated pharmacokinetic endpoints by age groups and adults ≥ 45 kg.

Age Group	**C_{max}**	**C_{min}**	**AUC_{tau}**

(Years)	(ng/mL)	(ng/mL)	(h*ng/mL)
12 to <16	1377 (42%)	8.06 (37%)	8581 (37%)
16 to <18	1275 (39%)	8.37 (38%)	8408 (37%)
12 to <18	1319 (41%)	8.23 (37%)	8483 (37%)
Adults	1191 (37%)	8.13 (41%)	7958 (35%)

Abbreviations: $AUC_{0\text{-}tau}$ = plasma concentration-time curve during a dosing interval at steady state ($AUC_{0\text{-}\tau}$); C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration; Note: Data are summarized as geometric mean (CV%)

[00166] Results of ANOVA analysis are presented in Table 14.

[00167] **Table 14. Summary of the ANOVA on predicted pharmacokinetic parameters for subjects weighing ≥ 45 kg.**

PK Endpoint	Age Group (Years)	Point Estimate (90% CI)
$AUC_{0\text{-}tau}$	12 to < 16	108 (98.6, 118)
	16 to < 18	106 (97.1, 115)
	12 to < 18	107 (99.0, 115)
C_{max}	12 to < 16	116 (105, 127)
	16 to < 18	107 (97.6, 117)
	12 to < 18	111 (102, 120)

Abbreviations: $AUC_{0\text{-}tau}$ = plasma concentration-time curve during a dosing interval at steady state; CI = confidence interval; C_{max} = maximum observed plasma concentration

[00168] The limited pharmacokinetic data support the 150 mg migalastat HCL capsule Q.O.D. dose in adolescents weighing ≥ 45 kg.

Example 3: PK/PD Model Validation in Adolescents

[00169] The example describes AT1001-020 study, which is an Open-label Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Migalastat in Pediatric Subjects (aged 12 to < 18 years) with Fabry Disease and Amenable GLA Variants.

[00170] The disclosure includes analysis of interim clinical study data, presenting the results of the stage 1 (1-month) safety and PK data only for subjects with Fabry disease in the

12 to < 16 years old age group who had Stage 1 plasma concentration-time data available as of the cut-off date.

Objectives

[00171] Stage 1 objective is to characterize the PK of migalastat in adolescents with Fabry disease, and to validate extrapolation of migalastat plasma exposure in adults to adolescents weighing ≥ 45 kg for the 123 mg migalastat capsule administered once every other day (QOD).

[00172] Another Stage 1 objective is to evaluate the safety of migalastat treatment in pediatric subjects with Fabry disease and who have variants in the gene encoding α-Gal A (GLA) amenable to treatment with migalastat.

Outcomes/endpoints

[00173] Pharmacokinetic Endpoints were as follows:

- Population PK model that describes the relationship between weight and age and migalastat pharmacokinetics in pediatric subjects (with primary PK parameter outputs listed in the following text).
- PK parameters based on simulated plasma-concentration data for migalastat after multiple-dose administration at steady-state concentration
  - C_{max}: maximum observed plasma concentration
  - C_{min}: minimum observed plasma concentration
  - t_{max}: time to reach C_{max}
  - $AUC_{0\text{-}tau}$: area under the plasma concentration-time curve from time 0 over the dosing interval (i.e. 48 hours)
  - $t_{½}$: terminal elimination half-life
  - CL_{ss}/F: apparent oral clearance at steady-state concentration
  - V_{ss}/F: apparent oral volume of distribution at steady-state concentration

Study Participants

[00174] The disclosure describes the PK/PD study in migalastat-treated patients who were either naïve to enzyme replacement therapy (ERT) or had stopped ERT at least 14 days at the time of screening

[00175] For inclusion in this study, subjects must have met all of the following criteria:

- Male or female, diagnosed with Fabry disease aged between 12 and <18 years at baseline, and who might benefit from specific treatment for their condition, in the opinion of the investigator.
- Confirmed, amenable GLA variant determined using the migalastat amenability assay (For subjects without a known amenable GLA variant, GLA genotyping must have been performed prior to Visit 2. Similarly, For subjects with a GLA variant that had not yet been tested in the migalastat amenability assay, amenability testing must have been completed before Visit 2).
- Weight of ≥45 kg (99 pounds) at screening.
- Treatment-naïve or discontinued ERT treatment at least 14 days prior to screening 5. Had at least one complication (i.e. historical or current laboratory abnormality and/or sign/symptom) of Fabry disease.
- Had no indication of moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) or kidney disease requiring dialysis or transplantation at screening.

Treatment

[00176] One migalastat 123 mg migalastat (= 150 mg migalastat HCL) capsule was administered to adolescents weighing ≥ 45 kg with water every other day during the study.

[00177] Due to the capsule size and inclusion criteria of study AT1001-020, the 123 mg migalastat capsules are not suitable for patients less than 45 kg body weight and for the lower weight and age groups. Thus, it was recommended to include a warning for the lower weight group within the proposed age group (12 to below 16 years).

[00178] Sparse sampling for plasma migalastat concentrations to estimate exposure was done at baseline and for one 24-hour period between days 15 and 30. As shown in Table 15, subjects were randomly assigned to one of the 3 PK sampling groups.

[00179] **Table 15. Sparse sampling schedule in study AT1001-020.**

PK Sampling Group	Time Post-dose			
	Sample 1	Sample 2	Sample 3	Sample 4
1	1h to 1h 15 min	1h 30min to 2 h	5h to 5h 30 min	6h 30min to 7h

2	1h to 1h 15 min	2h 45min to 3h 15 min	5h 15min to 5h 45 min	10h 45min to 11h 15 min
3	3h 15min to 3h 45 min	3h 45min to 4h 15 min	8h 15min to 8h 45 min	8h 45min to 9h 15 min

[00180] Patients with 1 plasma concentration-time data available as of the cut-off date were included in the interim analysis.

[00181] Plasma samples were analyzed using the LC-MS/MS method.

Analysis Populations for Interim Analysis

[00182] The safety population included all subjects aged 12 to < 16 years who received at least 1 dose or a partial dose of study drug and had Stage 1 plasma concentration-time data available as of the cut-off date. All safety analyses were performed using the safety population.

[00183] The PK population included data from subjects aged 12 to < 16 years who have completed Stage 1 and who received at least 1 dose of migalastat with at least 1 quantifiable concentration. All subjects included in the Interim Analysis population PK had a known weight and an eGFR.

Results

Baseline Data

[00184] A total of 22 subjects were enrolled in the study AT1001-020. As of the cut-off date, a total of 9 subjects, 4 females and 5 males, aged 12 to < 16 years were enrolled in Study AT1001-020, received study drug, and completed Stage 1 of the study with PK concentration data. They comprised the safety and PK populations for this interim analysis. The mean number of years since diagnosis of Fabry disease was 10.2 (± 4.12) years. Four subjects reported prior use of enzyme replacement therapy.

[00185] The median duration of migalastat exposure for the 9 subjects enrolled in Study AT1001-020 was 30 days with maximum exposure of 49 days.

[00186] Demographics and baseline characteristics are presented in **Error! Reference source not found.**16 and **Error! Reference source not found.**17.

[00187] Table 16. Demographics – Safety Population.

Parameter	Statistic	Migalastat
Number of Subjects in the safety population	N	9
Age (years)[a]	Mean (SD)	14.1 (1.17)
	Median	15.0
	Min, Max	12, 15
Sex		
Male	n (%)	5 (55.6)
Female	n (%)	4 (44.4)
Race		
White	n (%)	8 (88.9)
Black or African American	n (%)	0
Asian	n (%)	0
American Indian or Alaska Native	n (%)	0
Naïve Hawaiian or other Pacific Islander	n (%)	0
Other	n (%)	1 (11.1)
Ethnicity		
Hispanic or Latino	n (%)	2 (22.2)
Not Hispanic or Latino	n (%)	7 (77.8)
Height	Mean (SD)	167.09 (5.591)
	Median	168.50
	Min, Max	160.0, 175.3
Weight (kg)	Mean (SD)	67.56 (17.273)
	Median	66.50
	Min, Max	45.0, 100.6
Body Mass Index (kg/m^2)	Mean (SD)	24.25 (6.148)
	Median	24.10
	Min, Max	15.6, 33.5

Abbreviations: Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects in category indicated; SD = Standard deviation
Note: Percentages are based on the number of subjects in the safety population.
[a] Age = (informed consent date – date of birth + 1) / 365.25 and truncated to complete years

[00188] **Table 17. Baseline Characteristics – Safety Population.**

Parameter	Statistic	Migalastat
Number of Subjects in the safety population	N	9
Number of years since diagnosis of Fabry disease [a]	Mean (SD)	10.15 (4.119)
	Median	11.17
	Min, Max	3.4, 15.8
Previous use of ERT n (%)		
Yes	n (%)	4 (44.4)
No	n (%)	5 (55.6)

Abbreviations: Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects in category indicated; SD = Standard deviation
Note: Percentages are based on the number of subjects in the safety population.
[a] Age = (informed consent date – date of birth + 1) / 365.25 and truncated to complete years

Medical History

[00189] The most common system organ classes for medical history in the safety population were nervous system disorders (77.8%), ear and labyrinth disorders (66.7%), gastrointestinal disorders (66.7%), and general disorders and administration site conditions, investigations, psychiatric disorders, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders (all 55.6%). The most common medical history preferred terms (all reported by 55.6% of the subjects) were tinnitus, abdominal pain, diarrhea, headache, and paranesthesia, most of which are consistent with Fabry disease.

Prior and Concomitant Medications

[00190] All but 1 subject reported prior use of medications. The most common previous medication was paracetamol taken by 6 (66.7%) subjects. No other medication was taken by more than 2 subjects.

[00191] The most frequently used concomitant medication was paracetamol taken by 6 (66.7%) subjects. No other concomitant medication was taken by more than 2 subjects.

Adverse Events

[00192] An overall summary of TEAEs experienced by subjects in the safety population during Stage 1 is displayed in Table 18 and Table 19.

[00193] **Table 18. Summary of Treatment-emergent Adverse Events – Safety Population – Stage 1.**

Parameter	Statistic	Migalastat
Number of subjects in the safety population	N	9
Number of TEAEs	n	6
Number of subjects with TEAEs	n (%)	5 (55.6)
Number of subjects with related TEAEs	n (%)	1 (11.1)
Number of subjects with treatment-emergent SAEs	n (%)	0
Number of subjects discontinued due to TEAEs	n (%)	0
Number of subjects with AEs leading to death	n (%)	0

[00194] **Table 19. Frequency of Treatment-emergent Adverse Events Occurring in the Safety Population – Stage 1.**

System Organ Class Preferred Term	Number of Subjects n (%)	Number of Events n (%)
Number of subjects with TEAEs	5 (55.6)	6
Infections and infestations	4 (44.4)	4 (66.7)
Pharyngitis	1 (11.1)	1 (16.7)
Upper respiratory tract infection	3 (33.3)	3 (50.0)
Nervous system disorders	1 (11.1)	1 (16.7)
Headache	1 (11.1)	1 (16.7)
Skin and subcutaneous tissue disorders	1 (11.1)	1 (16.7)
Drug eruption	1 (11.1)	1 (16.7)

Laboratory Findings

[00195] During Stage 1, urinalysis (albumin, protein, specific gravity, pH, and microscopy) was the only laboratory parameter collected at Month 1 and therefore, the only laboratory parameter assessed for the Interim Analysis.

[00196] There were no clinically meaningful changes in mean values from baseline for urinalysis parameters at Month 1.

[00197] There were a few shifts from baseline to Month 1. Three subjects had pH values that went from normal at baseline to high at Month 1.

[00198] There were no potentially clinically significant abnormalities in urinalysis parameters.

[00199] Urine pregnancy tests were performed for all female subjects of childbearing potential at every visit. No female subject in the safety population had a positive pregnancy test result during Stage 1.

Conclusions on clinical safety

[00200] Based upon limited data obtained from adolescent patients aged 12 – 18 years (n=9), popPK data showed that exposure in adults and adolescents weighing ≥45 kg receiving the 123 mg migalastat capsule q.o.d. was comparable.

[00201] C_{max} levels observed in the pediatric patients were in line with the C_{max} levels observed in adults patients in the pivotal study AT1001-011.

[00202] No new safety findings have been observed during stage 1 of the study. Hence treatment with migalastat 123 mg in pediatric patients aged ≥12 to 16 years of age does not lead to a different safety profile than already known.

[00203] A new formulation, migalastat HCl oral formulation (sachet and/or capsules) for treatment of Fabry disease in pediatric and adolescent patients aged 2 to <18 years and with amenable GLA mutations may be designed and evaluated.

Example 4: Clinical Efficacy of Migalastat Treatment in Adolescents

[00204] The example describes AT1001-020 study, which can be an Open-label Study of Efficacy of 12-month Treatment with Migalastat in Pediatric Subjects (aged 12 to < 18 years) with Fabry Disease and Amenable GLA Variants. In some embodiments, the clinical efficacy study comprises stage 2.

[00205] Accordingly, in some embodiments, in Stage 2, Primary Objective can include evaluating the safety of migalastat treatment in pediatric subjects diagnosed with Fabry disease and who have GLA variants amenable to treatment with migalastat.

[00206] In some embodiments, in state 2, Secondary Objectives can include characterizing the pharmacodynamics (PD) of migalastat in pediatric subjects diagnosed with Fabry disease and who have GLA variants amenable to treatment with migalastat.

[00207] In some embodiments, in state 2, secondary objective can include evaluating the efficacy of migalastat in pediatric patients diagnosed with Fabry disease and who have GLA variants amenable to treatment with migalastat.

[00208] In some embodiments, in state 2, secondary objective can include evaluating the relationship between exposure to migalastat and response.

[00209] The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

[00210] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

[00211] The embodiments described herein are intended to be illustrative of the present compositions and methods and are not intended to limit the scope of the present invention. Various modifications and changes consistent with the description as a whole and which are readily apparent to the person of skill in the art are intended to be included. The appended claims should not be limited by the specific embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

[00212] Patents, patent applications, publications, product descriptions, GenBank Accession Numbers, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

What is claimed is:

1. A method of treatment of Fabry disease in a human patient in need thereof, the method comprising administering to the patient a formulation comprising therapeutically effective dose of migalastat or a salt thereof, wherein the patient is a pediatric patient.

2. The method of claim 1, wherein the patient has an age in a range of from about 2 year to about <18 year.

3. The method of claim 1, wherein the patient has a weight in a range of from about <15 kg to about ≥50 kg.

4. The method of any one of claims 1-3, wherein the therapeutically effective dose of migalastat or a salt thereof is in a range of from about 15 mg to about 150 mg every other day.

5. The method of any one of claims 1-4, wherein the therapeutically effective dose of migalastat hydrochloride at a dose in a range of from about 25 mg to about 150 mg every other day.

6. The method of any one of claims 1-5, wherein the therapeutically effective dose of migalastat FBE in a range of from about 15 mg to about 123 mg every other day.

7. The method of claim 1 or 2, wherein the patient has an age in a range of from about 12 year to about <18 year.

8. The method of claim 7, wherein the patient has a weight of about ≥25 kg.

9. The method of claim 8, wherein the therapeutically effective dose of migalastat hydrochloride is in a range of from about 80 mg to about 150 mg every other day.

10. The method of claim 7, wherein the patient has a weight of about ≥45 kg.

11. The method of claim 10, wherein the therapeutically effective dose of migalastat hydrochloride is about 150 mg every other day.

12. The method of claim 10 or 11, wherein the therapeutically effective dose of migalastat FBE is about 123 mg every other day.

13. The method of claim 1 or 2, wherein the patient has an age in a range of from 6 year to <12 year.

14. The method of claim 13, wherein the patient has a weight of about ≥25 kg.

15. The method of claim 13 or 14, wherein the therapeutically effective dose of migalastat hydrochloride is in a range of from about 80 mg to about 150 mg every other day.

16. The method of claim 1 or 2, wherein the patient has an age in a range of from 2 year to <6 year.

17. The method of claim 16, wherein the patient has a weight of about <35 kg.

18. The method of claim 16 or 17, wherein the therapeutically effective dose of migalastat hydrochloride is in a range of from about 40 mg to about 80 mg every other day.

19. The method of any one of claims 1-18, wherein the patient has an eGFR of about ≥60 mL/min/1.73 m^2.

20. The method of any one of claims 1-19, wherein the migalastat or salt thereof enhances or prolongs α-galactosidase A activity.

21. The method of any one of claims 1-20, wherein the formulation comprises an oral dosage form.

22. The method of claim 21, wherein the oral dosage form comprises a tablet, a capsule or a solution.

23. The method of any one of claims 1-22, wherein the patient is male.

24. The method of any one of claims 1-22, wherein the patient is female.

25. The method of any one of claims 1-24, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

26. The method of any one of claims 1-25, wherein the patient is an ERT-experienced patient who has stopped ERT for at least 14 days.

27. The method of any one of claims 1-26, wherein the patient has a HEK assay amenable mutation in α-galactosidase A.

28. The method of claim 27, wherein the mutation is disclosed in a pharmacological reference table.

29. The method of claim 28, wherein the pharmacological reference table is provided in a product label for a migalastat product approved for the treatment of Fabry disease.

30. The method of claim 29, wherein the pharmacological reference table is provided in a product label for GALAFOLD®.

31. The method of claim 30, wherein the pharmacological reference table is provided at a website.

32. The method of claim 31, wherein the website is one or more of www.galafoldamenabilitytable.com or www.fabrygenevariantsearch.com.

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FIG.1A

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FIG.1B

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FIG.1C

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tcaacactgcaagcctattgctgccccagggcctttacacttgctttttttctgcctaga 9120
acagttcttccccaaagatttttaaagggccgggctccttaacattgaagtcgcagacca 9180
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ttgttgacttgttaccatgtctccccactagagtgtaagtttcatgagggcagggacctt 9360
gtctgactttgactgtatctctcgcatatggttaagtgttaaatagttatttatggaatg 9420
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ggtggctcatgcctgtaatcccagcactttgggaggctgaggcgggcagatcacctgagg 11400
tcgggactttgagacccgcctggacaacatggtgaaaccccatttctaataaaaatataa 11460
aaattagccaggtgtggtggcgcacctgtggtcccagctactctgggggctgaggcatga 11520

FIG.1D

```
gaatcgcttgaacccgggagtggaggttgcattgagctgagatcatgccacctcactcca     11580
gcctgggcaacaaagattccatctcaaaaaaaaaaaaaaagccaggcacagtggctcatg     11640
cctggaatcccagcacttttggaagctgaggcaggcagatcacttgaggttaggatttca     11700
agaccagcctggctaacatagtaaagccctgtctctactaaaaatacaaaaattagccag     11760
gtatggtggcgagcttctgtagccccagctactcaggagactgaggcaggagaatcactt     11820
gaacccgggaagtgggggggtgcagtgacccaagatcacgccactgcattccagcctggg     11880
caacagagcaagactccatctcaaaaaaaaaagttctatttccttgaataaaattttccg     11940
aagtttaaactttaggaataaaactattaaacccgtatttactcatccagatacccaccc     12000
cccttgttgagattctctcccaattatcaaaatgtgtagcatatttaactaccaagagct     12060
aaacatcattaagactgaaatgtattaagaaggatgtataggccaggcacggtgtctcac     12120
gcctgtaatcccaacactttgggaggccaagtcgggcggatcacgaggtcaggagatgga     12180
gaccatcctggccaacatggtgaaacccccctctctactaaaaatacaaaaattagccagg     12240
caggtggcaggcacctgtaatcccagctactccagaggctgaggcaggacaatcacttga     12300
acctgggaggcagaggctgcagtgagctgaggttgtaccaattgcactccagcctaggta     12360
acgagcaacactccatctcaaaaaaagaaaaaaaaaaagatgtataatttggaactgtta     12420
agaggcattttaaaga                                                 12436
```

FIG.1E

```
MQLRNPELHL GCALALRFLA LVSWDIPGAR ALDNGLARTP TMGWLHWERF MCNLDCQEEP   60
DSCISEKLFM EMAELMVSEG WKDAGYEYLC IDDCWMAPQR DSEGRLQADP QRFPHGIRQL  120
ANYVHSKGLK LGIYADVGNK TCAGFPGSFG YYDIDAQTFA DWGVDLLKFD GCYCDSLENL  180
ADGYKHMSLA LNRTGRSIVY SCEWPLYMWP FQKPNYTEIR QYCNHWRNFA DIDDSWKSIK  240
SILDWTSFNQ ERIVDVAGPG GWNDPDMLVI GNFGLSWNQQ VTQMALWAIM AAPLFMSNDL  300
RHISPQAKAL LQDKDVIAIN QDPLGKQGYQ LRQGDNFEVW ERPLSGLAWA VAMINRQEIG  360
GPRSYTIAVA SLGKGVACNP ACFITQLLPV KRKLGFYEWT SRLRSHINPT GTVLLQLENT  420
MQMSLKDLL                                                          429
```

FIG.2

```
Atgcagctgaggaatcccgagctccacctgggctgtgctctggctctgcggttcctggcc      60
Ctcgtgtcctgggacatccctggcgctagggccctcgataacggactggcccggaccccc      120
Acaatgggatggctccactgggaaaggttcatgtgcaatctggactgtcaggaggaaccc      180
Gactcctgcatcagcgaaaagctcttcatggagatggccgagctgatggtgagcgagggc      240
Tggaaggacgccggctacgagtatctgtgcatcgatgactgctggatggcccctcaaagg      300
Gactccgaaggcaggctgcaggctgatccccaaaggtttccccacggaatccggcagctc      360
Gccaactacgtgcattccaagggcctcaagctcggcatctacgccgacgtgggcaacaaa      420
Acatgcgccggattccccggcagcttcggctactacgacatcgacgcccagacattcgct      480
Gattggggagtggacctgctgaagttcgacggctgttactgcgattccctggaaaacctg      540
Gccgacggctacaaacacatgtccctcgccctgaaccggacaggcaggtccatcgtgtac      600
Agctgcgagtggcccctgtacatgtggcctttccagaagcccaactacacagagatcagg      660
Cagtactgcaaccactggaggaacttcgctgacatcgacgactcctggaagagcatcaag      720
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Caggacccccctgggcaagcagggctaccagctgaggcaaggagataacttcgaggtgtgg     1020
Gagaggcccctgtccggactggcttgggccgtggccatgatcaatcggcaggagatcggc     1080
Ggaccccggtcctacaccattgctgtggccagcctgggaaaaggagtcgcctgcaacccc     1140
Gcctgcttcattacccagctgctccccgtgaagcggaagctgggcttctatgagtggacc     1200
Agcaggctgaggtcccatatcaatcctaccggcaccgtcctcctccagctcgagaatacc     1260
Atgcagatgagcctcaaggatctgctgtga                                   1290
```

FIG.3