



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION

(13) **A1**

(86) Date de dépôt PCT/PCT Filing Date: 2021/02/10
(87) Date publication PCT/PCT Publication Date: 2021/08/19
(85) Entrée phase nationale/National Entry: 2022/08/09
(86) N° demande PCT/PCT Application No.: US 2021/017446
(87) N° publication PCT/PCT Publication No.: 2021/163183
(30) Priorité/Priority: 2020/02/10 (US62/972,392)

(51) Cl.Int./Int.Cl. *A61K 31/445* (2006.01),
A61K 31/45 (2006.01), *A61K 31/7008* (2006.01),
A61K 9/00 (2006.01), *A61P 13/12* (2006.01),
A61P 3/00 (2006.01), *A61P 3/06* (2006.01),
A61P 3/10 (2006.01), *A61P 43/00* (2006.01)
(71) Demandeur/Applicant:
AMICUS THERAPEUTICS, INC., US
(72) Inventeur/Inventor:
SKUBAN, NINA, US
(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : METHODES DE TRAITEMENT DE LA MALADIE DE FABRY
(54) Title: METHODS OF TREATING FABRY DISEASE

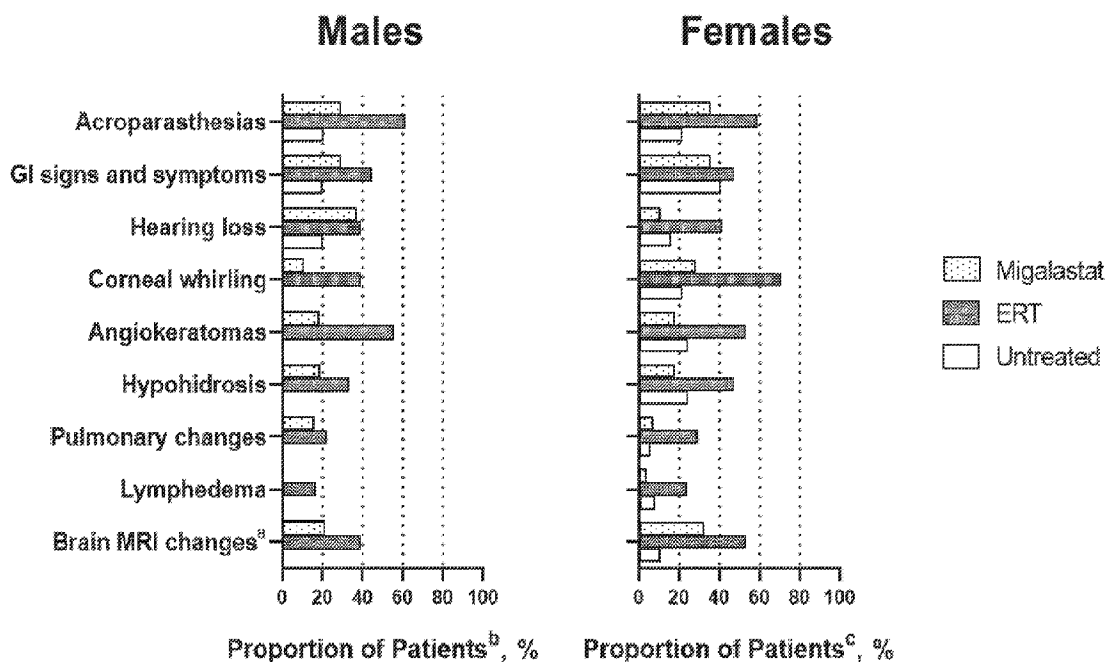


FIG. 5A

(57) Abrégé/Abstract:

Provided are methods for the treatment of Fabry disease in a patient, such as reducing the risk of composite clinical outcomes. Also provided are methods for assessing various symptoms of Fabry disease such as gastrointestinal symptoms. Also provided are methods of evaluating treatment therapies for Fabry disease.

Date Submitted: 2022/08/09

CA App. No.: 3167476

Abstract:

Provided are methods for the treatment of Fabry disease in a patient, such as reducing the risk of composite clinical outcomes. Also provided are methods for assessing various symptoms of Fabry disease such as gastrointestinal symptoms. Also provided are methods of evaluating treatment therapies for Fabry disease.

METHODS OF TREATING FABRY DISEASE

TECHNICAL FIELD

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

CROSS-REFERENCE TO SEQUENCE LISTING

[0002] The Sequence Listing identified as "AT20-01_Sequence_Listing.txt" (21,991
bytes), created February 10, 2021, is hereby incorporated by reference.
10

BACKGROUND

[0003] Fabry disease 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
15 can express varying degrees of clinical manifestations. 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
20 estimated.

[0004] 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
25 throughout the body. 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.

[0005] Cardiac disease as a result of Fabry disease occurs in most males and many
30 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.

[0006] 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. 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.

[0007] Accordingly, there remains a need for therapies for the treatment of Fabry disease.

SUMMARY

[0008] Various aspects of the present invention relate to the treatment of Fabry disease.

[0009] One aspect of the present invention pertains to a method of reducing the risk of composite clinical outcomes (CCO) in a patient having Fabry disease, the method comprising administering to the patient a formulation comprising an effective amount of migalastat or salt thereof every other day for at least 18 months, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE).

[0010] In one or more embodiments, the CCO comprises renal events, cardiac events, cerebrovascular events and death. In one or more embodiments, the renal events comprise one or more of: a decrease in $\text{eGFR}_{\text{CKD-EPI}} \geq 15 \text{ mL/min/1.73 m}^2$, with the decreased $\text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ relative to baseline; or an increase in 24-hour urine protein $\geq 33\%$, with elevated protein $\geq 300 \text{ mg}$ relative to baseline. In one or more embodiments, the cardiac events comprise one or more of: myocardial infarction; unstable cardiac angina; new symptomatic arrhythmia requiring antiarrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; or congestive heart failure [New York Association Class III or IV].

In one or more embodiments, the cerebrovascular events comprise one or more of stroke or transient ischemic attack.

[0011] In one or more embodiments, the migalastat or salt thereof enhances α -Gal A activity.

5 **[0012]** In one or more embodiments, the patient is administered about 123 mg FBE of the migalastat or salt thereof every other day.

[0013] In one or more embodiments, the patient is administered about 123 mg of migalastat free base every other day.

10 **[0014]** In one or more embodiments, the patient is administered about 150 mg of migalastat hydrochloride every other day.

[0015] In one or more embodiments, the formulation comprises an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[0016] In one or more embodiments, the migalastat or salt thereof is administered for at least 2 years.

15 **[0017]** In one or more embodiments, the migalastat or salt thereof is administered for at least 3 years.

[0018] In one or more embodiments, the migalastat or salt thereof is administered for at least 4 years.

20 **[0019]** In one or more embodiments, the CCO incidence rate for a group of patients on migalastat therapy for 18 months is less than 1.0 per patient•year. In one or more embodiments, the CCO incidence rate for a group of patients on migalastat therapy for 18 months is less than 0.5 per patient•year.

[0020] In one or more embodiments, the patient is male.

[0021] In one or more embodiments, the patient is female.

25 **[0022]** In one or more embodiments, the patient is an ERT-naïve patient.

[0023] In one or more embodiments, the patient is an ERT-experienced patient.

30 **[0024]** 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.

[0025] Another aspect of the present invention pertains to a method of assessing gastrointestinal (GI) outcomes in a patient having Fabry disease, the method comprising:
5 assessing the patient's disease-related GI symptom severity; assessing the patient's frequency of bowel movements; assessing the patient's frequency of diarrhea; and assessing the consistency of the patient's diarrhea.

[0026] In one or more embodiments, assessing the patient's disease-related GI symptom severity comprises assessing the severity of one or more of: bloating, stomach pain,
10 cramping, nausea, acid reflux, heartburn, constipation, or diarrhea.

[0027] In one or more embodiments, assessing the patient's disease-related GI symptom severity comprises assessing the severity of one or more of: the worst bloating over a time period; the worst stomach pain over a time period; the worst cramping over a time period; the worst nausea over a time period; the worst nausea over a time period; the worst
15 nausea over a time period; the worst nausea over a time period; or the worst nausea over a time period.

[0028] In one or more embodiments, the GI outcomes are assessed based on a 24-hour time period. In other embodiments, the assessments are based on a 6-hour, 8-hour, 12-hour, 36-hour, 48-hour, 3-day, 4-day, 5-day, 6-day or 7-day time period.

[0029] In one or more embodiments, the GI outcomes are assessed based on patient-reported symptoms.

[0030] In one or more embodiments, each item is assessed using a score on a 0-10 scale.

[0031] Another aspect of the present invention pertains to a method of evaluating a treatment therapy for Fabry disease, the method comprising assessing the GI at baseline,
25 assessing the GI outcome after a period of the treatment therapy, and comparing the GI outcome at baseline to the GI outcome after the period of the treatment therapy.

[0032] Another aspect of the present invention pertains to a method of treating Fabry disease, the method comprising assessing the GI to obtain a first GI score, initiating or
30 continuing a treatment therapy for Fabry disease for a time period, assessing the GI outcome after a period of the treatment therapy after the time period of treatment therapy to obtain a

second GI outcome score, and comparing the first GI outcome score and the second GI outcome score.

[0033] In one or more embodiments, the treatment therapy comprises ERT.

[0034] In one or more embodiments, the treatment therapy comprises substrate
5 reduction therapy.

[0035] In one or more embodiments, the treatment therapy comprises gene therapy.

[0036] In one or more embodiments, the treatment therapy comprises pharmacological
chaperone therapy. In one or more embodiments, the pharmacological chaperone therapy
comprises administration of an effective amount of migalastat or a salt thereof. In one or more
10 embodiments, the migalastat or salt thereof is administered every other day. In one or more
embodiments, the effective amount is about 100 mg to about 150 mg FBE.

[0037] In one or more embodiments, the patient is administered about 123 mg FBE of
the migalastat or salt thereof every other day.

[0038] In one or more embodiments, the patient is administered about 123 mg of
15 migalastat free base every other day.

[0039] In one or more embodiments, the patient is administered about 150 mg of
migalastat hydrochloride every other day.

[0040] In one or more embodiments, the formulation comprises an oral dosage form. In
one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

20 **[0041]** In one or more embodiments, the migalastat or salt thereof is administered for at
least 2 years.

[0042] In one or more embodiments, the migalastat or salt thereof is administered for at
least 3 years.

[0043] In one or more embodiments, the migalastat or salt thereof is administered for at
25 least 4 years.

[0044] In one or more embodiments, the patient is male.

[0045] In one or more embodiments, the patient is female.

[0046] In one or more embodiments, the patient is an ERT-naïve patient.

[0047] In one or more embodiments, the patient is an ERT-experienced patient.

30 **[0048]** 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
5 www.galafoldamenabilitytable.com or www.fabrygenevariantsearch.com.

[0049] Another aspect of the present invention pertains to a method of evaluating a treatment therapy for Fabry disease, the method comprising assessing one or more parameters in a patient population treated with the treatment therapy, wherein the one or more parameters comprise one or more of: incidence of Fabry signs and symptoms; renal parameters; and
10 cardiac parameters; and assessing the one or more parameters in an untreated patient population.

[0050] In one or more embodiments, the Fabry signs and symptoms comprise one or more of: acroparasthesias; GI signs and symptoms; hearing loss; corneal whirling; angiokeratomas; hypohidrosis; pulmonary changes; lymphedema; or brain MRI changes.

[0051] In one or more embodiments, the renal parameters comprise one or more of
15 eGFR_{CKD-EPI}; creatinine levels; urine protein levels; or incidence of detectable urine protein.

[0052] In one or more embodiments, the cardiac parameters comprise one or more of left ventricular mass index (LVMI) or incidence of left ventricular hypertrophy.

[0053] In one or more embodiments, the method further comprises assessing the one or
20 more parameters in a patient population treated with a different treatment therapy for Fabry disease.

[0054] In one or more embodiments, the method further comprises assessing the patient ages in each of the patient populations.

[0055] In one or more embodiments, the method further comprises assessing the patient
25 genotypes in each of the patient populations.

[0056] In one or more embodiments, the method further comprises assessing the patient genders in each of the patient populations.

[0057] In one or more embodiments, the treatment therapy comprises ERT.

[0058] In one or more embodiments, the treatment therapy comprises substrate
30 reduction therapy.

[0059] In one or more embodiments, the treatment therapy comprises gene therapy.

[0060] In one or more embodiments, the treatment therapy comprises pharmacological chaperone therapy. In one or more embodiments, the pharmacological chaperone therapy comprises administration of an effective amount of migalastat or a salt thereof. In one or more embodiments, the migalastat or salt thereof is administered every other day. In one or more
5 embodiments, the effective amount is about 100 mg to about 150 mg FBE.

[0061] In one or more embodiments, the patient is administered about 123 mg FBE of the migalastat or salt thereof every other day.

[0062] In one or more embodiments, the patient is administered about 123 mg of migalastat free base every other day.

10 [0063] In one or more embodiments, the patient is administered about 150 mg of migalastat hydrochloride every other day.

[0064] In one or more embodiments, the formulation comprises an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[0065] In one or more embodiments, the migalastat or salt thereof is administered for at
15 least 2 years.

[0066] In one or more embodiments, the migalastat or salt thereof is administered for at least 3 years.

[0067] In one or more embodiments, the migalastat or salt thereof is administered for at least 4 years.

20 [0068] In one or more embodiments, the patient is male.

[0069] In one or more embodiments, the patient is female.

[0070] In one or more embodiments, the patient is an ERT-naïve patient.

[0071] In one or more embodiments, the patient is an ERT-experienced patient.

[0072] In one or more embodiments, the patient has a HEK assay amenable mutation in
25 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
30 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.

[0073] In one or more embodiments, the method further comprises assessing the one or more parameters in a patient population treated with ERT.

[0074] In one or more embodiments, the one or more parameters are assessed for a time period of at least one year.

5

BRIEF DESCRIPTION OF THE DRAWINGS

[0075] Further features of the present invention will become apparent from the following written description and the accompanying figures, in which:

[0076] FIGS. 1A-E show the full DNA sequence of the human wild-type GLA gene
10 (SEQ ID NO: 1);

[0077] FIG. 2 shows the wild-type α -Gal A protein (SEQ ID NO: 2);

[0078] FIG. 3 shows the nucleic acid sequence encoding the wild-type α -Gal A protein
(SEQ ID NO: 3);

[0079] FIGS. 4A and 4B show the Fabry disease history of patients currently enrolled
15 in the followME registry (Safety Population); and

[0080] FIG. 5A shows Fabry disease signs and symptoms in patients currently enrolled
in the followME registry and FIG. 5B shows the median age at first occurrence of Fabry signs
and symptoms (Safety Population) by gender.

20 DETAILED DESCRIPTION

[0081] 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.

25 [0082] Various aspects of the present invention pertain to the administration of pharmacological chaperones such as migalastat for the treatment of Fabry disease. Various other aspects of the present invention relate to methods for assessing various symptoms in Fabry patients such as gastrointestinal (GI) symptoms. Various other aspects of the present invention relate to methods of evaluating treatment therapies for Fabry disease.

30 Definitions

[0083] 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.

[0084] 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-Gb₃").

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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).

[0090] 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.

[0091] 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.

[0092] As used herein, the term "pharmacological chaperone" ("PC") 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).

[0093] 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 K_m . 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.

[0094] 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.

[0095] "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).

[0096] 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.

[0097] 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.

[0098] 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.

5 **[0099]** 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-Gb₃;
10 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
15 hypohidrosis; the absence of angiokeratomas; and improvements in hearing abnormalities such as high frequency sensorineural hearing loss progressive hearing loss, sudden deafness, or tinnitus.

[00100] The dose that achieves one or more of the aforementioned responses is a "therapeutically effective dose."

20 **[00101]** 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
25 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
30 pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, 18th Edition, or other editions.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] The term "migalastat" encompasses migalastat free base or a pharmaceutically acceptable salt thereof (*e.g.*, migalastat HCl), unless specifically indicated to the contrary.

[00108] 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.

[00109] 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

[00110] Fabry disease is a rare, progressive and devastating X-linked 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.

[00111] 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.

[00112] More than 1,000 Fabry disease-causing GLA mutations have been identified. 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.

[00113] 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.

[00114] 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 GL-3 and related glycosphingolipids in many cell types including cells in the kidney. GL-3 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.

[00115] Because Fabry disease is rare, involves multiple organs, has a wide age range of onset, and is heterogeneous, proper diagnosis is a challenge. 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.

[00116] 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 μ M migalastat) of ≥ 1.20 -fold and an absolute increase (+ 10 μ M migalastat) of $\geq 3.0\%$ 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.

[00117] 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 $\pm$ 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
5 PC (*e.g.*, migalastat) using these methods are listed in U.S. Patent No. 8,592,362.

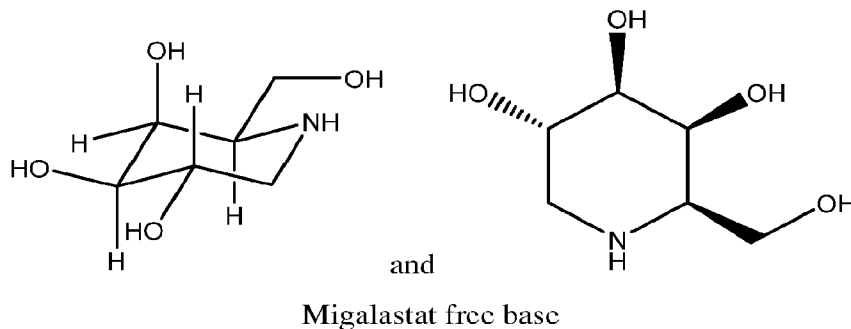
Pharmacological Chaperones

[00118] 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.
10 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
15 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
20 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
25 and be trafficked to lysosomes.

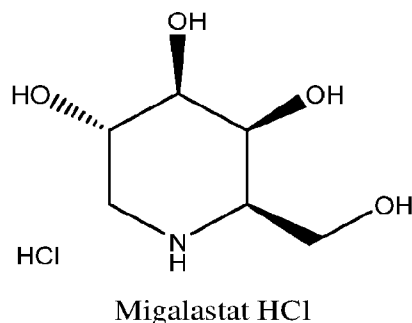
[00119] In one or more embodiments, the pharmacological chaperone comprises migalastat or a salt thereof. The compound migalastat, also known as 1-deoxygalactonojirimycin (1-DGJ) or (2R,3S,4R,5S)-2-(hydroxymethyl) piperidine-3,4,5-triol is a compound having the following chemical formula:

30

18



[00120] As discussed herein, pharmaceutically acceptable salts of migalastat may also
5 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:



10

[00121] 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
15 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
20 assay amenable mutations; the majority of which are associated with the classic phenotype of the disease.

[00122] 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.

[00123] 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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.265C>T	c.C265T	L89F
c.271A>C	c.A271C	I91L
c.271A>T	c.A271T	I91F
c.272T>C	c.T272C	I91T
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.319C>A	c.C319A	Q107K
c.319C>G	c.C319G	Q107E
c.320A>G	c.A320G	Q107R
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.377G>T	c.G377T	S126I
c.379A>G	c.A379G	K127E
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
c.428C>T	c.C428T	A143V
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
c.507T>A	c.T507A	F169L

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
c.551A>G	c.A551G	Y184C
c.551A>T	c.A551T	Y184F

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
c.614C>T	c.C614T	P205L
c.616C>A	c.C616A	L206I
c.616C>G	c.C616G	L206V
c.616C>T	c.C616T	L206F

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 1. HEK Assay Amenable Mutations

Nucleotide change	Nucleotide change	Protein sequence change
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
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

[00124] 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
5 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".

[00125] The effective amount of migalastat or salt thereof can be in the range from about 100 mg FBE to about 150 mg FBE. Exemplary doses include about 100 mg FBE, about
5 105 mg FBE, about 110 mg FBE, about 115 mg FBE, about 120 mg FBE, about 123 mg FBE, about 125 mg FBE, about 130 mg FBE, about 135 mg FBE, about 140 mg FBE, about 145 mg FBE or about 150 mg FBE.

[00126] 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
10 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. As set forth above, this dose is referred to as 123 mg FBE of migalastat. 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
15 once every other day.

[00127] In various embodiments, the effective amount is about 122 mg, about 128 mg, about 134 mg, about 140 mg, about 146 mg, about 150 mg, about 152 mg, about 159 mg, about 165 mg, about 171 mg, about 177 mg or about 183 mg of migalastat hydrochloride.

[00128] Accordingly, in various embodiments, migalastat therapy includes
20 administering 123 mg FBE at a frequency of once every other day, such as 150 mg of migalastat hydrochloride every other day.

[00129] 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 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16,
25 20, 24, 30 or 36 months or at least 1, 2, 3, 4 or 5 years. In various embodiments, the migalastat therapy is a long-term migalastat therapy of at least about 2, 3, 4 or 5 years.

[00130] 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. As one example, the patient is
30 orally administered capsules each containing 150 mg migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt.

[00131] 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.

5 [00132] 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
10 prevent enzyme aggregation *in vitro* prior to administration.

[00133] 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
15 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).
20 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.

[00134] The pharmaceutical formulations of the PC (*e.g.*, migalastat or salt thereof) suitable for parenteral/injectable use generally include sterile aqueous solutions (where water
30 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.

10 Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00135] 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.

[00136] 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; polyvinylpyrrolidone; 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.

[00137] 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.

[00138] 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
5 by intravenous or intraperitoneal administration from a reservoir which is external (*e.g.*, an i.v. bag) or internal (*e.g.*, a bioerodable implant).

[00139] 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
10 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
15 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.

[00140] 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
20 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
25 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).

30 **[00141]** 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.

Composite Clinical Outcomes

5 [00142] The dosing regimens described herein can reduce the risk of composite clinical outcomes (CCOs) in Fabry patients. As described in further detail in the Examples below, Phase 3 studies have found that migalastat therapy reduces the incidence of CCOs in Fabry patients. Accordingly, migalastat therapy can be used to reduce the risk of CCOs in Fabry patients and/or treat Fabry patients that have a high risk of CCOs, including for patients that
10 have a history of cardiovascular, renal or cerebrovascular events or patients that do not have a history of these events.

[00143] In one or more embodiments, the CCO comprises renal events, cardiac events, cerebrovascular events and death. In one or more embodiments, the renal events comprise one or more of: a decrease in $\text{eGFR}_{\text{CKD-EPI}} \geq 15 \text{ mL/min/1.73 m}^2$, with the decreased $\text{eGFR} < 90$
15 mL/min/1.73 m^2 relative to baseline; or an increase in 24-hour urine protein $\geq 33\%$, with elevated protein $\geq 300 \text{ mg}$ relative to baseline. In one or more embodiments, the cardiac events comprise one or more of: myocardial infarction; unstable cardiac angina; new symptomatic arrhythmia requiring antiarrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; or congestive heart failure [New York Association Class III or IV].
20 In one or more embodiments, the cerebrovascular events comprise one or more of stroke or transient ischemic attack.

[00144] In one or more embodiments, the incidence rate of CCOs is less than 1.0 per patient•year, such as less than 0.9, 0.8, 0.7, 0.6, 0.5 or 0.4 per patient•year.

[00145] In one or more embodiments, the migalastat therapy provides a lower CCO
25 incidence rate than a different treatment therapy. In one or more embodiments, the other treatment therapy comprises one or more of ERT, substrate reduction therapy or gene therapy. In one or more embodiments, the other therapy is ERT.

[00146] In one or more embodiments, the CCO incidence rate is evaluated after 18 months of treatment. In one or more embodiments, the CCO incidence rate is evaluated over
30 long-term treatment periods of at least 2, 3, 4 or more years.

[00147] In one or more embodiments, the median time to first CCO is greater than 0.5 years, such as greater than 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months or 1 year.

[00148] In one or more embodiments, the migalastat therapy provides a longer time to first CCO than a different treatment therapy. In one or more embodiments, the other treatment therapy comprises one or more of ERT, substrate reduction therapy or gene therapy. In one or more embodiments, the other therapy is ERT.

EXAMPLES

10 EXAMPLE 1: Composite Clinical Outcomes During Migalastat Therapy

[00149] This example describes the incidence of composite clinical outcomes (CCOs) in migalastat-treated patients who were previously treated with ERT.

Study Designs

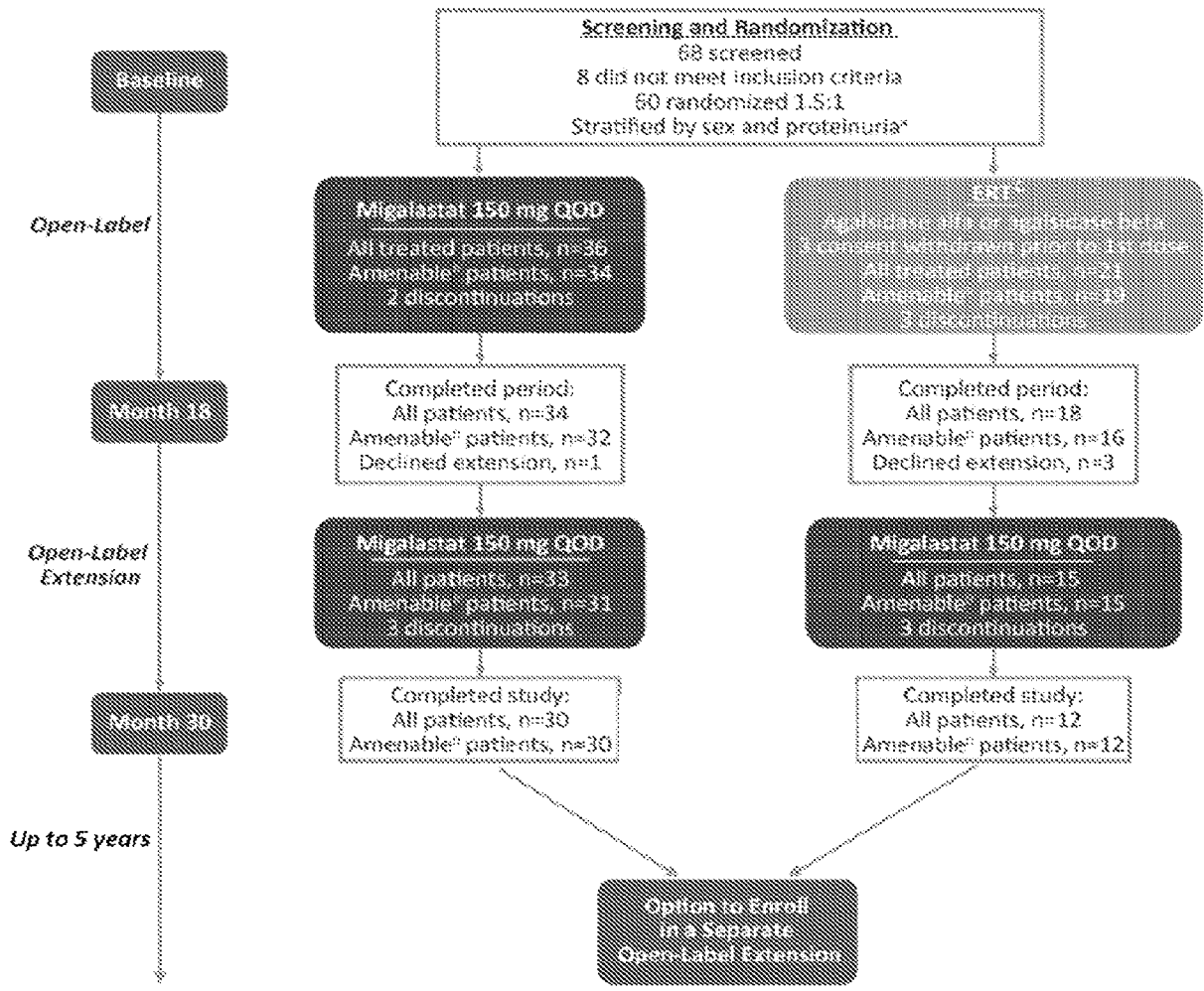
15 [00150] The analysis included data from 3 Phase 3 clinical trials with the data cutoff of May 25, 2019 as shown below. The analysis included ERT-experienced patients with migalastat-amenable GLA variants who had received migalastat in ATTRACT and the subsequent open-label extension (OLE) studies (AT1001-041 [NCT01458119] and/or AT1001-042, [NCT02194985]). Patients initiated ERT $\geq$ 12 months prior to the study.

20 [00151] ATTRACT (AT1001-012, NCT01218659) was a phase 3, open-label, active-controlled study to compare the efficacy and safety of 18 months of migalastat HCl 150 mg QOD versus ERT, followed by a 12-month OLE of migalastat, in ERT-treated patients with migalastat-amenable GLA variants.

[00152] AT1001-041 (NCT01458119) was a long-term OLE study evaluating the long-term safety and efficacy of migalastat in patients completing a previous migalastat study.

[00153] 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.

Clinical Studies Included in the Analysis



^aProteinuria stratification: high, ≥ 0.1 g/24 h; low, < 0.1 g/24 h.

5 ^bDetermination of amenability was based on the Good Laboratory Practice–validated migalastat amenability assay, which became available during the study. Therefore, some enrolled patients were later determined to be not amenable.

^cEight (38%) and 13 (62%) patients were receiving agalsidase beta and agalsidase alfa, respectively.

[00154] CCOs were defined prior to the planned analysis and included:

- Renal events (a decrease in $\text{eGFR}_{\text{CKD-EPI}} \geq 15 \text{ mL/min/1.73 m}^2$, with the decreased $\text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ relative to baseline; or an increase in 24-hour urine protein $\geq 33\%$, with elevated protein $\geq 300 \text{ mg}$ relative to baseline)
- Cardiac events (myocardial infarction; unstable cardiac angina; new symptomatic arrhythmia requiring antiarrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; congestive heart failure [New York Association Class III or IV])
- Cerebrovascular events (stroke or transient ischemic attack)
- Death

Data Analysis

[00155] Exposure to migalastat was calculated from the day of the first dose to the last available data point or the date of discontinuation; for this analysis, the exposure to ERT comprised the duration of participation in the ATTRACT study, and lasted up to 18 months.

[00156] Incidence rates were calculated for renal, cerebrovascular, and cardiac events separately and for the composite clinical outcomes. All individual events were accounted for when calculating incidence. Median times to the first clinical event were calculated based on the same data used for the incidence rates.

[00157] A direct comparison between migalastat and ERT was based on the 18 months exposure (the ERT data were from first 18 months in ATTRACT only); in addition, the incidence of CCOs for the whole follow-up period was calculated for migalastat (ATTRACT and subsequent OLE studies)

[00158] The long-term incidence for migalastat was calculated based on all available data for migalastat.

Results

Demographics and Baseline Characteristics

[00159] The mean (standard deviation) age of patients was 49.4 (14.1) years; on average, patients received 3.4 years of ERT prior to migalastat treatment (Table 2). The median (Q1–Q3) migalastat exposure was 4.8 (2.1, 5.5) years; individual patient values ranged from 0.1 to 7.2 years. Patients received migalastat at initiation of ATTRACT or switched from ERT after 18 months.

Table 2. Patient Demographics and Baseline Characteristics^a

Parameters	ERT-experienced Patients N=49		
	Overall (N=49)	Males n=19	Females n=30
Age, years			
Mean (SD)	49.4 (14.1)	48.1 (14.7)	50.2 (14.0)
Median (range)	53.0 (18.0–70.0)	48.0 (18.0–67.0)	53.5 (18.0–70.0)
Years since Fabry diagnosis, years			
Mean (SD)	11.6 (12.0)	9.2 (10.6)	13.0 (12.8)
Median (range)	5.7 (1.2–42.9)	4.4 (1.9–38.2)	6.3 (1.2–42.9)
Duration of ERT exposure, years			
Mean (SD)	3.4 (2.4)	3.5 (2.3)	3.4 (2.5)
Median (range)	2.3 (0.3–8.6)	2.4 (0.5–8.5)	2.2 (0.3–8.6)
eGFR_{CKD-EPI}, mean (SD), mL/min/1.73 m²	89.3 (20.5)	90.1 (21.6)	88.8 (20.1)
LVMi, mean (SD), g/m²	93.0 (25.6)	107.5 (29.5)	84.5 (18.9)

^aValues were from the beginning of migalastat treatment.

5 Incidence of Clinical Events

[00160] During the first 18 months of migalastat or ERT treatment, the incidence rate of CCOs was 0.41 per patient•year for migalastat and 0.85 per patient•year for ERT. In male and female patients receiving migalastat treatment, the incidence rate of CCOs during the first 18 months was 0.50 and 0.34 per patient•year, respectively (Table 3).

- 10 **[00161]** The incidence rate of CCOs remained low during long-term follow-up and was 0.45 per patient•year at the data cutoff. During long-term follow-up, the incidence rate of

CCOs was 0.56 and 0.37 per patient•year at the data cutoff in male and female patients, respectively (Table 3).

Table 3. Incidence Rate of Composite Clinical Outcomes by Treatment and Sex

Per patient•year	ERT At 18 months		Migalastat At 18 months		Migalastat At 4.8 years ^a	
	Males N=8	Females N=10	Males N=19	Females N=30	Males N=19	Females N=30
Composite clinical outcome	0.68	0.98	0.50	0.34	0.56	0.37
Renal event	0.58	0.56	0.43	0.29	0.51	0.33
Cardiac event	0	0.42	0.07	0.05	0.04	0.02
Cerebrovascular event	0.10	0	0	0	0.01	0.02
Death	0	0	0	0	0	0

5

Time to Clinical Events

[00162] Overall, median time to first CCO was 1.17 and 0.25 years with migalastat and ERT, respectively. Median time to first CCOs by treatment and sex are shown in Table 4.

10 **Table 4. Median Time to First Composite Clinical Outcome by Treatment and Sex**

Years	ERT (0-18 months)		Migalastat (0-4.8 years)	
	Males	Females	Males	Females
Composite clinical outcome	0.25	0.35	1.30	1.15

15

[00163] As can be seen from the tables above, the incidence rate of CCOs in patients on migalastat was lower and time to first CCO was longer with migalastat compared with ERT during the 18-month treatment period in the ATTRACT study. This CCO incidence rate was maintained for patients who continued migalastat for up to 7.2 years (median follow-up: 4.8 years) in the open label extension. These data demonstrated long-term benefits of migalastat treatment in ERT-experienced patients with Fabry disease and amenable GLA mutations.

EXAMPLE 2: FABry Disease Patient-Reported Outcome-Gastrointestinal (FABPRO-GI)

[00164] This example describes the development of a new Fabry disease-specific gastrointestinal (GI) outcomes instrument.

5

Current GI Instruments

[00165] The Gastrointestinal Symptom Rating Scale has been used to assess GI symptoms in a clinical trial of migalastat; however, no validated Fabry disease-specific instruments to fully evaluate the impact of treatments on Fabry disease-related GI symptoms are available (Table 5).

10

Table 5. Instruments Used to Assess GI Symptoms in Patients With Fabry Disease

Instrument	Advantages	Disadvantages
Gastrointestinal Symptom Rating Scale	- Assesses a broad range of GI symptoms - Can be used in its entirety or as a pool of items from which appropriate items can be selected - Is a patient-reported outcome	- Does not assess multiple items for diarrhea (e.g., frequency and severity) - Not validated for GI symptoms associated with Fabry disease
Rome III criteria (for adult and pediatric patients)	- Can be reported by caregivers or patients - Validated for several functional GI disorders	- Recommends that symptoms originate 6 months prior to diagnosis and be active for 3 months - Not validated for GI symptoms associated with Fabry disease

^aDiagnostic scoring system for irritable bowel syndrome given that Fabry disease-related GI symptoms mimic irritable bowel syndrome

15

[00166] Based on the shortcomings of these other instruments, the FABry disease Patient-Reported Outcome-Gastrointestinal (FABPRO-GI) instrument was developed to be a literature review- and quantitative analysis-based instrument designed to assess GI symptoms in patients with Fabry disease.

Methods

20

[00167] The FABPRO-GI instrument was drafted based on results from a comprehensive literature review, expert advice meetings, and patient concept elicitation interviews consistent with measurement best practices and regulatory guidance.

[00168] Patient perspectives regarding Fabry-disease related GI symptoms were obtained via concept elicitation interviews. 15 patients who had self-reported Fabry disease, were fluent in English, and aged ≥ 16 years with ≥ 1 self-reported GI symptom in the 14 days prior to study entry were included in the study. After development of the initial FABPRO-GI instrument, cognitive debriefing interviews with an additional 15 patients were conducted to evaluate its content and produce the final FABPRO-GI instrument. Demographics of patients interviewed in concept elicitation interviews and cognitive debriefing interviews are presented in Table 6.

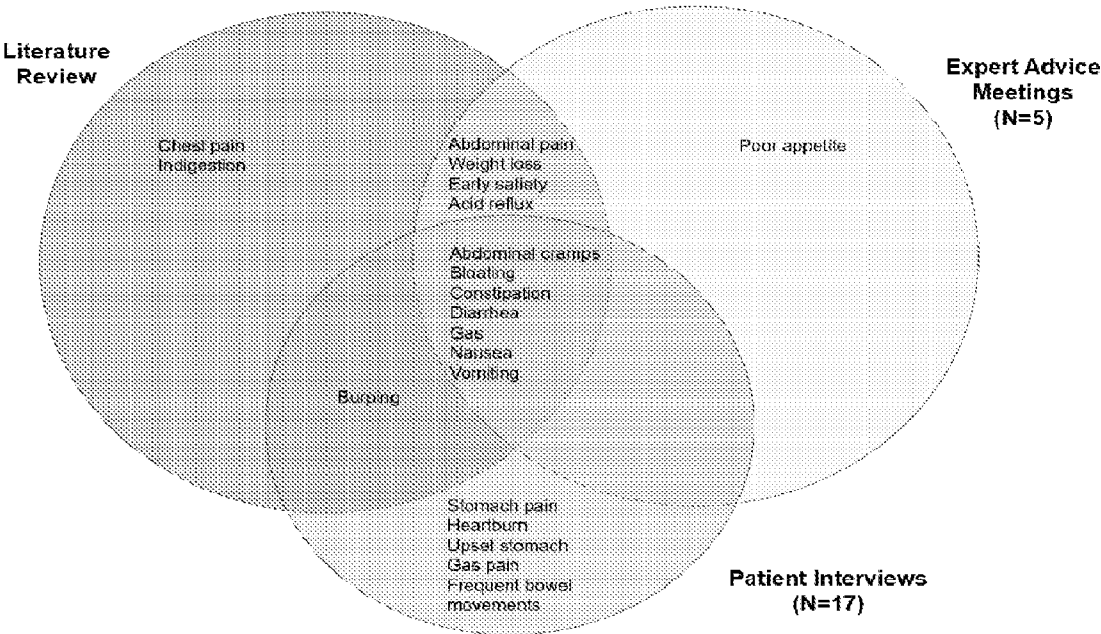
10 **Table 6. Demographics and Disease Characteristics of Patients With Fabry Disease Participating in CEIs and CDIs**

	CEIs (N=17)	CDIs (N=15)
Age, years, mean (SD)	33.7 (14.2)	39.6 (16.7)
Female, n (%)	10 (58.8)	11 (73.3)
Race, n (%)		
White	11 (64.7)	13 (86.7)
Black or African American	—	2 (13.3)
Other	5 (29.4)	—
Not answered	1 (5.8)	—
Time since diagnosis, mean (SD)	11.8 (12.2)	7.9 (6.2)
Fabry disease-related GI symptom severity, n (%) ^a		
Very mild	1 (5.9)	1 (6.7)
Mild	3 (17.6)	2 (13.3)
Moderate	11 (64.7)	11 (73.3)
Severe	1 (5.9)	1 (6.7)
Very severe	1 (5.9)	—

CDI=cognitive debriefing interviews; CEI=concept elicitation interviews;
NSAIDs=nonsteroidal anti-inflammatory drugs;

^aPatient-reported; ^bNot mutually exclusive; ^cEnzyme replacement therapy was excluded; ^dFor example, phenytoin, carbamazepine, or gabapentin; ^eFor example, narcotics, opioids such as codeine, hydrocodone, Demerol, OxyContin, or Percocet.

[00169] Three sets of conceptual models were derived from the literature review, expert advice meetings, and patient concept elicitation interviews, which show largely overlapping GI symptoms:



5

[00170] The initial FABPRO-GI instrument was revised based on feedback from cognitive debriefing interviews to produce the final 11-item FABPRO-GI instrument (Table 7).

Table 7. Final Items of the Final FABPRO-GI Instrument ^a

10

Domain	Item
Disease-related GI symptom severity	1. Over the past 24 hours, how severe was your worst bloating?
	2. Over the past 24 hours, how severe was your worst stomach pain?
	3. Over the past 24 hours, how severe was your worst cramping?
	4. Over the past 24 hours, how severe was your worst nausea?
	5. Over the past 24 hours, how severe was your worst acid reflux?
	6. Over the past 24 hours, how severe was your worst heartburn?
	8. Over the past 24 hours, how severe was your worst constipation?
	12. Over the past 24 hours, how severe was your worst diarrhea?

Frequency of bowel movements	9. Over the past 24 hours, how many bowel movements did you have?
Frequency of diarrhea	10. Over the past 24 hours, how many times did you have diarrhea ?
Consistency of diarrhea	11. Over the past 24 hours, what was the consistency of your worst diarrhea ?

^aItems were scored on a 0-10 scale.

[00171] Of the Fabry disease-related GI symptoms identified by the experts, abdominal pain, diarrhea, and early satiety were considered to be some of the most important to target during treatment. Of the Fabry disease-related GI symptoms mentioned by patients during the concept elicitation interviews, the most commonly reported symptoms included diarrhea, bloating, and bloating. On a 0-10 scale, where higher scores indicated more bother, worry, and impact, patients most frequently ranked diarrhea, bloating, and constipation as the top symptoms (Table 8).

Table 8. GI Symptoms and Their Bother, Worry, and Impact

Concept ^a	Patient-rated -reported symptoms ^b	Bother rating ^c	Worry rating ^c	Impact rating ^c
		Mean (SD)	Mean (SD)	Mean (SD)
Diarrhea	11/13	6.4 (2.0)	3.5 (2.9)	5.1 (3.3)
Bloating	9/10	4.9 (2.3)	3.6 (3.2)	3.3 (3.3)
Constipation	9/10	6.4 (3.0)	5.5 (3.3)	5.8 (2.8)
Cramping	8/9	6.5 (2.3)	4.4 (2.7)	6.0 (3.4)
Stomach pain	7/7	6.1 (2.9)	4.9 (1.7)	5.0 (2.9)
Nausea	5/8	6.2 (2.8)	2.4 (1.9)	4.0 (3.5)
Gas	4/4	3.8 (3.3)	4.5 (5.3)	5.0 (4.2)
Heartburn	4/4	5.5 (3.7)	4.5 (3.8)	3.8 (1.7)
Upset stomach	3/4	5.7 (2.1)	3.0 (2.6)	5.0 (4.4)
Gas pain	2/3	6.5 (0.7)	3.0 (4.2)	4.5 (4.9)

Frequent bowel movements	1/2	7.0	8.0	6.0
Burping	0/1	-	-	-
Vomiting	1/1	8.0	4.0	5.0

^aBased on the CEIs. ^bThe second number indicates the total number of patients that reported experiencing the symptom during the open-ended discussion; the number of patients who had the opportunity to provide a rating for the symptom may be less than the total frequency count for some symptoms as patients were only able to rate symptoms that the interviewer

specifically asked about during the interview, prior to the complete analysis of qualitative data.

^cRated on a 0-10 scale where a higher score indicates more bother, worry, or impact.

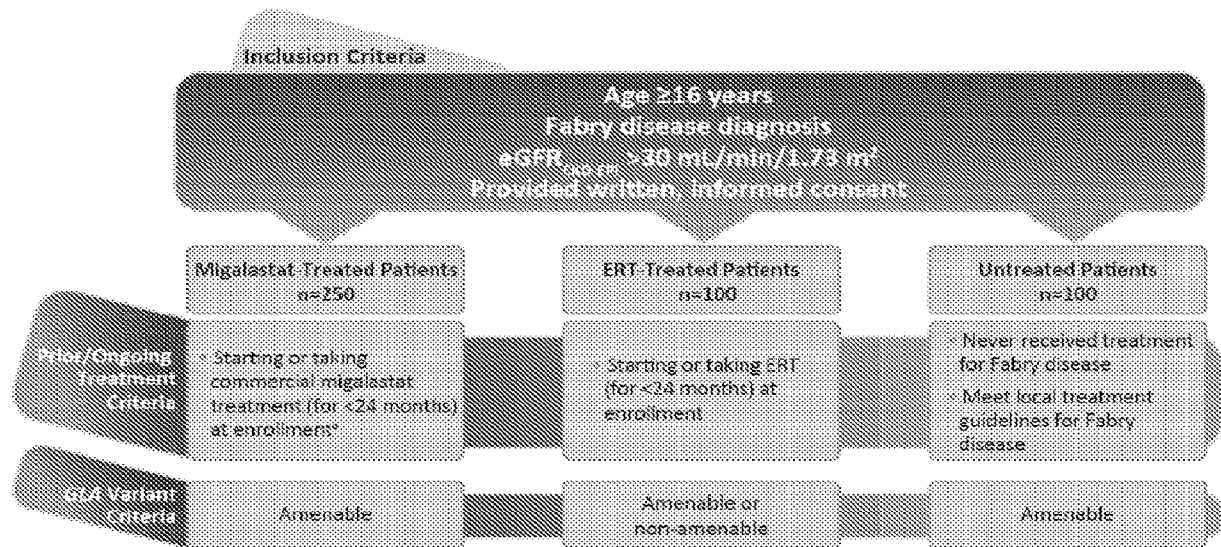
[00172] Based on the above, the FABPRO-GI is a new content-validated instrument developed based on literature review, expert advice, and patient perspectives that can be used to assess GI symptoms over a 24-hour recall period in patients with Fabry disease. General understandability, relevance, and comprehensiveness of the FABPRO-GI instrument was validated in a subset of patients with Fabry disease.

EXAMPLE 3: Baseline Patient Characteristics of followME, a New Patient-centric, Prospective, Observational Fabry Registry That Evaluates Migalastat, ERT, and a Natural History Cohort

[00173] This example describes followME, a unique patient-focused, prospective, observational, multinational registry designed to assess the real-world impact of migalastat treatment via safety, effectiveness, and patient-reported outcomes (PROs). The demographics and baseline characteristics of patients currently enrolled in the followME registry was analyzed and is presented below.

Study Design

Patients receiving migalastat, ERT, or no Fabry-disease specific therapy (natural history control) are enrolled and followed for up to 5 years. Eligibility criteria are presented below:



^aPatients receiving migalastat during a clinical trial must have switched to commercial drug at or before enrollment.

Methods

5 **[00174]** Following confirmation of patient consent, physicians collect baseline data for each patient at enrollment in the registry, which include demographics, genotype, and medical history (e.g., Fabry disease history and clinical event history).

[00175] The Safety Population includes all patients with Fabry disease who consented to participate in the registry and received at least 1 dose of migalastat or ERT or have never
10 received treatment

[00176] Demographics, baseline characteristics, and medical history (e.g., Fabry disease history and clinical event history) are summarized by initial treatment group/

Results

15 Patient Demographics

[00177] A total of 144 patients (migalastat: 67; ERT: 35; untreated: 42) from 15 centers in North America and Europe have been enrolled in the registry. Patient demographics are presented in Table 9. Female patients comprise 41.8%, 48.6%, and 88.1% of the migalastat, ERT, and untreated cohorts, respectively.

Table 9. Demographics of Patients Currently Enrolled in the followME Registry (Safety Population)

Parameter	Overall N=144	Migalastat (n=67)	ERT (n=35)	Untreated^a (n=42)
Age at enrollment, years				
Mean (SD)	50.2 (15.3)	52.8 (15.5)	50.4 (13.6)	45.8 (15.5)
Median (range)	52.0 (16–81)	56.0 (16–78)	52.0 (20–76)	45.0 (18–81)
Age categories, n (%)				
≥10-<20 years	2 (1.4)	1 (1.5)	0 (0.0)	1 (2.4)
≥20-<30 years	15 (10.4)	7 (10.4)	3 (8.6)	5 (11.9)
≥30-<40 years	22 (15.3)	6 (9.0)	4 (11.4)	12 (28.6)
≥40-<50 years	24 (16.7)	7 (10.4)	9 (25.7)	8 (19.0)
≥50 years	80 (55.6)	46 (68.7)	19 (54.3)	15 (35.7)
Missing	1 (0.7)	0 (0.0)	0 (0.0)	1 (2.4)
Gender, n (%)^b				
Male	61 (42.4)	38 (56.7)	18 (51.4)	5 (11.9)
Female	82 (56.9)	28 (41.8)	17 (48.6)	37 (88.1)
Ethnicity, n (%)				
Asian	3 (2.1)	1 (1.5)	1 (2.9)	1 (2.4)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	26 (18.1)	14 (20.9)	5 (14.3)	7 (16.7)
White	35 (83.3)	66 (98.5)	31 (88.6)	35 (83.3)
Other	6 (14.3)	0 (0.0)	3 (8.6)	6 (14.3)

^aAge information is missing for 1 patient in the untreated cohort.^bGender information is missing for 1 patient in the migalastat cohort.

Fabry Disease History

[00178] Overall, the median age at symptom onset was 45.5 years in males, and 28 years in females across treatment groups; distribution of age of symptom onset by treatment group and gender is shown in Figure 4A. The median time between earliest symptom onset and diagnosis was 1.2 years in males and 1.4 years in females (Figure 4B).

[00179] In the migalastat cohort, the median time between diagnosis and treatment initiation was 2.4 years in males and 1.8 years in females; in the ERT cohort, the median time between diagnosis and treatment initiation was 0.6 years in males and 9.6 years in females (Figure 4B).

Treatment History

[00180] In the migalastat cohort, 3.0% of patients were previously treated with ERT.

[00181] In the ERT cohort, 85.7% were treated with ERT prior to enrollment (median [range] ERT treatment duration: 1.3 (0–15.6) years)

Patient Genotypes

[00182] GLA genotype was assessed in 86.6.1%, 82.9%, and 100% of the migalastat, ERT, and untreated cohorts, respectively. 17 variants occurred in more than 1 patient and account for 74.2% of patients with known genotype (Table 10). The most common variant was p.N215S (n=24 [18.8%]), a variant associated with the late-onset phenotype of Fabry disease.

Table 10. Patient Genotypes Represented by ≥ 1 Patient in the followME Registry (Safety Population)^a

	Amenability	Total N=144	Migalastat N=67	ERT N=35	Untreated N=42
p.N215S	Amenable	24	15	2	7
p.R301Q	Amenable	10	5	0	5
p.R301G	Amenable	9	6	2	1
p.R356W	Amenable	7	2	2	3
p.S238N	Amenable	7	4	0	3
p.R118C	Amenable	6	3	1	2
p.T194I	Amenable	5	2	0	3
p.S345P	Amenable	5	1	3	1
p.A143T	Amenable	4	3	0	1
p.R227Q	Non-Amenable	3	0	2	1

p.F113L	Amenable	3	1	2	0
c.1201dupT	Non-Amenable	2	0	0	2
c.1288delT	Non-Amenable	2	0	1	1
p.I232T	Amenable	2	1	1	0
p.I317T	Amenable	2	1	0	1
p.Q386X	Non-Amenable	2	0	2	0
p.R342Q	Non-Amenable	2	0	1	1

^aThis is an ongoing study. Genotype has not been confirmed in 10 and 6 patients in the migalastat and ERT groups, respectively.

Fabry Signs and Symptoms

- 5 **[00183]** Fabry signs and symptoms reported by patients involve multiple organ systems (Figure 5A). The most commonly reported signs and symptoms among male patients were acroparathesias (37.7%), hearing loss (36.1%), and GI signs and symptoms (32.8%) across treatment groups. Among female patients, the most commonly reported signs and symptoms were GI signs and symptoms (40.2%), corneal whirling (34.1%) and acroparathesias (34.1%).
- 10 **[00184]** Only a subset of patients provided the age of onset for specific signs and symptoms (Figure 5B). Among male patients with data, hypohidrosis, gastrointestinal signs and symptoms, and acroparasthesias were the earliest signs and symptoms. Among female patients with data, corneal whirling, GI signs and symptoms, and acroparasthesias were the earliest signs and symptoms.
- 15 **[00185]** In FIGS 5A and 5B, a = White matter lesions; b = Symptom data were not collected for a small subset of patients: corneal whirling (1 ERT and 1 migalastat patients), angiokeratoma (4 migalastat patients), GI signs and symptoms (1 migalastat patient), MRI changes (4 migalastat patients), lymphedema (7 migalastat patients), pulmonary changes (5 migalastat patients); c = Symptom data of 1 untreated and 1 migalastat patients were not
- 20 collected for corneal whirling, angiokeratoma, acroparasthesias, hypohidrosis, GI signs and symptoms, hearing loss, lymphedema, and pulmonary changes. Brain MRI history was not collected for 1 untreated patient and 3 migalastat patients.

Cardiac Manifestations

- 25 **[00186]** Summary statistics for left ventricular mass index (LVMI) are shown in Table 11. Untreated female patients had the least cardiac involvement both in terms of mean LVMI

and the percentage of patients with left ventricular hypertrophy (LVH). However, ~40% of female patients in the migalastat and ERT groups manifested LVH.

5 **Table 11. Cardiac Parameters in Patients Enrolled in the followME Registry (Safety Population)**

	Male			Female		
Parameter	Migalastat N=38	ERT N=18	Untreated N=5	Migalastat N=28	ERT N=17	Untreated N=37
LVMi^a, g/m²						
n	15	12	2	11	10	16
Mean (SD)	96.3 (61.6)	83.8 (37.5)	102.4 (63.4)	90.5 (44.5)	87.1 (20.7)	67.7 (21.4)
LVH, n (%)^b	4 (26.7)	2 (16.7)	1 (50)	4 (36.4)	4 (40)	2 (12.5)

^aCalculated based on echocardiography measurements.

^bLVH defined as baseline LVMi value >115 g/m² for males and >95 g/m² for females. Percentages were calculated based on the number of patients with echocardiogram.

10 Renal Manifestations

15 **[00187]** Most patients have renal involvement based on the percentages of patients with detectable urine protein (all except 1 ERT-treated patient) and decreased estimated glomerular filtration rate (33.3% to 55%) in the untreated, ERT, and migalastat cohorts, respectively (Table 12). No patient was undergoing dialysis at enrollment; 1 female ERT patient had a kidney transplant.

Table 12. Renal Disease in Patients Enrolled in followME Registry (Safety Population)

	Male			Female		
	Migalastat N=38	ERT N=18	Untreated N=5	Migalastat N=28	ERT N=17	Untreated N=37
eGFR_{CKD-EPI}, mL/min/1.73 m²						
n	33	17	5	20	13	24
Mean (SD)	81.7 (29.0)	91.3 (23.9)	66.1 (36.8)	88.5 (15.1)	91.0 (17.5)	100.0 (15.3)
eGFR_{CKD-EPI} category, n (%)						

≥90 mL/min/1.73 m ²	16 (48.5)	9 (52.9)	2 (40.0)	9 (45.0)	7 (53.8)	16 (66.7)
≥60 and <90 mL/min/1.73 m ²	10 (30.3)	6 (35.3)	1 (20.0)	10 (50.0)	6 (46.2)	8 (33.3)
≥30 and <60 mL/min/1.73 m ²	7 (21.2)	2 (11.8)	1 (20.0)	1 (5.0)	0	0
Creatinine, mg/dL						
n	33	16	5	20	15	30
Mean (SD)	1.1 (0.4)	1.0 (0.3)	2.6 (3.6)	0.8 (0.2)	1.2 (1.8)	0.7 (0.1)
Urine protein , mg/dL						
n	27	14	5	12	10	18
Median (range)	10.7 (3–1800)	13.6 (0–100)	7.1 (4–108)	6.9 (3–148)	11.5 (2–43)	7.4 (3–500)
Detectable Urine Protein, n (%)	27 (100.0)	13 (92.9)	5 (100.0)	12 (100.0)	10 (100.0)	18 (100.0)

History of Cardiac, Renal, and Cerebrovascular Events

[00188] In male patients, prior cardiac events (18.0%) were more common than renal (8.2%) or cerebrovascular events (1.6%); in female patients, prior renal events (7.3%) were more common than cardiac (4.9%) or cerebrovascular events (4.9%) (Table 13).

Table 13. History of Clinical Events Prior to Enrollment in the followME Registry (Safety Population)

	Male			Female		
	Migalastat N=38	ERT N=18	Untreated N=5	Migalastat N=28	ERT N=17	Untreated N=37
Renal events^a, n (%)	1 (20)	1 (5.6)	3 (7.9)	5 (17.9)	0	1 (2.7)
Cardiac events^b, n (%)	7 (18.4)	4 (22.2)	0	2 (7.1)	0	2 (5.4)
Cerebrovascular events^c, n (%)	0	1 (5.6)	0	4 (14.3)	0	0

^aRenal events include development of ESRD requiring long-term dialysis or transplant.

^bCardiac events included myocardial infarction; palpitations as a symptom of arrhythmia; symptomatic arrhythmia requiring medication, direct current cardioversion, or interventional procedure (e.g., ablation, pacemaker or defibrillator implantation; unstable angina accompanied by electrocardiographic changes resulting in hospitalization or accompanied by elevated B-type natriuretic peptide; any major cardiac medical procedure (e.g. valve replacement, stent-implantation or transplant).

^cCerebrovascular events included transient ischemic attack and stroke.

[00189] Analysis of baseline characteristics of patients currently enrolled shows that patients in the followME registry are representative of patients with Fabry disease in real-world settings.

[00190] Acroparasthesias and GI signs and symptoms are among the most common and earliest Fabry signs and symptoms. Most patients had renal involvement and ~26% of patients experienced LVH.

[00191] Compared with male patients, female patients are more likely to be untreated even though some experienced classic Fabry signs and symptoms. Female patients experienced a much longer delay between diagnosis and ERT treatment initiation than male patients

[00192] Follow-up of these patients will generate long-term outcome data with migalastat, ERT, and the natural history of Fabry disease that will provide valuable insights regarding real-world experience with migalastat and other treatments for Fabry disease.

[00193] 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.

[00194] 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 reducing the risk of composite clinical outcomes (CCO) in a patient having Fabry disease, the method comprising administering to the patient a formulation comprising an effective amount of migalastat or salt thereof every other day for at least 18 months, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE).
2. The method of claim 1, wherein the CCO comprises renal events, cardiac events, cerebrovascular events and death.
3. The method of claim 2, wherein the renal events comprise one or more of: a decrease in $\text{eGFR}_{\text{CKD-EPI}} \geq 15 \text{ mL/min/1.73 m}^2$, with the decreased $\text{eGFR} < 90 \text{ mL/min/1.73 m}^2$ relative to baseline; or an increase in 24-hour urine protein $\geq 33\%$, with elevated protein $\geq 300 \text{ mg}$ relative to baseline.
4. The method of claim 2 or 3, wherein the cardiac events comprise one or more of: myocardial infarction; unstable cardiac angina; new symptomatic arrhythmia requiring antiarrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; or congestive heart failure [New York Association Class III or IV].
5. The method of any one of claims 2-4, wherein the cerebrovascular events comprise one or more of stroke or transient ischemic attack.
6. The method of any one of claims 1-5, wherein the migalastat or salt thereof enhances α -galactosidase A activity.
7. The method of any one of claims 1-6, wherein the patient is administered about 123 mg FBE of the migalastat or salt thereof every other day.
8. The method of any one of claims 1-7, wherein the patient is administered about 123 mg of migalastat free base every other day.
9. The method of any one of claims 1-7, wherein the patient is administered about 150 mg of migalastat hydrochloride every other day.
10. The method of any one of claims 1-9, wherein the formulation comprises an oral dosage form.

11. The method of claim 10, wherein the oral dosage form comprises a tablet, a capsule or a solution.
12. The method of any one of claims 1-11, wherein the migalastat or salt thereof is administered for at least 3 years.
- 5 13. The method of any one of claims 1-12, wherein the migalastat or salt thereof is administered for at least 4 years.
14. The method of any one of claims 1-13, wherein the CCO incidence rate for a group of patients on migalastat therapy for 18 months is less than 1.0 per patient•year.
15. The method of any one of claims 1-14, wherein the CCO incidence rate for a group of
10 patients on migalastat therapy for 18 months is less than 0.5 per patient•year.
16. The method of any one of claims 1-15, wherein the patient is male.
17. The method of any one of claims 1-15, wherein the patient is female.
18. The method of any one of claims 1-17, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.
- 15 19. The method of any one of claims 1-17, wherein the patient is an ERT-experienced patient.
20. The method of any one of claims 1-19, wherein the patient has a HEK assay amenable mutation in α -galactosidase A.
21. The method of claim 20, wherein the mutation is disclosed in a pharmacological
20 reference table.
22. The method of claim 21, wherein the pharmacological reference table is provided in a product label for a migalastat product approved for the treatment of Fabry disease.
23. The method of claim 22, wherein the pharmacological reference table is provided in a product label for GALAFOLD®.
- 25 24. The method of claim 22, wherein the pharmacological reference table is provided at a website.
25. The method of claim 24, wherein the website is one or more of
www.galafoldamenabilitytable.com or www.fabrygenevariantsearch.com.

26. A method of assessing gastrointestinal (GI) outcomes in a patient having Fabry disease, the method comprising:

assessing the patient's disease-related GI symptom severity;

assessing the patient's frequency of bowel movements;

5 assessing the patient's frequency of diarrhea; and

assessing the consistency of the patient's diarrhea.

27. The method of claim 26, wherein assessing the patient's disease-related GI symptom severity comprises assessing the severity of one or more of: bloating, stomach pain, cramping, nausea, acid reflux, heartburn, constipation, or diarrhea.

10 28. The method of claim 26 or 27, wherein assessing the patient's disease-related GI symptom severity comprises assessing the severity of one or more of: the worst bloating over a time period; the worst stomach pain over a time period; the worst cramping over a time period; the worst nausea over a time period; the worst nausea over a time period; the worst nausea over a time period; or the worst nausea over a time period.
15

29. The method of any one of claims 26-28, wherein the GI outcomes are assessed based on a 24-hour time period.

30. The method of any one of claims 26-29, wherein the GI outcomes are assessed based on patient-reported symptoms.

20 31. The method of any one of claims 26-30, wherein each item is assessed using a score on a 0-10 scale.

32. A method of evaluating a treatment therapy for Fabry disease, the method comprising:

assessing the GI outcome of any one of claims 26-31 at baseline;

25 assessing the GI outcome of any one of claims 26-31 after a period of the treatment therapy; and

comparing the GI outcome at baseline to the GI outcome after the period of the treatment therapy.

33. A method of treating Fabry disease, the method comprising:

assessing the GI outcome of any one of claims 26-31 to obtain a first GI outcome score;

initiating or continuing a treatment therapy for Fabry disease for a time period;

assessing the GI outcome of any one of claims 26-31 after the time period of treatment therapy to obtain a second GI outcome score; and

5 comparing the first GI outcome score and the second GI outcome score.

34. The method of claim 32 or 33, wherein the treatment therapy comprises enzyme replacement therapy (ERT).

35. The method of claim 32 or 33, wherein the treatment therapy comprises substrate reduction therapy.

10 36. The method of claim 32 or 33, wherein the treatment therapy comprises gene therapy.

37. The method of claim 32 or 33, wherein the treatment therapy comprises pharmacological chaperone therapy.

38. The method of claim 37, wherein the pharmacological chaperone therapy comprises administration of an effective amount of migalastat or a salt thereof.

15 39. The method of claim 38, wherein the migalastat or salt thereof is administered every other day.

40. The method of claim 39, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE).

41. A method of evaluating a treatment therapy for Fabry disease, the method comprising:

20 assessing one or more parameters in a patient population treated with the treatment therapy, wherein the one or more parameters comprise one or more of: incidence of Fabry signs and symptoms; renal parameters; and cardiac parameters; and

 assessing the one or more parameters in an untreated patient population.

42. The method of claim 41, wherein the Fabry signs and symptoms comprise one or more
25 of: acroparasthesias; gastrointestinal (GI) signs and symptoms; hearing loss; corneal whirling; angiokeratomas; hypohidrosis; pulmonary changes; lymphedema; or brain MRI changes.

43. The method of claim 41 or 42, wherein the renal parameters comprise one or more of cGFR_{CKD-EPI}; creatinine levels; urine protein levels; or incidence of detectable urine protein.

44. The method of any one of claims 41-43, wherein the cardiac parameters comprise one or more of left ventricular mass index (LVMI) or incidence of left ventricular hypertrophy.

45. The method of any one of claims 41-44, further comprising assessing the one or more parameters in a patient population treated with a different treatment therapy for Fabry disease.

5 46. The method of any one of claims 41-45, further comprising assessing the patient ages in each of the patient populations.

47. The method of any one of claims 41-46, further comprising assessing the patient genotypes in each of the patient populations.

10 48. The method of any one of claims 41-47, further comprising assessing the patient genders in each of the patient populations.

49. The method of any one of claims 41-48, wherein the treatment therapy comprises enzyme replacement therapy (ERT).

50. The method of any one of claims 41-48, wherein the treatment therapy comprises substrate reduction therapy.

15 51. The method of any one of claims 41-48, wherein the treatment therapy comprises gene therapy.

52. The method of any one of claims 41-48, wherein the treatment therapy comprises pharmacological chaperone therapy.

20 53. The method of claim 52, wherein the pharmacological chaperone therapy comprises administration of an effective amount of migalastat or a salt thereof.

54. The method of claim 53, wherein the migalastat or salt thereof is administered every other day.

55. The method of claim 54, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE).

25 56. The method of any one of claims 52-55, further comprising assessing the one or more parameters in a patient population treated with ERT.

57. The method of any one of claims 41-56, wherein the one or more parameters are assessed for a time period of at least one year.

ctgtaggggcagagagggtttctacttcattactgcgtctcctgggaaggccatcag	ccctt
gactgctggctaaagtgggaaccaggactctttgtgagtttaagaatttgtgtatttatat	60
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gagcgttccatgtgcaaccttgactgcccaggaagagccagattcctgcacaggtatcag	1320
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gagtcctcaacgggaacagtttgagcccgaggggagagctcccccacccagactctgctgtgc	1440
tttttttatcccccagcaaacctgtcccgcaatcaggactagccctaaaactttctctgtgtgac	1500
ctttccctgggatgggagtcgggcccagcggcccccctgtttctttctctctctctctctct	1560
cgttctccttct	1620
ttct	1680
agccctgcgcggttctattccagacccttcttggtaactctctgctcttctctctctctctct	1740
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tttctccttttgggggtcgtggatttctcggcagttatctcgaggaggttagagagaccata	1860
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gagataacctattttaagtaacatagcagcagcgttgaccattcaactgcgcttacagagc	2160
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cccagaaataatcatgggttaaatgttaatatatacaaaccttacaattgttttctatatataa	2640
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tgtttggctaatggcaagaccctggcaccacagctctgggctcaaattctgcctcattgtta	2760
cttagccctgtgacattgggttaaattacaacttttttttttttttttttttttttttttttt	2820
	2880

FIG.1A

tctatcaacagtccttccaccagttatctctaaaaatatctcctgaatcagcccaacttctct	8700
ccatcttcaactacatgcacccctggccttccaaagctactatcggctctcaaccagactgct	8760
gggaccacctgatctctctgcttccactctgtctcaacccccatctatctttccaaagcagc	8820
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gtctgactttgactgtatctctcgcataatgggttaagtgttaaatagttattttatggaatg	9420
aatccctatttattccctcatttatctctgcaaaaatagttctttttctcaacatcttaaac	9480
tgtatctccacctgcctatctacaaaacttttttttggcagacaggtctcactgtcaccca	9540
ggctagagtgcaagtggcgccatctcgggtcactgcaacctccgcctcccggttttaagcg	9600
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aatttttgtatttttagtagagatgggttccaccatggtggccagggttctctcgaactcc	9720
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acogtgcccagcctctacaaaactttttattccatttaacaaaactatatgctgggttttaag	9840
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aaagtataaaagagtatcttggaactggacatcttttaaccaggagagaatttgttgatgttg	10260
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acccctgggtaggcttgttttctatttttgacattcaagggtaaatacagggtaaagttcctg	10380
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ttttctcagttagtgattggcaactttggcctcagctggaatcagcaagtaactcagatg	10560
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cctcaagccaaagctctccttcaggataagggaactaatggccatcaatcaggaccccttg	10680
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gacaactttgaagtgtgggaacgacctctctcagggttagcctgggtgtagctatgata	11040
aacgggcaggagattgggtggacctcgtctcttataccatcgcagttgcttccctgggtaaa	11100
ggagtggcctgtaatcctgcctgcttcaatcacacagctcctccctgtgaaaaagggaagcta	11160
gggttctatgaatggacttcaagggttaagaagtcacataaatcccacaggcactgttttg	11220
cttcagctagaaaaatacaatgcagatgtcattaaaagaacttactttaaaatgtttatttt	11280
attgccactactacttctgtccacctttttctccattcactttaaaagctcaaggcta	11340
ggtggctcatgtgaatccagcactttgggaggctgaggcgggcagatcacctgagg	11400
tgggaactttgagacccgcctggacaacatggtgaaaccccatttotaataaaaaatataa	11460
aaattagccagggtgtggtggcgccactgtggtcccagctactctgggggtgaggcatga	11520

FIG.1D

gaatcgcttgaaccgggagtgagggttgcattgagctgagatcatgccacctcactcca	11580
gcctgggcaacaaagattccatctcaaaaaaaaaaaaaagccaggccacagtgggtcatg	11640
cctggaatcccagcacttttggaaagctgaggcaggcagatcacttgagggttaggatttca	11700
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aaacatcattaaagactgaaatgtatttaagaaggatgtataggccaggcaagggtgtctcac	12120
gcctgtaatcccaacacttttgggaggccaagtccggcggatcacgaggtcaggagatgga	12180
gaccatcctggccaacatggtgaaaacccctctctactaaaaatacaaaaaattagccagg	12240
cagggtggcaggccacctgtaatcccagctactccagaggctgaggcaggacaatcacttga	12300
acctgggaggcagaggctgcagtgagctgagggttgtaaccaattgcactccagcctaggta	12360
acgagcaacactccatctcaaaaaaagaaaaaaaaaagatgtataatttggaactgtta	12420
agaggcatttttaaaga	12436

FIG.1E

MQLRNPFLHL	GCAIAIRFLA	IVSWDTPGAR	ALDNGIARTP	TMGWIHWRRF	MCNIDCQFEP	60
DSCISEKLFM	EMAELMVSEG	WKDAGYEYLC	IDDCWMAPOK	DSEGRLOADP	QRFPHGIRQL	120
ANYVHSKGLK	LGIYADVGNK	TCAGFFGSFG	YYDIDAQTFA	DWGVDLLKFD	GCYCDSLENL	180
ADGYKHMSLA	LNRTGRSIVY	SCEWPLYMWP	FQKPNYTEIR	QYCNHWRNFA	DIDDSWKSIL	240
SILDWTSFNQ	ERIVDVAGPG	GWNDPDLVI	GNFGLSWNQO	VTQMALWAIM	AAPLFMSNDL	300
RHISPQAKAL	LQDKDVIAIN	QDPLGKQGYQ	LRQGDNFEVW	ERPLSGLAWA	VAMINRQEIG	360
GPRSYTIAVA	SLGKGVACNP	ACFITQLLPV	KRKLGFEYEW	SRLRSHINPT	GTVLLQLENT	420
MQMSLKDLL						429

FIG.2

Atgcagctgaggaatcccgagctccacctgggctgtgctctggctctgcgggttcctggcc	60
Ctctgtgtcctgggacatccctggcgctagggccctcgataacggactggcccggaacccc	120
Acaatgggatggctccactgggaagggttcattgtgcaatctggaactgtcaggaggaacccc	180
Gactcctgcacagcgaaaagctcttcatggagatggccgagctgatggtgagcgagggc	240
Tggaaggacgcggctacgagtatctgtgcacatcgatgactgctggatggccctcaaagg	300
Gactccgaaggcaggtgcaggtgatcccaagggtttcccccacggaatccggcagctc	360
Gccaactacgtgcattccaaggccctcaagctcggcatctacgcgcgacgtgggcaacaaa	420
Acatgogccgattccccggcagcttcggctactacgacatcgacgcccagacattcgct	480
Gattggggagtggaactgctgaagttogaaggctgttactgcgattccctggaaaactg	540
Gccgacggctacaaaacacatgtccctcgccctgaacgggacaggcaggtccatcgtgtac	600
Agctgcgagtgggccctgtacatgtggcctttccagaagcccaactacacagagatcagg	660
Cagtactgcaaccactggaggaacttcgctgacatcgacgactcctggaagagcatcaag	720
Agcatcctggactggaccagcttcaaccaggagaggatcgtggacgtggctggaccggga	780
Ggctggaacgaccccgatatgctggtgattggcaacttcggactgagctggaaccagcag	840
Gtgacccagatggccctgtggggccattatggccgctccctgttcattgtccaacgacctg	900
Aggcacatcagccccaggccaaaggctctgctgcaggacaaggatgtgatcgccatcaac	960
Caggacccctgggcaagcagggtaccagctgaggcaaggagataacttcgaggtgtgg	1020
Gagaggccctgtccggactggcttggggccgtggccatgatcaatcggcaggagatcggc	1080
Ggaacccggctcctacaccattgctgtggccagcctgggaaaaggagtcgctgcaacccc	1140
Gcctgcttcattaccagctgctcccgctgaagcggaagctgggcttcctatgagtggacc	1200
Agcaggctgaggtcccatatcaatcctaccggcacccgtcctcctccagctcgagaatacc	1260
Atgcagatgagcctcaaggatctgctgtga	1290

FIG.3

Distribution of Age of Symptom Onset

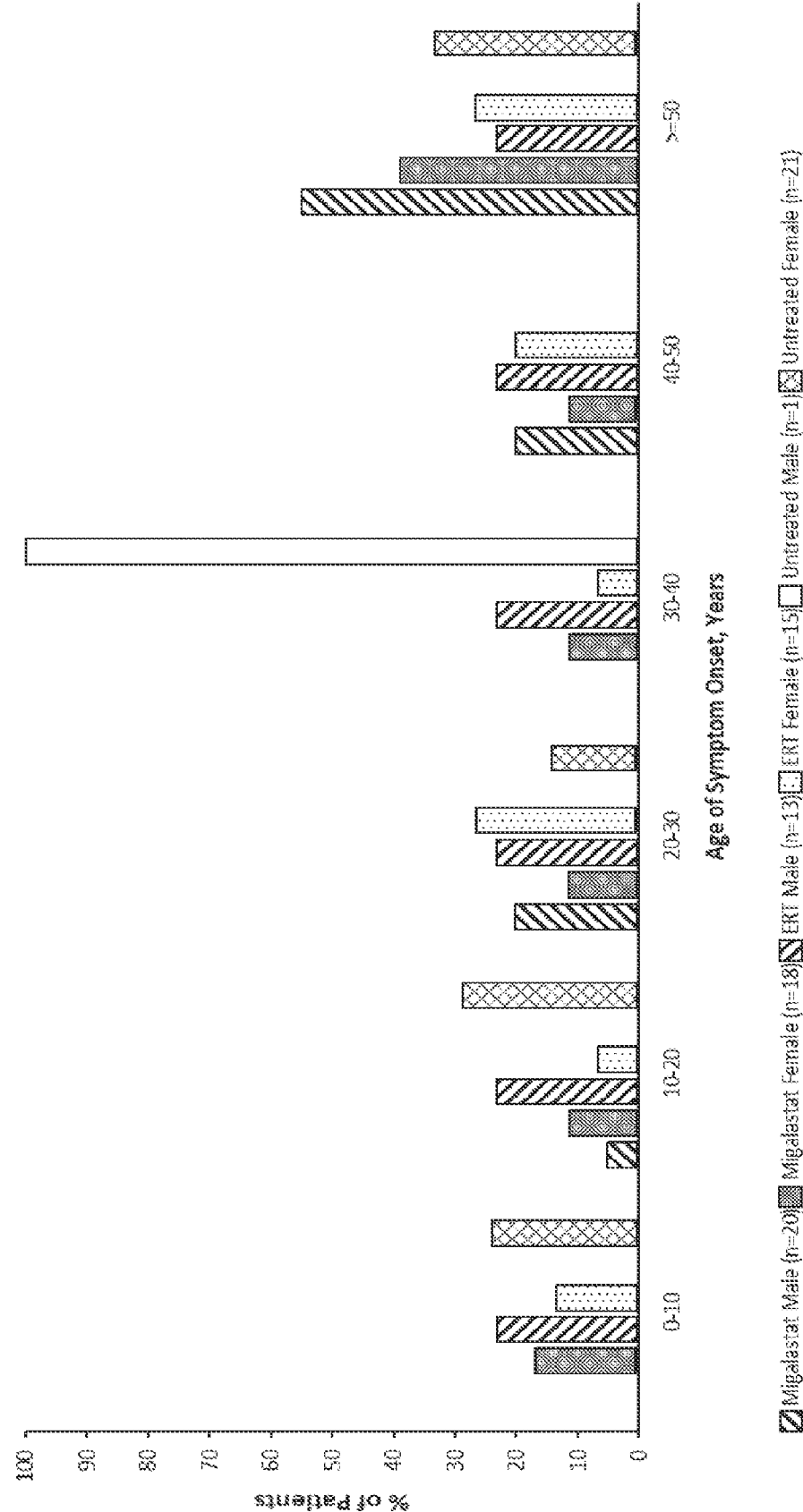


FIG. 4A

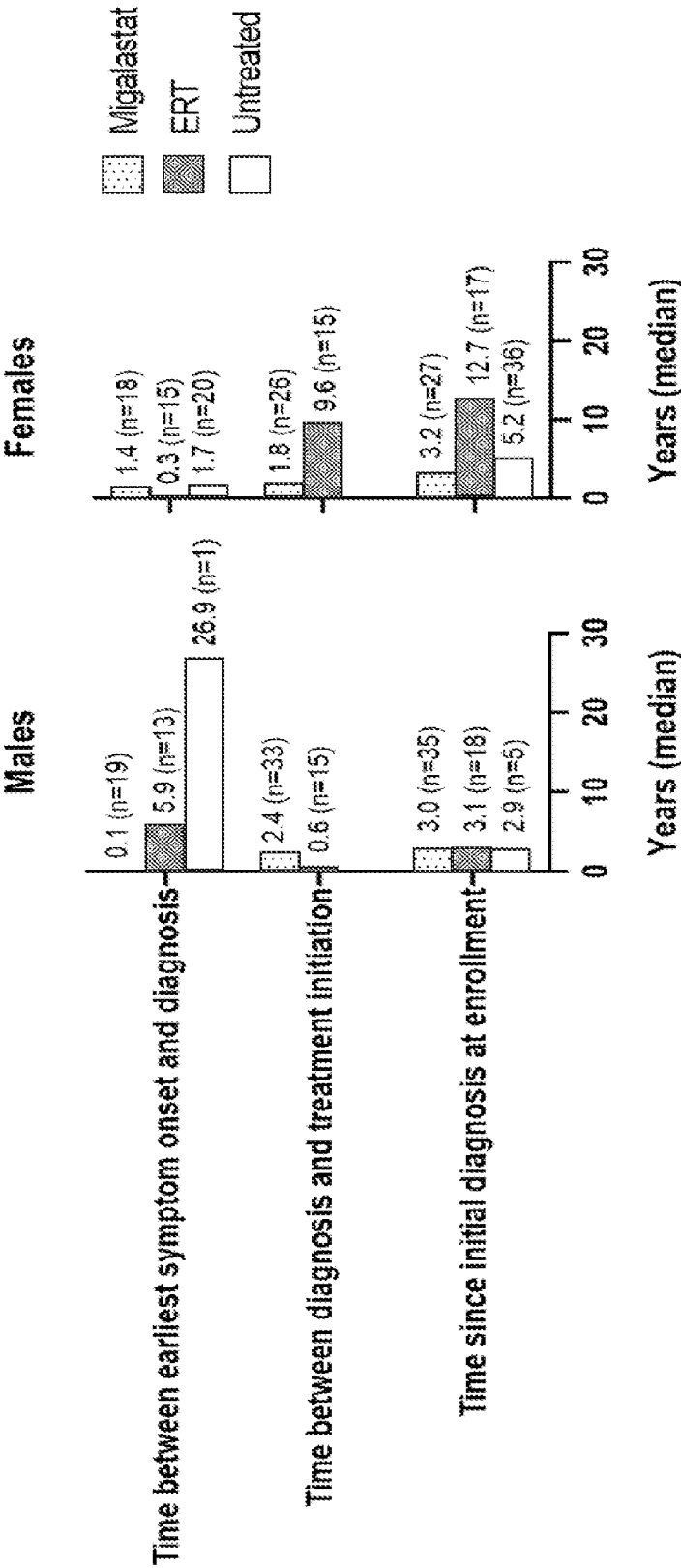


FIG. 4B

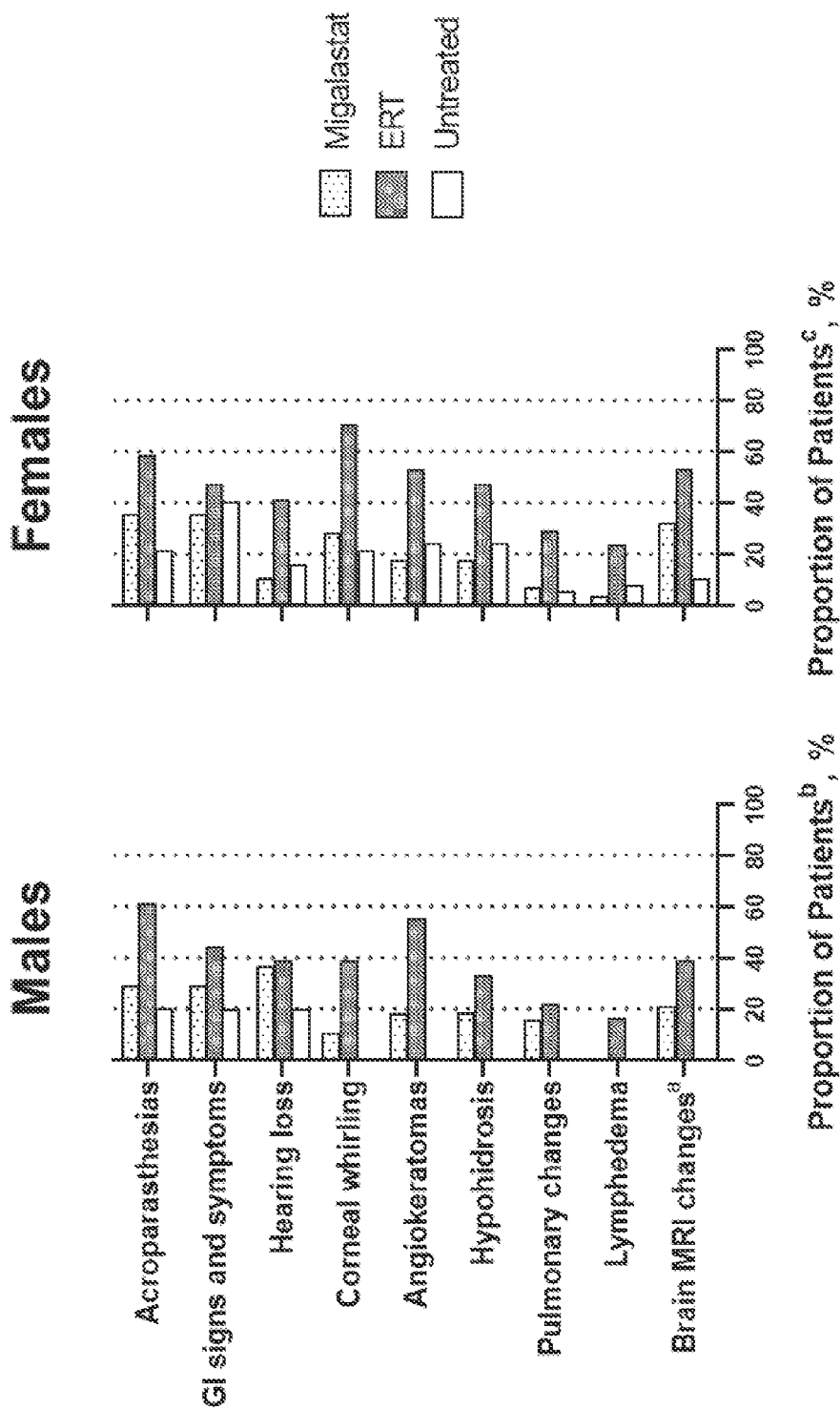


FIG. 5A

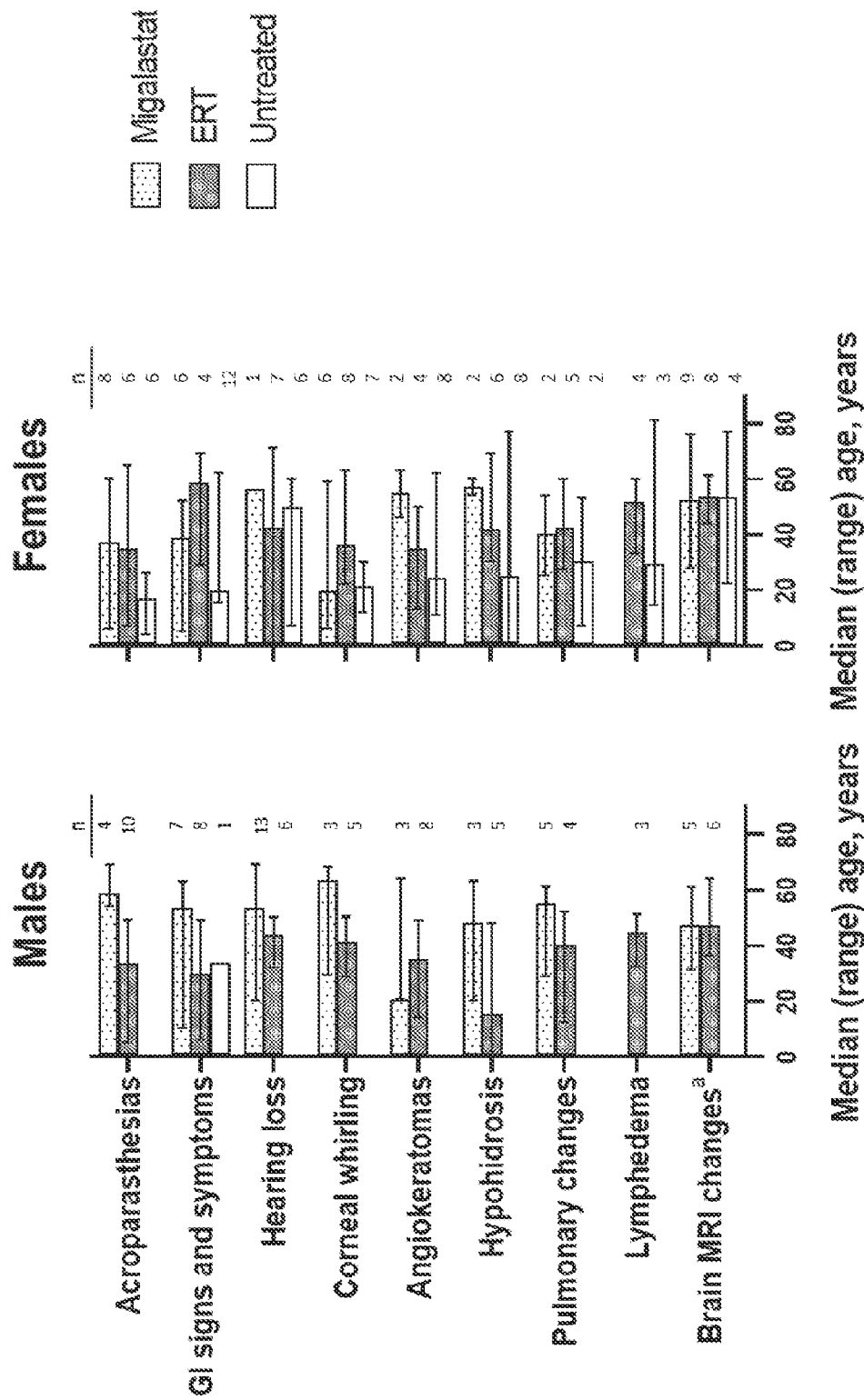


FIG. 5B

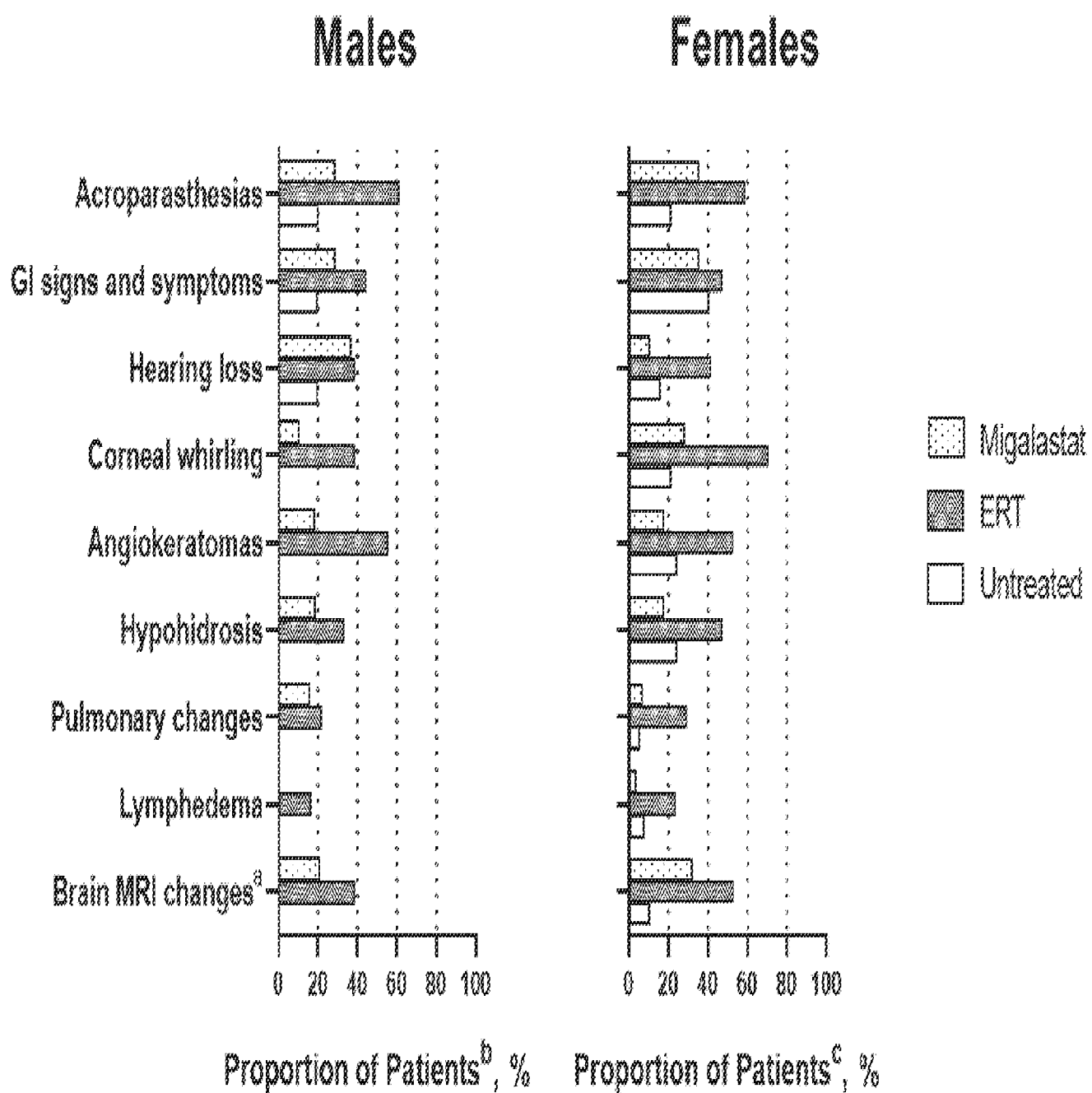


FIG. 5A