METHODS OF TREATING FABRY PATIENTS HAVING RENAL IMPAIRMENT

TECHNICAL FIELD

[0001] Principles and embodiments of the present invention relate generally to the use of pharmacological chaperones for the treatment of Fabry disease, particularly in patients with varying degrees of renal impairment.

BACKGROUND

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

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

[0004] Fabry Disease is a LSD caused by a mutation to the GLA gene, which encodes the enzyme α-galactosidase A (α-Gal A). α-Gal A is required for glycosphingolipid

metabolism. The mutation causes the substrate globotriaosylceramide (GL-3) to accumulate in various tissues and organs. Males with Fabry disease are hemizygotes because the disease genes are encoded on the X chromosome. Fabry disease is estimated to affect 1 in 40,000 and 60,000 males, and occurs less frequently in females.

[0005] There have been several approaches to treatment of Fabry disease. One approved therapy for treating Fabry disease is enzyme replacement therapy (ERT), which typically involves intravenous infusion of a purified form of the corresponding wild-type protein. 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). ERT has several drawbacks, however. One of the main complications with ERT is rapid degradation of the infused protein, which leads to the need for numerous, costly high dose infusions. ERT has several additional caveats, such as difficulties with large-scale generation, purification, and storage of properly folded protein; obtaining glycosylated native protein; generation of an anti-protein immune response; and inability of protein to cross the blood-brain barrier to mitigate central nervous system pathologies (i.e., low bioavailability). In addition, replacement enzyme cannot penetrate the heart or kidney in sufficient amounts to reduce substrate accumulation in the renal podocytes or cardiac myocytes, which figure prominently in Fabry pathology.

[0006] Another approach to treating some enzyme deficiencies involves the use of small molecule inhibitors to reduce production of the natural substrate of deficient enzyme proteins, thereby ameliorating the pathology. This "substrate reduction" approach has been specifically described for a class of about 40 LSDs that include glycosphingolipid storage disorders. The small molecule inhibitors proposed for use as therapy are specific for inhibiting the enzymes involved in synthesis of glycolipids, reducing the amount of cellular glycolipid that needs to be broken down by the deficient enzyme.

[0007] A third approach to treating Fabry disease has been treatment with what are called pharmacological chaperones (PCs). Such PCs include small molecule inhibitors of α-Gal A, which can bind to the α-Gal A to increase the stability of both mutant enzyme and the corresponding wild type.

[0008] One problem with current treatments is difficulty in treating patients exhibiting renal impairment, which is very common in Fabry patients and progresses with disease. On average, it take between about 10-20 years for patients to decline from normal kidney function

to severe renal impairment, with some countries reporting even faster declines. By some estimates, about 10% of Fabry patients receiving ERT may have moderate renal impairment. Another 25% of males and 5% of females receiving ERT have an estimated glomerular filtration rate (eGFR) of less than 30, corresponding to severe kidney impairment or even renal failure. Of these, about half have severe kidney impairment, and about half are on dialysis.

[0009] Unfortunately, renal impairment will progress despite ERT treatment. A patient having an eGFR of 30 may deteriorate to the point of needing dialysis in two to five years. About 30% of patients receiving ERT will end up on dialysis or needing a kidney transplant, depending on the start of ERT. The earlier ERT is commenced, the longer renal function may be preserved, but commencement of ERT may be delayed because Fabry disease is rare and often misdiagnosed.

[0010] Further, and as discussed above, ERT often does not sufficiently penetrate the kidneys to reduce substrate accumulation, thereby allowing further damage during disease progression. With PC treatment, the kidneys are often how the drug is cleared from the body, and renal impairment may affect drug pharmacokinetics and/or drug pharmacodynamics. Thus, there is still a need for a treatment of Fabry patients who have renal impairment.

SUMMARY

[0011] Various aspects of the present invention relate to the treatment of Fabry patients having renal impairment and/or elevated proteinuria using migalastat. Such treatment can include stabilizing renal function, reducing left ventricular mass index (LVMi), reducing plasma globotriaosylsphingosine (lyso-Gb_3) and/or increasing α-Gal A activity in the patient.

[0012] One aspect of the present invention pertains to a method for the treatment of Fabry disease in a patient having renal impairment, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day. In one or more embodiments, the effective amount is about 100 mg to about 150 mg free base equivalent (FBE).

[0013] In one or more embodiments, the patient has mild or moderate renal impairment.

[0014] In one or more embodiments, the patient has mild renal impairment.

[0015] In one or more embodiments, the patient has moderate renal impairment.

[0016] In one or more embodiments, the patient has severe renal impairment.

[0017] In one or more embodiments, the patient is an ERT-experienced patient.

[0018] In one or more embodiments, the patient is an ERT-naïve patient.

[0019] In one or more embodiments, the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0020] In one or more embodiments, the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0021] In one or more embodiments, the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0022] In one or more embodiments, the migalastat or salt thereof enhances α-Gal A activity in the patient. In one or more embodiments, the α-Gal A activity is white blood cell (WBC) α-Gal A activity.

[0023] In one or more embodiments, the administration of the migalastat or salt thereof is effective to reduce LVMi in the patient.

[0024] In one or more embodiments, the administration of the migalastat or salt thereof is effective to stabilize plasma lyso-Gb_3 in the patient.

[0025] In one or more embodiments, the administration of the migalastat or salt thereof is effective to stabilize renal function in the patient.

[0026] In one or more embodiments, the effective amount is about 123 mg FBE.

[0027] In one or more embodiments, the effective amount is about 123 mg of migalastat free base.

[0028] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[0029] In one or more embodiments, the effective amount is about 150 mg of migalastat hydrochloride.

[0030] In one or more embodiments, the migalastat or salt thereof is in an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[0031] In one or more embodiments, the migalastat or salt thereof is administered for at least 28 days.

[0032] In one or more embodiments, the migalastat or salt thereof is administered for at least 6 months.

[0033] In one or more embodiments, the migalastat or salt thereof is administered for at least 12 months.

[0034] Another aspect of the present invention pertains to the use of migalastat to stabilize renal function in a patient diagnosed with Fabry disease and having renal impairment. In various embodiments, the method comprises administering to the patient about 100 mg to about 150 mg FBE of migalastat or salt thereof at a frequency of once every other day.

[0035] In one or more embodiments, the patient has mild or moderate renal impairment.

[0036] In one or more embodiments, the patient has mild renal impairment.

[0037] In one or more embodiments, the patient has moderate renal impairment.

[0038] In one or more embodiments, the patient has severe renal impairment.

[0039] In one or more embodiments, the patient is an ERT-experienced patient.

[0040] In one or more embodiments, the patient is an ERT-naïve patient.

[0041] In one or more embodiments, the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0042] In one or more embodiments, the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0043] In one or more embodiments, the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0044] In one or more embodiments, the migalastat or salt thereof enhances α-Gal A activity.

[0045] In one or more embodiments, the effective amount is about 123 mg FBE.

[0046] In one or more embodiments, the effective amount is about 123 mg of migalastat free base.

[0047] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[0048] In one or more embodiments, the effective amount is about 150 mg of migalastat hydrochloride.

[0049] In one or more embodiments, the migalastat or salt thereof is in an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[0050] In one or more embodiments, the migalastat or salt thereof is administered for at least 28 days.

[0051] In one or more embodiments, the migalastat or salt thereof is administered for at least 6 months.

[0052] In one or more embodiments, the migalastat or salt thereof is administered for at least 12 months.

[0053] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of patients having mild or moderate renal impairment provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ of greater than -1.0 mL/min/1.73 m^2.

[0054] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of patients having mild renal impairment provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ of greater than -1.0 mL/min/1.73 m^2.

[0055] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of patients having moderate renal impairment provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ of greater than -1.0 mL/min/1.73 m^2.

[0056] Another aspect of the present invention pertains to the use of migalastat to stabilize plasma lyso-Gb_3 in a patient diagnosed with Fabry disease and having renal impairment. In various embodiments, the method comprises administering to the patient about 100 mg to about 150 mg FBE of migalastat or salt thereof at a frequency of once every other day.

[0057] In one or more embodiments, the patient has mild or moderate renal impairment.

[0058] In one or more embodiments, the patient has mild renal impairment.

[0059] In one or more embodiments, the patient has moderate renal impairment.

[0060] In one or more embodiments, the patient has severe renal impairment.

[0061] In one or more embodiments, the patient is an ERT-experienced patient.

[0062] In one or more embodiments, the patient is an ERT-naïve patient.

[0063] In one or more embodiments, the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0064] In one or more embodiments, the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0065] In one or more embodiments, the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0066] In one or more embodiments, the migalastat or salt thereof enhances α-Gal A activity.

[0067] In one or more embodiments, the effective amount is about 123 mg FBE.

[0068] In one or more embodiments, the effective amount is about 123 mg of migalastat free base.

[0069] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[0070] In one or more embodiments, the effective amount is about 150 mg of migalastat hydrochloride.

[0071] In one or more embodiments, the migalastat or salt thereof is in an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[0072] In one or more embodiments, the migalastat or salt thereof is administered for at least 28 days.

[0073] In one or more embodiments, the migalastat or salt thereof is administered for at least 6 months.

[0074] In one or more embodiments, the migalastat or salt thereof is administered for at least 12 months.

[0075] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of ERT-naïve patients having moderate renal impairment provides a mean reduction of plasma lyso-Gb_3 of at least about 5 nmol/L after 24 months of the administration of the migalastat or salt thereof.

[0076] Another aspect of the present invention pertains to the use of migalastat to reduce LVMi in a patient diagnosed with Fabry disease and having renal impairment. In various embodiments, the method comprises administering to the patient about 100 mg to about 150 mg FBE of migalastat or salt thereof at a frequency of once every other day.

[0077] In one or more embodiments, the patient has mild or moderate renal impairment.

[0078] In one or more embodiments, the patient has mild renal impairment.

[0079] In one or more embodiments, the patient has moderate renal impairment.

[0080] In one or more embodiments, the patient has severe renal impairment.

[0081] In one or more embodiments, the patient is an ERT-experienced patient.

[0082] In one or more embodiments, the patient is an ERT-naïve patient.

[0083] In one or more embodiments, the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0084] In one or more embodiments, the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0085] In one or more embodiments, the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[0086] In one or more embodiments, the migalastat or salt thereof enhances α-Gal A activity.

[0087] In one or more embodiments, the effective amount is about 123 mg FBE.

[0088] In one or more embodiments, the effective amount is about 123 mg of migalastat free base.

[0089] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[0090] In one or more embodiments, the effective amount is about 150 mg of migalastat hydrochloride.

[0091] In one or more embodiments, the migalastat or salt thereof is in an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[0092] In one or more embodiments, the migalastat or salt thereof is administered for at least 28 days.

[0093] In one or more embodiments, the migalastat or salt thereof is administered for at least 6 months.

[0094] In one or more embodiments, the migalastat or salt thereof is administered for at least 12 months.

[0095] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of ERT-naïve patients having moderate renal impairment provides a mean reduction of LVMi of at least about 2 g/m^2 after 24 months of the administration of the migalastat or salt thereof.

[0096] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of ERT-experienced patients having moderate renal impairment provides a mean reduction of LVMi of at least about 2 g/m^2 after 18 months of the administration of the migalastat or salt thereof.

[0097] Another aspect of the present invention pertains to the use of migalastat to increase WBC α-Gal A activity in a patient diagnosed with Fabry disease and having renal impairment. In various embodiments, the method comprises administering to the patient about 100 mg to about 150 mg FBE of migalastat or salt thereof at a frequency of once every other day.

[0098] In one or more embodiments, the patient has mild or moderate renal impairment.

[0099] In one or more embodiments, the patient has mild renal impairment.

[00100] In one or more embodiments, the patient has moderate renal impairment.

[00101] In one or more embodiments, the patient has severe renal impairment.

[00102] In one or more embodiments, the patient is an ERT-experienced patient.

[00103] In one or more embodiments, the patient is an ERT-naïve patient.

[00104] In one or more embodiments, the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[00105] In one or more embodiments, the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[00106] In one or more embodiments, the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[00107] In one or more embodiments, the effective amount is about 123 mg FBE.

[00108] In one or more embodiments, the effective amount is about 123 mg of migalastat free base.

[00109] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[00110] In one or more embodiments, the effective amount is about 150 mg of migalastat hydrochloride.

[00111] In one or more embodiments, the migalastat or salt thereof is in an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[00112] In one or more embodiments, the migalastat or salt thereof is administered for at least 28 days.

[00113] In one or more embodiments, the migalastat or salt thereof is administered for at least 6 months.

[00114] In one or more embodiments, the migalastat or salt thereof is administered for at least 12 months.

[00115] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of ERT-naïve patients having moderate renal impairment provides a mean increase in WBC α-Gal A activity of at least about 1 4MU/hr/mg after 24 months of the administration of the migalastat or salt thereof.

[00116] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of ERT-experienced patients having moderate renal impairment provides a mean increase in WBC α-Gal A activity of at least about 1 4MU/hr/mg after 18 months of the administration of the migalastat or salt thereof.

[00117] Another aspect of the present invention pertains to the use of migalastat to stabilize renal function in a patient diagnosed with Fabry disease and having elevated proteinuria. In various embodiments, the method comprises administering to the patient about 100 mg to about 150 mg FBE of migalastat or salt thereof at a frequency of once every other day.

[00118] In one or more embodiments, the patient has mild or moderate renal impairment.

[00119] In one or more embodiments, the patient has mild renal impairment.

[00120] In one or more embodiments, the patient has moderate renal impairment.

[00121] In one or more embodiments, the patient has severe renal impairment.

[00122] In one or more embodiments, the patient is an ERT-experienced patient.

[00123] In one or more embodiments, the patient is an ERT-naïve patient.

[00124] In one or more embodiments, the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[00125] In one or more embodiments, the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[00126] In one or more embodiments, the migalastat or salt thereof enhances α-Gal A activity.

[00127] In one or more embodiments, the effective amount is about 123 mg FBE.

[00128] In one or more embodiments, the effective amount is about 123 mg of migalastat free base.

[00129] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[00130] In one or more embodiments, the effective amount is about 150 mg of migalastat hydrochloride.

[00131] In one or more embodiments, the migalastat or salt thereof is in an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[00132] In one or more embodiments, the migalastat or salt thereof is administered for at least 28 days.

[00133] In one or more embodiments, the migalastat or salt thereof is administered for at least 6 months.

[00134] In one or more embodiments, the migalastat or salt thereof is administered for at least 12 months.

[00135] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD-EPI}$ of greater than -2.0 mL/min/1.73 m2.

[00136] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD-EPI}$ of greater than -5.0 mL/min/1.73 m^2.

[00137] Another aspect of the present invention pertains to a method for the treatment of Fabry disease in a patient having elevated proteinuria, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day. In one or more embodiments, the effective amount is about 100 mg to about 150 mg FBE.

[00138] In one or more embodiments, the patient has mild or moderate renal impairment.

[00139] In one or more embodiments, the patient has mild renal impairment.

[00140] In one or more embodiments, the patient has moderate renal impairment.

[00141] In one or more embodiments, the patient has severe renal impairment.

[00142] In one or more embodiments, the patient is an ERT-experienced patient.

[00143] In one or more embodiments, the patient is an ERT-naïve patient.

[00144] In one or more embodiments, the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[00145] In one or more embodiments, the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

[00146] In one or more embodiments, the migalastat or salt thereof enhances α-Gal A activity.

[00147] In one or more embodiments, the effective amount is about 123 mg FBE.

[00148] In one or more embodiments, the effective amount is about 123 mg of migalastat free base.

[00149] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[00150] In one or more embodiments, the effective amount is about 150 mg of migalastat hydrochloride.

[00151] In one or more embodiments, the migalastat or salt thereof is in an oral dosage form. In one or more embodiments, the oral dosage form comprises a tablet, a capsule or a solution.

[00152] In one or more embodiments, the migalastat or salt thereof is administered for at least 28 days.

[00153] In one or more embodiments, the migalastat or salt thereof is administered for at least 6 months.

[00154] In one or more embodiments, the migalastat or salt thereof is administered for at least 12 months.

[00155] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ of greater than -2.0 mL/min/1.73 m2.

[00156] In one or more embodiments, administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ of greater than -5.0 mL/min/1.73 m^2.

[00157] Various embodiments are listed below. It will be understood that the embodiments listed below may be combined not only as listed below, but in other suitable combinations in accordance with the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[00158] FIG. 1A shows the migalastat plasma concentrations for non-Fabry patients with varying degrees of renal impairment as a function of CL_{CR};

[00159] FIG. 1B shows the migalastat plasma concentrations for non-Fabry patients with varying degrees of renal impairment as a function of time post-dose;

[00160] FIG. 1C shows the area under the curve (AUC) for non-Fabry patients with varying degrees of renal impairment;

[00161] FIG. 2 shows migalastat concentration as a function of time for patients having moderate to severe renal impairment;

[00162] FIG. 3 shows the correlation between $AUC_{0-\infty}$ and migalastat concentration after 48 hours for non-Fabry patients with varying degrees of renal impairment;

[00163] FIG. 4 shows plasma migalastat concentration after 48 hours as a function of $eGFR_{MDRD}$ for non-Fabry patients with varying degrees of renal impairment and two Fabry patients with renal impairment;

[00164] FIG. 5 shows plasma $AUC_{0-\infty}$ for non-Fabry patients with varying degrees of renal impairment and two Fabry patients with renal impairment;

[00165] FIGS. 6A-D show simulated median and observed migalastat concentration versus time for normal, severe, mild and moderate renal impairment subjects, respectively;

[00166] FIGS. 7A-D show simulated C_{max}, AUC, C_{min} and C_{48}, respectively, for normal, mild, moderate and severe renal impairment subjects;

[00167] FIGS. 8A-D show the steady state prediction for QOD for normal, severe, mild and moderate renal impairment subjects, respectively;

[00168] FIGS. 9A-D show C_{max}, AUC, C_{min} and C_{48}, respectively, for normal, mild, moderate and severe renal impairment subjects;

[00169] FIGS. 10A-B show the study designs for two studies investigating the use of migalastat in Fabry patients;

[00170] FIG. 11 shows annualized rate of change of $eGFR_{CKD-EPI}$ for Fabry patients on migalastat therapy having normal renal function and mild and moderate renal impairment;

[00171] FIGS. 12A-B show annualized rate of change of $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$, respectively, for Fabry patients on migalastat therapy and ERT having normal renal function and renal impairment;

[00172] FIG. 13 shows annualized rate of change of $eGFR_{CKD-EPI}$ for Fabry patients on migalastat therapy and ERT having normal renal function and mild and moderate renal impairment;

[00173] FIG. 14A-E show the full DNA sequence of human wild type GLA gene (SEQ ID NO: 1); and

[00174] FIG. 15 shows the wild type GLA protein (SEQ ID NO: 2).

DETAILED DESCRIPTION

[00175] 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.

[00176] It has surprisingly been discovered that migalastat therapy stabilizes renal function, reduces LVMi, reduces plasma lyso-Gb_3 and increases WBC α-Gal A activity in Fabry patients with mild and moderate renal impairment. Accordingly, various aspects of the present invention pertain to particular dosing regimens of migalastat for Fabry patients having renal impairment. Migalastat is a pharmacological chaperone used in the treatment of Fabry disease. This pharmacological chaperone is usually cleared from the body by the kidneys. However, patients who have renal impairment (a common problem for Fabry patients) may not be able to clear the migalastat from the body, and it was not previously known how patients with both Fabry disease and renal impairment would respond to migalastat therapy. Because pharmacological chaperones are also inhibitors, balancing the enzyme-enhancing and inhibitory effects of pharmacological chaperones such as migalastat is very difficult. Moreover, due to the complex interactions between Fabry disease and renal function, and the lack of knowledge on the role of a pharmacological chaperone, migalastat dosing for Fabry patients with renal impairment is difficult to ascertain without significant clinical data and/or computer modeling.

[00177] Accordingly, aspects of the present invention pertain to methods of treating Fabry patients having renal impairment and/or elevated proteinuria using migalastat or a salt thereof, such as by stabilizing renal function, reducing LVMi, reducing plasma lyso-Gb_3 and/or increasing α-Gal A activity in the patient.

[00178] In one or more embodiments, the method comprises administering to the patient about 100 mg to about 150 mg FBE of migalastat or salt thereof at a frequency of once every other day. The patient may have mild, moderate or severe renal impairment. In one or more embodiments, the patient has mild or moderate renal impairment. In specific embodiments, the patient has mild renal impairment. In other specific embodiments, the patient has moderate renal impairment.

[00179] Definitions

[00180] 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.

[00181] 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 Gb_3 or ceramide trihexoside) and related glycosphingolipids in vascular endothelial lysosomes of the heart, kidneys, skin, and other tissues. Another substrate of the enzyme is plasma globotriaosylsphingosine ("plasma lyso-Gb_3").

[00182] 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.

[00183] 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.

[00184] 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.

[00185] 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.

[00186] 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.

[00187] 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 SEQ ID NO: 1 and FIGS. 14A-E. 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 SEQ ID NO: 2 and FIG. 15.

[00188] 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 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.

[00189] 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.

[00190] As used herein, the term "specific pharmacological chaperone" ("SPC") or "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.

[00191] A "competitive inhibitor" of an enzyme can refer to a compound which structurally resembles the chemical structure and molecular geometry of the enzyme substrate to bind the enzyme in approximately the same location as the substrate. Thus, the inhibitor competes for the same active site as the substrate molecule, thus increasing the Km. Competitive inhibition is usually reversible if sufficient substrate molecules are available to displace the inhibitor, i.e., competitive inhibitors can bind reversibly. Therefore, the amount of enzyme inhibition depends upon the inhibitor concentration, substrate concentration, and the relative affinities of the inhibitor and substrate for the active site.

[00192] 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.

[00193] "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).

[00194] 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.

[00195] 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.

[00196] A "responder" is an individual diagnosed with or suspected of having a lysosomal storage disorder, 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-Gb_3 and those disclosed in U.S. Patent Application Publication No. US 2010/0113517, which is hereby incorporated by reference in its entirety.

[00197] Non-limiting examples of improvements in surrogate markers for Fabry disease disclosed in US 2010/0113517 include increases in α-Gal A levels or activity in cells (*e.g.*, fibroblasts) and tissue; reductions in of GL-3 accumulation; decreased plasma concentrations of homocysteine and vascular cell adhesion molecule-1 (VCAM-1); decreased GL-3 accumulation within myocardial cells and valvular fibrocytes; reduction in plasma lyso-Gb_3; reduction in cardiac hypertrophy (especially of the left ventricle), amelioration of valvular insufficiency, and arrhythmias; amelioration of proteinuria; decreased urinary concentrations of lipids such as CTH, lactosylceramide, ceramide, and increased urinary concentrations of glucosylceramide and sphingomyelin; the absence of laminated inclusion bodies (Zebra bodies) in glomerular epithelial cells; improvements in renal function; mitigation of hypohidrosis; the absence of angiokeratomas; and improvements hearing abnormalities such as high frequency sensorineural hearing loss progressive hearing loss, sudden deafness, or tinnitus. Improvements in neurological symptoms include prevention of transient ischemic attack (TIA) or stroke; and amelioration of neuropathic pain manifesting itself as acroparaesthesia (burning or tingling in extremities). Another type of clinical marker that can be assessed for Fabry disease is the prevalence of deleterious cardiovascular manifestations. Common cardiac-related signs and symptoms of Fabry disease include left ventricular hypertrophy, valvular disease (especially mitral valve prolapse and/or regurgitation), premature coronary artery disease, angina, myocardial infarction, conduction abnormalities, arrhythmias, congestive heart failure.

[00198] As used herein, the phrase "stabilizing renal function" and similar terms, among others things, refer to reducing decline in renal function and/or restoring renal function. As untreated Fabry patients are expected to have significant decreases in renal function, improvements in the rate of renal function deterioration and/or improvements in renal function demonstrate a benefit of migalastat therapy as described herein. In particular, stabilizing renal function may manifest in a Fabry patient, regardless of the severity of kidney function and whether ERT-naïve or experienced, by improving renal function or delaying the rate of renal function deterioration when compared to an analogous patient not treated with a therapy of the present invention, for example, as much as 0.2 mL/min/1.73m^2 for one particular patient population. An advantage of the method of treatment disclosed herein compared to non-

treatment (no chaperone or ERT-treatment) or ERT-treatment is that Fabry patients treated with the present invention exhibit less or no decline in his or her renal function. For example, improvements may be observed with ERT-treatment initially but the renal function of ERT-treated patients experiences a precipitous decline after the initial two or three years of the therapy – similar to the degree of decline observed prior to ERT-treatment. In contrast, the therapy described herein clears lysosomal GL-3 more efficiently and has been shown to elicit improvement in patients (e.g., see Example 5) not expected to improve, for example, in an ERT-experienced patient. Clinical data to date using the therapy described herein is expected to deliver continued improvements in patient outcomes even after two years post-treatment. Thus, in some embodiments, a patient treated with the therapy described herein continues to stabilize renal function for more than two years after treatment (e.g., by improving a glomerular filtration rate (GFR) or delaying the rate of decline of a GFR in the patient).

[00199] "Renal impairment" refers to a patient having a GFR less than 90 mL/min/1.73m^2. Two of the most commonly used equations for calculating an estimated glomerular filtration rate (eGFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD), which are referred to as $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$, respectively. The severity of chronic kidney disease has been defined in six stages:

a. (Stage 0) Normal kidney function – GFR above 90 mL/min/1.73 m^2 and no proteinuria;
b. (Stage 1) – GFR above 90 mL/min/1.73 m^2 with evidence of kidney damage;
c. (Stage 2) (mild) – GFR of 60 to 89 mL/min/1.73 m^2 with evidence of kidney damage;
d. (Stage 3) (moderate) – GFR of 30 to 59 mL/min/1.73 m^2;
e. (Stage 4) (severe) – GFR of 15 to 29 mL/min/1.73 m^2;
f. (Stage 5) kidney failure – GFR less than 15 mL/min/1.73 m^2.

[00200] "Elevated proteinuria" refers to urine protein levels that are above the normal range. The normal range for urine protein is 0-150 mg per day, so elevated proteinuria is urine protein levels about 150 mg per day.

[00201] As used herein, the phrase "stabilize plasma lyso-Gb_3" and similar terms refer to reducing the increase in plasma lyso-Gb_3 and/or reducing plasma lyso-Gb_3. As untreated Fabry patients are expected to have significant increases in plasma lyso-Gb_3, improvements in the

rate of plasma lyso-Gb_3 accumulation and/or improvements in plasma lyso-Gb_3 demonstrate a benefit of migalastat therapy as described herein.

[00202] The dose that achieves one or more of the aforementioned responses is a "therapeutically effective dose."

[00203] The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a human. In some embodiments, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans. The term "carrier" in reference to a pharmaceutical carrier refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils. Water or aqueous solution saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, 18th Edition, or other editions.

[00204] 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.

[00205] 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.

[00206] 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.

[00207] 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.

[00208] The term "migalastat" encompasses migalastat free base or a pharmaceutically acceptable salt thereof (e.g., migalastat HCl), unless specifically indicated to the contrary.

[00209] Fabry Disease

[00210] Fabry disease is a rare, progressive and devastating X-linked lysosomal storage disorder. 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-Gb_3, 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.

[00211] 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.

[00212] More than 800 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 endoplasmic reticulum 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.

[00213] The clinical manifestations of Fabry disease span a broad spectrum of severity and roughly correlate with a patient's residual α-GAL levels. The majority of currently treated patients are referred to as classic Fabry disease 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 late-onset Fabry disease, tend to have higher residual α-GAL levels than classic Fabry disease patients. Individuals with late-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, late-onset Fabry disease may also present in the form of strokes of unknown cause.

[00214] 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.

[00215] Because Fabry disease can cause progressive worsening in renal function, it is important to understand the pharmacokinetics (PK) of potential therapeutic agents in individuals with renal impairment and particularly so for therapeutic agents that are predominantly cleared by renal excretion. Impairment of renal function may lead to accumulation of the therapeutic agent to levels that become toxic.

[00216] 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.

[00217] Mutant forms of α-galactosidase A considered to be amenable to migalastat are defined as showing a relative increase (+10 μM migalastat) of ≥1.20-fold and an absolute increase (+ 10 μM migalastat) of ≥ 3.0% wild-type when the mutant form of α-galactosidase 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.

[00218] Previous screening methods have been provided that assess enzyme enhancement prior to the initiation of treatment. For example, an assay using HEK-293 cells

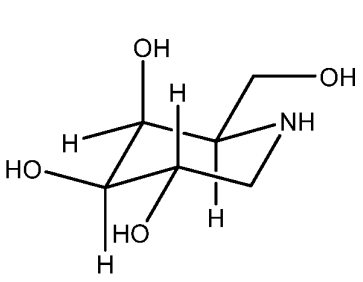
has been utilized in clinical trials to predict whether a given mutation will be responsive to pharmacological chaperone (*e.g.*, migalastat) treatment. In this assay, cDNA constructs are created. The corresponding α-Gal A mutant forms are transiently expressed in HEK-293 cells. Cells are then incubated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

[00219] Pharmacological Chaperones

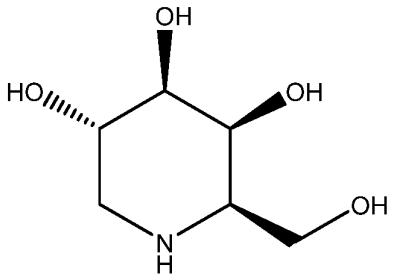
[00220] The binding of small molecule inhibitors of enzymes associated with LSDs can increase the stability of both mutant enzyme and the corresponding wild-type enzyme (see U.S. Pat. Nos. 6,274,597; 6,583,158; 6,589,964; 6,599,919; 6,916,829, and 7,141,582 all incorporated herein by reference). In particular, administration of small molecule derivatives of glucose and galactose, which are specific, selective competitive inhibitors for several target lysosomal enzymes, effectively increased the stability of the enzymes in cells *in vitro* and, thus, increased trafficking of the enzymes to the lysosome. Thus, by increasing the amount of enzyme in the lysosome, hydrolysis of the enzyme substrates is expected to increase. The original theory behind this strategy was as follows: since the mutant enzyme protein is unstable in the ER (Ishii et al., *Biochem. Biophys. Res. Comm.* 1996; 220: 812-815), the enzyme protein is retarded in the normal transport pathway (ER→Golgi apparatus→endosomes→lysosome) and prematurely degraded. Therefore, a compound which binds to and increases the stability of a mutant enzyme, may serve as a "chaperone" for the enzyme and increase the amount that can exit the ER and move to the lysosomes. In addition, because the folding and trafficking of some wild-type proteins is incomplete, with up to 70% of some wild-type proteins being degraded in some instances prior to reaching their final cellular location, the chaperones can be used to stabilize wild-type enzymes and increase the amount of enzyme which can exit the ER and be trafficked to lysosomes.

[00221] In one or more embodiments, the pharmacological chaperone comprises migalastat or a salt thereof. The compound migalastat, also known as 1-

deoxygalactonojirimycin (1-DGJ) or (2R,3S,4R,5S)-2-(hydroxymethyl) piperdine-3,4,5-triol is a compound having the following chemical formula:

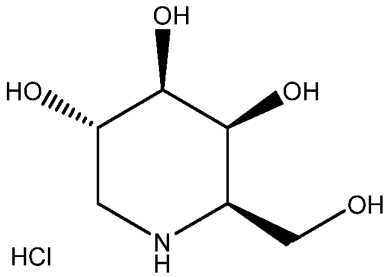


and



Migalastat free base

[00222] As discussed herein, pharmaceutically acceptable salts of migalastat may also be used in the present invention. When a salt of migalastat is used, the dosage of the salt will be adjusted so that the dose of migalastat received by the patient is equivalent to the amount which would have been received had the migalastat free base been used. One example of a pharmaceutically acceptable salt of migalastat is migalastat HCl:



Migalastat HCl

[00223] Migalastat is a low molecular weight iminosugar and is an analogue of the terminal galactose of GL-3. *In vitro* and *in vivo* pharmacologic studies have demonstrated that migalastat acts as a pharmacological chaperone, selectively and reversibly binding, with high affinity, to the active site of wild-type α-Gal A and specific mutant forms of α-Gal A, the genotypes of which are referred to as HEK assay amenable mutations. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum facilitating their proper trafficking to lysosomes where dissociation of migalastat allows α-Gal A to reduce the level of GL-3 and other substrates. Approximately 30-50% of patients with Fabry disease have HEK assay amenable mutations; the majority of which are associated with the classic phenotype of

the disease. A list of HEK assay amenable mutations includes at least those mutations listed 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. In addition to Table 1 below, HEK assay amenable mutations can also 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 the website www.galafoldamenabilitytable.com, each of which is hereby incorporated by reference in its entirety.

Table 1

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.37G>A	c.G37A	A13T
c.37G>C	c.G37C	A13P
c.43G>A	c.G43A	A15T
c.44C>G	c.C44G	A15G
c.53T>G	c.T53G	F18C
c.58G>C	c.G58C	A20P
c.59C>A	c.C59A	A20D
c.70T>C or c.70T>A	c.T70C or c.T70A	W24R
c.70T>G	c.T70G	W24G
c.72G>C or c.72G>T	c.G72C or c.G72T	W24C
c.95T>C	c.T95C	L32P
c.97G>T	c.G97T	D33Y
c.98A>G	c.A98G	D33G
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>T	c.G104T	G35V
c.107T>C	c.T107C	L36S
c.107T>G	c.T107G	L36W
c.108G>C or c.108G>T	c.G108C or c.G108T	L36F
c.109G>A	c.G109A	A37T

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.110C>T	c.C110T	A37V
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.137A>C	c.A137C	H46P
c.142G>C	c.G142C	E48Q
c.152T>A	c.T152A	M51K
c.153G>A or c.153G>T or c.153G>C	c.G153A or c.G153T or c.G153C	M51I
c.157A>G	c.A157G	N53D
c.[157A>C; 158A>T]	c.A157C/A158T	N53L
c.160C>T	c.C160T	L54F
c.161T>C	c.T161C	L54P
c.164A>G	c.A164G	D55G
c.164A>T	c.A164T	D55V
c.[164A>T; 170A>T]	c.A164T/A170T	D55V/Q57L
c.167G>T	c.G167T	C56F
c.167G>A	c.G167A	C56Y
c.170A>T	c.A170T	Q57L
c.175G>A	c.G175A	E59K
c.178C>A	c.C178A	P60T
c.178C>T	c.C178T	P60S
c.179C>T	c.C179T	P60L
c.196G>A	c.G196A	E66K
c.197A>G	c.A197G	E66G
c.207C>A or c.207C>G	c.C207A or c.C207G	F69L
c.214A>G	c.A214G	M72V
c.216G>A or c.216G>T or c.216G>C	c.G216A or c.G216T or c.G216C	M72I
c.218C>T	c.C218T	A73V
c.227T>C	c.T227C	M76T
c.239G>A	c.G239A	G80D
c.247G>A	c.G247A	D83N
c.253G>A	c.G253A	G85S
c.254G>A	c.G254A	G85D
c.[253G>A; 254G>A]	c.G253A/G254A	G85N
c.[253G>A; 254G>T; 255T>G]	c.G253A/G254T/T255G	G85M
c.261G>C or c.261G>T	c.G261C or c.G261T	E87D
c.265C>T	c.C265T	L89F
c.272T>C	c.T272C	I91T

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.288G>A or c.288G>T or c.288G>C	c.G288A or c.G288T or c.G288C	M96I
c.289G>C	c.G289C	A97P
c.290C>T	c.C290T	A97V
c.305C>T	c.C305T	S102L
c.311G>T	c.G311T	G104V
c.316C>T	c.C316T	L106F
c.322G>A	c.G322A	A108T
c.326A>G	c.A326G	D109G
c.334C>G	c.C334G	R112G
c.335G>A	c.G335A	R112H
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.352C>T	c.C352T	R118C
c.361G>A	c.G361A	A121T
c.368A>G	c.A368G	Y123C
c.373C>T	c.C373T	H125Y
c.374A>T	c.A374T	H125L
c.376A>G	c.A376G	S126G
c.383G>A	c.G383A	G128E
c.399T>G	c.T399G	I133M
c.404C>T	c.C404T	A135V
c.408T>A or c.408T>G	c.T408A or c.T408G	D136E
c.416A>G	c.A416G	N139S
c.419A>C	c.A419C	K140T
c.427G>A	c.G427A	A143T
c.431G>A	c.G431A	G144D
c.431G>T	c.G431T	G144V
c.434T>C	c.T434C	F145S
c.436C>T	c.C436T	P146S
c.437C>G	c.C437G	P146R
c.454T>C	c.T454C	Y152H
c.455A>G	c.A455G	Y152C
c.466G>A	c.G466A	A156T
c.467C>T	c.C467T	A156V
c.471G>C or c.471G>T	c.G471C or c.G471T	Q157H
c.484T>G	c.T484G	W162G
c.493G>C	c.G493C	D165H
c.494A>G	c.A494G	D165G
c.[496C>G; 497T>G]	c.C496G/T497G	L166G
c.496C>G	c.C496G	L166V
c.496_497delinsTC	c.496_497delinsTC	L166S
c.499C>G	c.C499G	L167V
c.506T>C	c.T506C	F169S

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.511G>A	c.G511A	G171S
c.520T>C	c.T520C	C174R
c.520T>G	c.T520G	C174G
c.525C>G or c.525C>A	c.C525G or c.C525A	D175E
c.539T>G	c.T539G	L180W
c.540G>C	c.G540C	L180F
c.548G>C	c.G548C	G183A
c.548G>A	c.G548A	G183D
c.550T>A	c.T550A	Y184N
c.551A>G	c.A551G	Y184C
c.553A>G	c.A553G	K185E
c.559A>G	c.A559G	M187V
c.559_564dup	c.559_564dup	p.M187_S188dup
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.572T>A	c.T572A	L191Q
c.581C>T	c.C581T	T194I
c.584G>T	c.G584T	G195V
c.586A>G	c.A586G	R196G
c.593T>C	c.T593C	I198T
c.595G>A	c.G595A	V199M
c.596T>C	c.T596C	V199A
c.596T>G	c.T596G	V199G
c.599A>G	c.A599G	Y200C
c.602C>T	c.C602T	S201F
c.602C>A	c.C602A	S201Y
c.608A>T	c.A608T	E203V
c.609G>C or c.609G>T	c.G609C or c.G609T	E203D
c.613C>A	c.C613A	P205T
c.613C>T	c.C613T	P205S
c.614C>T	c.C614T	P205L
c.619T>C	c.T619C	Y207H
c.620A>C	c.A620C	Y207S
c.623T>G	c.T623G	M208R
c.628C>T	c.C628T	P210S
c.629C>T	c.C629T	P210L
c.638A>G	c.A638G	K213R
c.638A>T	c.A638T	K213M
c.640C>T	c.C640T	P214S
c.641C>T	c.C641T	P214L
c.643A>G	c.A643G	N215D
c.644A>G	c.A644G	N215S
c.644A>T	c.A644T	N215I
c.[644A>G; 937G>T]	c.A644G/G937T	N215S/D313Y

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.646T>G	c.T646G	Y216D
c.647A>G	c.A647G	Y216C
c.655A>C	c.A655C	I219L
c.656T>A	c.T656A	I219N
c.656T>C	c.T656C	I219T
c.659G>A	c.G659A	R220Q
c.659G>C	c.G659C	R220P
c.662A>C	c.A662C	Q221P
c.671A>C	c.A671C	N224T
c.671A>G	c.A671G	N224S
c.673C>G	c.C673G	H225D
c.683A>G	c.A683G	N228S
c.687T>A or c.687T>G	c.T687A or c.T687G	F229L
c.695T>C	c.T695C	I232T
c.713G>A	c.G713A	S238N
c.716T>C	c.T716C	I239T
c.720G>C or c.720G>T	c.G720C or c.G720T	K240N
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.728T>G	c.T728G	L243W
c.729G>C or c.729G>T	c.G729C or c.G729T	L243F
c.730G>A	c.G730A	D244N
c.730G>C	c.G730C	D244H
c.733T>G	c.T733G	W245G
c.740C>G	c.C740G	S247C
c.747C>G or c.747C>A	c.C747G or c.C747A	N249K
c.749A>C	c.A749C	Q250P
c.749A>G	c.A749G	Q250R
c.750G>C	c.G750C	Q250H
c.758T>C	c.T758C	I253T
c.758T>G	c.T758G	I253S
c.760-762delGTT	c.760_762delGTT	p.V254del
c.769G>C	c.G769C	A257P
c.770C>G	c.C770G	A257G
c.772G>C or c.772G>A	c.G772C or c.G772A	G258R
c.773G>T	c.G773T	G258V
c.776C>G	c.C776G	P259R
c.776C>T	c.C776T	P259L
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

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.788A>G	c.A788G	N263S
c.790G>T	c.G790T	D264Y
c.794C>T	c.C794T	P265L
c.800T>C	c.T800C	M267T
c.805G>A	c.G805A	V269M
c.806T>C	c.T806C	V269A
c.809T>C	c.T809C	I270T
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.823C>G	c.C823G	L275V
c.827G>A	c.G827A	S276N
c.829T>G	c.T829G	W277G
c.831G>T or c.831G>C	c.G831T or c.G831C	W277C
c.832A>T	c.A832T	N278Y
c.835C>G	c.C835G	Q279E
c.838C>A	c.C838A	Q280K
c.840A>T or c.840A>C	c.A840T or c.A840C	Q280H
c.844A>G	c.A844G	T282A
c.845C>T	c.C845T	T282I
c.850A>G	c.A850G	M284V
c.851T>C	c.T851C	M284T
c.860G>T	c.G860T	W287L
c.862G>C	c.G862C	A288P
c.866T>G	c.T866G	I289S
c.868A>C or c.868A>T	c.A868C or c.A868T	M290L
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.877C>A	c.C877A	P293T
c.881T>C	c.T881C	L294S
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.893A>G	c.A893G	N298S
c.897C>G or c.897C>A	c.C897G or c.C897A	D299E
c.898C>T	c.C898T	L300F
c.899T>C	c.T899C	L300P
c.901C>G	c.C901G	R301G
c.902G>C	c.G902C	R301P

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.902G>A	c.G902A	R301Q
c.902G>T	c.G902T	R301L
c.907A>T	c.A907T	I303F
c.908T>A	c.T908A	I303N
c.911G>A	c.G911A	S304N
c.911G>C	c.G911C	S304T
c.919G>A	c.G919A	A307T
c.922A>G	c.A922G	K308E
c.924A>T or c.924A>C	c.A924T or c.A924C	K308N
c.925G>C	c.G925C	A309P
c.926C>T	c.C926T	A309V
c.928C>T	c.C928T	L310F
c.931C>G	c.C931G	L311V
c.935A>G	c.A935G	Q312R
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.946G>A	c.G946A	V316I
c.947T>G	c.T947G	V316G
c.950T>C	c.T950C	I317T
c.955A>T	c.A955T	I319F
c.956T>C	c.T956C	I319T
c.959A>T	c.A959T	N320I
c.962A>G	c.A962G	Q321R
c.962A>T	c.A962T	Q321L
c.963G>C or c.963G>T	c.G963C or c.G963T	Q321H
c.964G>A	c.G964A	D322N
c.964G>C	c.G964C	D322H
c.966C>A or c.966C>G	c.C966A or c.C966G	D322E
c.968C>G	c.C968G	P323R
c.973G>A	c.G973A	G325S
c.973G>C	c.G973C	G325R
c.978G>C or c.978G>T	c.G978C or c.G978T	K326N
c.979C>G	c.C979G	Q327E
c.980A>T	c.A980T	Q327L
c.983G>C	c.G983C	G328A
c.989A>G	c.A989G	Q330R
c.1001G>A	c.G1001A	G334E
c.1010T>C	c.T1010C	F337S
c.1012G>A	c.G1012A	E338K
c.1016T>A	c.T1016A	V339E
c.1027C>A	c.C1027A	P343T
c.1028C>T	c.C1028T	P343L
c.1033T>C	c.T1033C	S345P

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.1046G>C	c.G1046C	W349S
c.1055C>G	c.C1055G	A352G
c.1055C>T	c.C1055T	A352V
c.1061T>A	c.T1061A	I354K
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.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.1076T>C	c.T1076C	I359T
c.1078G>A	c.G1078A	G360S
c.1078G>T	c.G1078T	G360C
c.1079G>A	c.G1079A	G360D
c.1082G>A	c.G1082A	G361E
c.1082G>C	c.G1082C	G361A
c.1084C>A	c.C1084A	P362T
c.1085C>T	c.C1085T	P362L
c.1087C>T	c.C1087T	R363C
c.1088G>A	c.G1088A	R363H
c.1102G>A	c.G1102A	A368T
c.1117G>A	c.G1117A	G373S
c.1124G>A	c.G1124A	G375E
c.1153A>G	c.A1153G	T385A
c.1168G>A	c.G1168A	V390M
c.1172A>C	c.A1172C	K391T
c.1184G>A	c.G1184A	G395E
c.1184G>C	c.G1184C	G395A
c.1192G>A	c.G1192A	E398K
c.1202_1203insGACTTC	c.1202_1203insGACTTC	p.T400_S401dup
c.1208T>C	c.T1208C	L403S
c.1225C>G	c.C1225G	P409A
c.1225C>T	c.C1225T	P409S
c.1225C>A	c.C1225A	P409T
c.1228A>G	c.A1228G	T410A
c.1229C>T	c.C1229T	T410I
c.1232G>A	c.G1232A	G411D
c.1235C>A	c.C1235A	T412N
c.1253A>G	c.A1253G	E418G
c.1261A>G	c.A1261G	M421V

[00224] Kidney Function in Fabry Patients

[00225] Progressive decline in renal function is a major complication of Fabry disease. For example, patients associated with a classic Fabry phenotype exhibit progressive renal impairment that may eventually require dialysis or renal transplantation.

[00226] A frequently used method in the art to assess kidney function is GFR. Generally, the GFR is the volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time. Clinically, estimates of GFR are made based upon the clearance of creatinine from serum. GFR can be estimated by collecting urine to determine the amount of creatinine that was removed from the blood over a given time interval. Age, body size and gender may also be factored in. The lower the GFR number, the more advanced kidney damage is.

[00227] Some studies indicate that untreated Fabry patients experience an average decline in GFR between 7.0 and 18.9 mL/min/1.73 m^2 per year, while patients receiving ERT may experience an average decline in GFR between 2.0 and 2.7 mL/min/1.73 m^2 per year, although more rapid declines may occur in patients with more significant proteinuria or with more severe chronic kidney disease.

[00228] An estimated GFR (eGFR) is calculated from serum creatinine using an isotope dilution mass spectrometry (IDMS) traceable equation. Two of the most commonly used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease (MDRD) Study equation. Both the MDRD Study and CKD-EPI equations include variables for age, gender, and race, which may allow providers to observe that CKD is present despite a serum creatinine concentration that appears to fall within or just above the normal reference interval.

[00229] The CKD-EPI equation uses a 2-slope "spline" to model the relationship between GFR and serum creatinine, age, sex, and race. CKD-EPI equation expressed as a single equation:

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr} /κ or 1, and

max indicates the maximum of S_{cr} /κ or 1.

[00230] The following is the IDMS-traceable MDRD Study equation (for creatinine methods calibrated to an IDMS reference method):

GFR (mL/min/1.73 m^2) = $175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times$ (0.742 if female) × (1.212 if African American)

[00231] The equation does not require weight or height variables because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area. The equation has been validated extensively in Caucasian and African American populations between the ages of 18 and 70 with impaired kidney function (eGFR < 60 mL/min/1.73 m^2) and has shown good performance for patients with all common causes of kidney disease.

[00232] One method for estimating the creatinine clearance rate (eC_{Cr}) is using the Cockcroft-Gault equation, which in turn estimates GFR in mL/min:

Creatinine Clearance (mL/min) = [(140-Age) x Mass(Kg)*] ÷ 72 x Serum Creatinine(mg/dL)

[* multiplied by 0.85 if female]

[00233] The Cockcroft-Gault equation is the equation suggested for use by the Food and Drug Administration for renal impairment studies. It is common for the creatinine clearance calculated by the Cockcroft-Gault formula to be normalized for a body surface area of 1.73 m^2. Therefore, this equation can be expressed as the estimated eGFR in mL/min/1.73 m^2. The normal range of GFR, adjusted for body surface area, is 100-130 mL/min/1.73m2 in men and 90-120 mL/min/1.73m2 in women younger than the age of 40.

[00234] The severity of chronic kidney disease has been defined in six stages (see also Table 2): (Stage 0) Normal kidney function – GFR above 90 mL/min/1.73 m^2 and no proteinuria; (Stage 1) – GFR above 90 mL/min/1.73 m^2 with evidence of kidney damage; (Stage 2) (mild) – GFR of 60 to 89 mL/min/1.73 m^2 with evidence of kidney damage; (Stage 3) (moderate) – GFR of 30 to 59 mL/min/1.73 m^2; (Stage 4) (severe) – GFR of 15 to 29 mL/min/1.73 m^2; (Stage 5) kidney failure - GFR less than 15 mL/min/1.73 m^2. Table 2 below shows the various kidney disease stages with corresponding GFR levels.

Table 2

Chronic Kidney Disease Stage	GFR level (mL/min/1.73 m^2)
Stage 1 (Normal)	≥ 90
Stage 2 (Mild)	60 – 89
Stage 3 (Moderate)	30 – 59
Stage 4 (Severe)	15 – 29
Stage 5 (Kidney Failure)	< 15

[00235] Dosing, Formulation and Administration

[00236] One or more of the dosing regimens described herein are particularly suitable for Fabry patients who have some degree of renal impairment. Several studies have investigated using 150 mg of migalastat hydrochloride every other day (QOD) in Fabry patients. One study was a 24-month trial, including a 6-month double-blind, placebo-controlled period, in 67 ERT-naïve patients. Another study was an active-controlled, 18-month trial in 57 ERT-experienced patients with a 12-month open-label extension (OLE). Both studies included patients having an estimated glomerular filtration rate (eGFR) of ≥30mL/min/1.73m^2. Accordingly, both studies included Fabry patients with normal renal function as well as patients with mild and moderate renal impairment, but neither study included patients with severe renal impairment.

[00237] The studies of migalastat treatment of Fabry patients established that 150 mg of migalastat hydrochloride every other day slowed the progression of the disease as shown by surrogate markers.

[00238] Thus, in one or more embodiments, the Fabry patient is administered migalastat or salt thereof at a frequency of once every other day (also referred to as "QOD"). In various embodiments, the doses described herein pertain to migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt. In some embodiments, these doses pertain to the free base of migalastat. In alternate embodiments, these doses pertain to a salt of migalastat. In further embodiments, the salt of migalastat is migalastat

hydrochloride. The administration of migalastat or a salt of migalastat is referred to herein as "migalastat therapy".

[00239] 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 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.

[00240] Again, it is noted that 150 mg of migalastat hydrochloride is equivalent to 123 mg of the free base form of migalastat. Thus, in one or more embodiments, the dose is 150 mg of migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt, administered at a frequency of once every other day. 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 once every other day.

[00241] 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.

[00242] Accordingly, in various embodiments, migalastat therapy includes administering 123 mg FBE at a frequency of once every other day, such as 150 mg of migalastat hydrochloride every other day.

[00243] 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, 20, 24, 30 or 36 months or at least 1, 2, 3, 4 or 5 years. In various embodiments, the migalastat therapy is long-term migalastat therapy of at least 6 months, such as at least 6, 7, 8, 9, 10, 11, 12, 16, 20, 24, 30 or 36 months or at least 1, 2, 3, 4 or 5 years.

[00244] 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 orally administered capsules each containing 150 mg migalastat hydrochloride or an equivalent dose of migalastat or a salt thereof other than the hydrochloride salt.

[00245] 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.

[00246] In one or more embodiments, the PC (*e.g.*, migalastat or salt thereof) is administered as monotherapy, and can be in a form suitable for any route of administration, including *e.g.*, orally in the form tablets or capsules or liquid, or in sterile aqueous solution for injection. In other embodiments, the PC is provided in a dry lyophilized powder to be added to the formulation of the replacement enzyme during or immediately after reconstitution to prevent enzyme aggregation in vitro prior to administration.

[00247] When the PC (*e.g.*, migalastat or salt thereof) is formulated for oral administration, the tablets or capsules can be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or another suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-p- hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active chaperone compound.

[00248] The pharmaceutical formulations of the PC (*e.g.*, migalastat or salt thereof) suitable for parenteral/injectable use generally include sterile aqueous solutions (where water soluble), or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and

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

[00249] 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.

[00250] The formulation can contain an excipient. Pharmaceutically acceptable excipients which may be included in the formulation are buffers such as citrate buffer, phosphate buffer, acetate buffer, bicarbonate buffer, amino acids, urea, alcohols, ascorbic acid, and phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrollidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (*e.g.*, PEG-4000, PEG-6000); glycerol; glycine or other amino acids; and lipids. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers. Phosphate buffer is a preferred embodiment.

[00251] 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.

[00252] Administration of the above-described parenteral formulations of the chaperone compound may be by periodic injections of a bolus of the preparation, or may be administered by intravenous or intraperitoneal administration from a reservoir which is external (*e.g.*, an i.v. bag) or internal (*e.g.*, a bioerodable implant).

[00253] 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 patients with Fabry disease, methods of reducing kidney GL-3, methods of stabilizing renal function, methods of reducing LVM or LVMi, methods of reducing plasma lyso-Gb_3 and/or methods of treating gastrointestinal symptoms (*e.g.* diarrhea), methods of enhancing α-Gal A in a patient diagnosed with or suspected of having Fabry disease, use of a pharmacological chaperone for α-Gal A for the manufacture of a medicament for treating a patient diagnosed with Fabry disease or to a pharmacological chaperone for α-Gal A for use in treating a patient diagnosed with Fabry disease as well as embodiments relating to amenable mutations, the PCs and suitable dosages thereof.

[00254] In one or more embodiments, the PC (*e.g.*, migalastat or salt thereof) is administered in combination with ERT. ERT increases the amount of protein by exogenously introducing wild-type or biologically functional enzyme by way of infusion. This therapy has been developed for many genetic disorders, including LSDs such as Fabry disease, as referenced above. After the infusion, the exogenous enzyme is expected to be taken up by tissues through non-specific or receptor-specific mechanism. In general, the uptake efficiency is not high, and the circulation time of the exogenous protein is short. In addition, the exogenous protein is unstable and subject to rapid intracellular degradation as well as having the potential for adverse immunological reactions with subsequent treatments. In one or more embodiments, the chaperone is administered at the same time as replacement enzyme (*e.g.*, replacement α-Gal A). In some embodiments, the chaperone is co-formulated with the replacement enzyme (*e.g.*, replacement α-Gal A).

[00255] 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.

[00256] Stabilization of Renal Function

[00257] The dosing regimens described herein can stabilize renal function in Fabry patients with varying degrees of renal impairment. In one or more embodiments, a Fabry patient having renal impairment is administered about 100 mg to about 150 mg FBE of migalastat or salt thereof at a frequency of once every other day. In one or more embodiments, the patient is administered 123 mg FBE of migalastat or salt thereof, such as 123 mg of migalastat or 150 mg of migalastat hydrochloride every other day. In one or more embodiments, the patient has mild or moderate renal impairment. In specific embodiments, the patient has mild renal impairment. In other specific embodiments, the patient has moderate renal impairment. The patient may be ERT-naïve or ERT-experienced.

[00258] The administration of migalastat may be for a certain period of time. In one or more embodiments, the migalastat is administered for 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, 20 or 24 months or at least 1, 2, 3, 4 or 5 years. In various embodiments, the migalastat therapy is long-term migalastat therapy of at least 6 months, such as at least 6, 7, 8, 9, 10, 11, 12, 16, 20 or 24 months or at least 1, 2, 3, 4 or 5 years.

[00259] The migalastat therapy may reduce the decline in renal function for a Fabry patient compared to the same patient without treatment with migalastat therapy. In one or more embodiments, the migalastat therapy provides an annualized change in $eGFR_{CKD\text{-}EPI}$ for a patient that is greater than (i.e. more positive than) -5.0 mL/min/1.73 m^2/year, such as greater than -4.5, -4.0, -3.5, -3.0, -2.5, -2.0, -1.5, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, -0.1 or even greater than 0 mL/min/1.73 m^2/year. In one or more embodiments, the migalastat therapy provides an annualized change in $mGFR_{iohexol}$ for a patient that is greater than -5.0 mL/min/1.73 m^2/year, such as greater than -4.5, -4.0, -3.5, -3.0, -2.5, -2.0, -1.5, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, -0.1 or even greater than 0 mL/min/1.73 m^2/year Accordingly, the migalastat therapy may reduce the decline or even improve the renal function of the patient. These annualized rates of change can be measured over a specific time period, such as over 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months or 60 months.

[00260] The migalastat therapy may reduce the decline in renal function for a group of Fabry patients, such as subpopulations of Fabry patients having varying degrees of renal impairment. In one or more embodiments, the migalastat therapy provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ in Fabry patients having mild, moderate or severe renal impairment that is greater than -5.0 mL/min/1.73 m^2/year, such as greater than -4.5, -4.0, -3.5, -3.0, -2.5, -2.0, -1.5, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, -0.1 or even greater than 0 mL/min/1.73 m^2/year. In one or more embodiments, the migalastat therapy provides a mean annualized rate of change in $mGFR_{iohexol}$ in patients having mild, moderate or severe renal impairment that is greater than -5.0 mL/min/1.73 m^2/year, such as greater than -4.5, -4.0, -3.5, -3.0, -2.5, -2.0, -1.5, -1.0, -0.9, -0.8, -0.7, -0.6, -0.5, -0.4, -0.3, -0.2, -0.1 or even greater than 0 mL/min/1.73 m^2/year. These mean annualized rates of change can be measured over a specific time period, such as over 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months or 60 months.

Left Ventricular Mass

[00261] The dosing regimens described herein can improve LVMi in Fabry patients. The natural history of LVMi and cardiac hypertrophy in untreated Fabry patients regardless of phenotype (Patel, O'Mahony *et al.* 2015) is a progressive increase in LVMi between +4.07 and +8.0 g/m^2/year (Kampmann, Linhart *et al.* 2008; Wyatt, Henley *et al.* 2012; Germain, Weidemann *et al.* 2013). As untreated Fabry patients typically exhibit an increase in LVMi over time, both decreases in and maintenance of LVMi are indications of a benefit of migalastat therapy.

[00262] The migalastat therapy may reduce the increase in LVMi for a Fabry patient compared to the same patient without treatment with migalastat therapy. In one or more embodiments, the migalastat therapy provides a change in LVMi for a patient that is less than (*i.e.*, more negative than) 0 g/m^2, such as less than or equal to about -0.5, -1, -1.5, -2, -2.5, -3, -3.5, -4, -4.5, -5, -5.5, -6, -7, -8, -9, -10, -11, -12, -13, -14, -15, -16, -17, -18, -19 or -20 g/m^2. Expressed differently, in one or more embodiments, the migalastat therapy provides a reduction in LVMi of greater than 0 g/m^2, such as reductions of at least about 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 g/m^2. In one or more embodiments, the patient has mild or moderate renal impairment. In specific embodiments, the

patient has mild renal impairment. In other specific embodiments, the patient has moderate renal impairment. The patient may be ERT-naïve or ERT-experienced.

[00263] In one or more embodiments, the migalastat therapy provides an average decrease of LVMi in a group of ERT-experienced patients of at least about 1 g/m^2 after 18 months of administration of migalastat or a salt thereof. In various embodiments, the average decrease in the group of ERT-experienced patients after 18 months of administration of migalastat or a salt thereof is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 g/m^2.

[00264] In one or more embodiments, the migalastat therapy provides an average decrease of LVMi in a group of ERT-experienced patients having moderate renal impairment of at least about 1 g/m^2 after 18 months of administration of migalastat or a salt thereof. In various embodiments, the average decrease in the group of ERT-experienced patients after 18 months of administration of migalastat or a salt thereof is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 g/m^2.

[00265] In one or more embodiments, the migalastat therapy provides an average decrease of LVMi in a group of ERT-naïve patients of at least about 1 g/m^2 after 24 months of administration of migalastat or a salt thereof. In various embodiments, the average decrease in the group of ERT-naïve patients after 24 months of administration of migalastat or a salt thereof is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 g/m^2.

[00266] In one or more embodiments, the migalastat therapy provides an average decrease of LVMi in a group of ERT-naïve patients having moderate renal impairment of at least about 1 g/m^2 after 24 months of administration of migalastat or a salt thereof. In various embodiments, the average decrease in the group of ERT-naïve patients after 24 months of administration of migalastat or a salt thereof is at least about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 g/m^2.

[00267] Reference throughout this specification to "one embodiment," "certain embodiments," "various embodiments," "one or more embodiments" or "an embodiment" means that a particular feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. Thus, the appearances of the phrases such as "in one or more embodiments," "in certain embodiments," "in various embodiments," "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily referring to the same embodiment of the invention. Furthermore, the particular features, structures, materials, or characteristics may be combined in any suitable manner in one or more embodiments.

[00268] Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It will be apparent to those skilled in the art that various modifications and variations can be made to the method and apparatus of the present invention without departing from the spirit and scope of the invention. Thus, it is intended that the present invention include modifications and variations that are within the scope of the appended claims and their equivalents.

[00269] Patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

EXAMPLES

[00270] Example 1: Pharmacokinetics of Migalastat in Non-Fabry Patients with Renal Impairment

[00271] A clinical trial was conducted to study the pharmacokinetics and safety of migalastat HCl in non-Fabry subjects with renal impairment. A single 150 mg migalastat HCl dose was administered to subjects with mild, moderate, and severe renal impairment, and normal renal function. The eGFR was estimated by the Cockcroft-Gault equation per the FDA Guidance for renal impairment studies.

[00272] Volunteers were enrolled into two cohorts stratified for renal function calculated using the Cockcroft–Gault equation for creatinine clearance (CL_{CR}). Subjects were assigned to groups based on an estimated CL_{CR} at screening as calculated using the Cockcroft-Gault equation. For each subject, the following plasma migalastat PK parameters were determined by noncompartmental analysis with WinNonlin® software (Pharsight Corporation, Version 5.2).

C_{max} maximum observed concentration

t_{max} time to maximum concentration

AUC_{0-t} area under the concentration-time curve from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations

$AUC_{0-\infty}$ area under the concentration-time curve extrapolated to infinity, calculated using the formula:

$AUC0\text{-}\infty = AUC0\text{-}t + Ct/\lambda Z$

where Ct is the last measurable concentration and λZ is the apparent terminal elimination rate constant

λz apparent terminal elimination rate constant, where λZ is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase

$t_{1/2}$ apparent terminal elimination half-life (whenever possible), where $t_{1/2} = (\ln 2)/ \lambda Z$

CL/F oral clearance, calculated as Dose/AUC0-∞

Vd/F oral volume of distribution, calculated as Dose/ AUC0-∞·λZ

C_{48} concentration at 48 hours post-dose

[00273] Pharmacokinetic parameters determined were: area under the concentration–time curve (AUC) from time zero to the last measurable concentration post-dose (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$), maximum observed concentration (C_{max}), time to C_{max} (t_{max}), concentration at 48 hours post-dose (C_{48}), terminal elimination half-life ($t_{1/2}$), oral clearance (CL/F), and apparent terminal elimination rate constant (λz).

[00274] Study subjects were defined as having renal impairment if creatinine clearance (CL_{CR}) was less than 90 mL/min (i.e. CL_{CR} <90 mL/min) as determined using the Cockcroft-Gault formula. Subjects were grouped according to degree of renal dysfunction: mild (CLcr ≥60 and <90 mL/min), moderate (CL_{CR} ≥30 and <60 mL/min), or severe (CL_{CR} ≥15 and <30 mL/min)

[00275] The plasma and urine pharmacokinetics of migalastat have been studied in healthy volunteers and Fabry patients with normal to mildly impaired renal function. In the single-dose studies, migalastat had a moderate rate of absorption reaching maximum concentrations in approximately 3 hours (range, 1 to 6 hrs) after oral administration over the dose range studied. Mean C_{max} and AUC_{0-t} values increased in a dose-proportional manner following oral doses from 75 mg to 1250 mg migalastat. The mean elimination half-lives ($t_{1/2}$) ranged from 3.04 to 4.79 hours. Mean percent of the dose recovered in urine from doses evaluated in the single ascending dose (SAD) study were 32.2%, 43.0%, 49.3%, and 48.5% for the 25 mg, 75 mg, 225 mg, and 675 mg dose groups, respectively. In multiple ascending dose studies, only minimal accumulation of plasma migalastat was observed. In a TQT study, migalastat was negative for effect on cardiac repolarization at 150 mg and 1250 mg single doses (Johnson et al., Clin Pharmacol Drug Dev. 2013 Apr;2(2):120-32).

[00276] In this single dose renal impairment study conducted in non-Fabry subjects, plasma concentrations of single-dose migalastat HCl 150 mg increased with increasing degree of renal failure compared to subjects with normal renal function. Following a single oral dose of migalastat HCl 150 mg, mean plasma migalastat $AUC_{0-\infty}$ increased in subjects with mild, moderate, or severe renal impairment by 1.2-fold, 1.8-fold, and 4.5-fold, respectively, compared to healthy control subjects. Increases in plasma migalastat $AUC_{0-\infty}$ values were statistically significant in subjects with moderate or severe renal impairment but not in subjects with mild renal impairment following single-dose administration compared to subjects with normal renal function. Migalastat t_{max} was slightly delayed in the severe group; C_{max} was not increased across any of the groups following a single oral dose of migalastat HCl 150 mg in subjects with varying degrees of renal impairment compared to healthy control subjects. Plasma migalastat C_{48} levels were elevated in subjects with moderate (predominantly from subjects with Cr_{CL} <50mL/min) and severe renal impairment compared with healthy control subjects. The $t_{1/2}$ of migalastat in plasma increased as the degree of renal impairment increased (arithmetic mean [min, max]: 6.4 [3.66, 9.47], 7.7 [3.81, 13.8], 22.2 [6.74, 48.3], and 32.3 [24.6, 48.0] h) in subjects with normal renal function and those with mild, moderate, or severe renal impairment, respectively. Mean CL/F decreased with increasing degree of renal failure and ranged from 12.1 to 2.7 L/hr from mild to severe renal impairment (Johnson, et al., American College of Clinical Pharmacology 4.4 (2015): 256–261).

[00277] Migalastat clearance decreased with increasing renal impairment, resulting in increases in migalastat HCl plasma $t_{1/2}$, $AUC_{0-\infty}$, and C_{48} compared with subjects with normal renal function. Incidence of adverse events was comparable across all renal function groups.

[00278] Following a single oral dose of 150 mg migalastat HCl plasma exposure (expressed as AUC_{0-t}) increased as the degree of renal impairment increased. FIG. 1A shows an increase in migalastat AUC_{0-t} values as CL_{CR} values decrease. FIG. 1B shows the mean (SE) plasma migalastat concentration-time profiles for each renal function group. BLQ values were entered as zero and included in the calculation of means.

[00279] As demonstrated in FIG. 1C, as renal impairment worsens, plasma migalastat AUC_{0-t} values increase in a nonlinear manner. Results demonstrated that, as renal impairment worsened, the clearance of plasma migalastat decreased, resulting in prolonged $t_{1/2}$, higher C_{48} values, and higher overall plasma exposure ($AUC_{0-\infty}$), in particular in subjects with severe

renal impairment. Migalastat is primarily excreted unchanged in urine. Thus, an increase in plasma migalastat exposure is consistent with worsening renal impairment.

[00280] Conclusions: Plasma migalastat clearance decreased as degree of renal impairment increased.

[00281] A summary of the PK results are shown in Table 3 below.

Table 3

PK		Renal Function Group			
Parameter	**Units**	**Normal (N=8)**	**Mild (N=8)**	**Moderate (N=8)**	**Severe (N=8)**
AUC_{0-t}	(ng·hr/mL)	12306 (27.9)	14389 (31.1)	22126 (42.8)	53070 (27.0)
$AUC_{0-\infty}$	(ng·hr/mL)	12397 (27.7)	14536 (30.7)	22460 (42.2)	56154 (24.9)
C_{max}	(ng/mL)	2100 (26.0)	2191 (28.8)	1868 (32.1)	2078 (45.5)
t_{max}	(hr)	2.50 (1.50, 3.00)	2.50 (1.50, 4.00)	3.00 (1.50, 4.00)	4.27 (3.00, 8.00)
$t_{½}$	(hr)	6.42 (1.93)	7.66 (3.02)	22.2 (14.2)	32.3 (7.35)
CL/F	(L/hr)	12.1 (27.7)	10.3 (30.7)	6.68 (42.2)	2.67 (24.9)
C_{48}	(ng/mL)	5.70 (3.63)	9.34 (7.57)	64.5 (68.1)	334 (126)

[00282] Example 2: Multiple Dose Simulations on Renal Impairment Subjects

[00283] In the renal impairment study of Example 1, consistent increases in area under the curve (AUC) and trough concentration of migalastat at 48 hours post-dose following QOD dosing (C_{48}) of 2- to 4-fold were observed at eGFR values $\leq$ 35 mL/min relative to subjects with normal renal function.

[00284] A population PK model was developed to predict exposures and time above IC_{50} in Fabry patients with varying degrees of renal impairment. This example provides computer simulations of dosing the renal impairment subjects of Example 1. The key assumption was exposure characterized in non-Fabry subjects with renal impairment is the same as in Fabry patients with renal impairment. The software program was WinNonlin version 5.2 or higher. The conditions of the model are described below. 11 subjects who had BSA-adjusted $eGFR_{Cockcroft-Gault} \leq 35$ mL/min/1.73m^2 were included in the modeling exercise; 3 had moderate renal impairment, but were ≥ 30 mL/min/1.73m^2 and ≤ 35 mL/min/1.73m^2 ,

and 8 were ≥ 14 mL/min/1.73m^2 and < 30 mL/min/1.73m^2. Steady state was assumed by 7th dose.

[00285] A 2-compartment model was used to estimate Vd and elimination rate constants from single dose data. These estimates were inputted into each molecular dose simulation regimen.

[00286] FIG. 2 shows the mean simulation plots for the dosing regimen of 150 mg migalastat HCl QOD. Table 4 below shows the exposures and accumulation ratios.

[00287] FIG. 3 shows AUC versus C_{48} from Example 1. This stick plot provides a visual correlation of AUC to C_{48} concentration across all levels of renal function, and demonstrates the two values are well visually correlated.

Table 4

Subject	Renal Function Group	BSA-Adj eGFR-Cockcroft-Gault (mL/min/1.73m^2)	AUC_{0-48h}	R_{ac48h}
1	Moderate (≥30 - ≤35)	35.3	31920	1.12
2	Moderate (≥30 - ≤35)	35.0	35320	1.17
3	Moderate (≥30 - ≤35)	32.2	17507	1.12
4	Severe (<30)	18.4	59178	1.42
5	Severe (<30)	17.0	44124	1.21
6	Severe (<30)	20.6	37409	1.28
7	Severe (<30)	15.8	41687	1.54
8	Severe (<30)	21.9	45790	1.29
9	Severe (<30)	29.3	56331	1.17
10	Severe (<30)	14.4	23732	1.45
11	Severe (<30)	24.4	39012	1.26
Geometric Mean		22.9	37256	1.27
CV%		33.8	33.4	11.1

Example 3: Pharmacokinetics of Migalastat in Fabry Patients with Renal Impairment

[00288] The computer modeling above provides scenarios for plasma migalastat exposure, but it does not account for renal impairment in Fabry patients. That is, the data does not include the pharmacodynamic component (plasma lyso-GB_3). Thus, two Fabry patients with renal impairment were evaluated. One patient (P1) had moderate renal impairment, while the other patient (P2) had severe renal impairment. Table 5 below shows plasma migalastat concentration for P1 compared with a study of ERT-naïve Fabry patients and moderately impaired subjects from the renal impairment study of Example 1. There are two sets of

migalastat concentration measurements taken 6 months apart, and the patient had been previously treated with migalastat. Table 6 shows similar information for P2, except compared with severely impaired patients from the renal impairment study of Example 1. The ERT-naïve study was carried out in Fabry patients with amenable mutations where population PK was performed from sparse blood sampling. The comparison with the results from the ERT-naïve study allows for comparison of PK in the Fabry population with mostly normal, but some mild and a few moderately impaired Fabry patients. None of the patients in the ERT-naïve study had severe renal impairment because these patients were excluded from the study.

Table 5

Hour Nominal	Time (hr)	Migalastat Conc (ng/mL)	Migalastat Conc 6 months later (ng/mL)	Comparison to ERT-Naïve Study PK	Comparison to Example 1 Moderate Impairment
0	Pre-dose	19.9	36.4	8.70	64.5 (105.6%)
3	3 Hrs Post	1620	2160	1180 (31.0%)	1868 (29.7%)
24	24 Hrs Post	168	211	-	239 (85.1%)
48	48 Hrs Post	41.8	62.4	8.70	64.5 (105.6%)

Table 6

Hour Nominal	Time Text	Occasion	Migalastat Concentration (ng/mL)	Comparison to ERT-Naïve Study PPK	Comparison to Example 1 Severe Impairment
2	2h	1	564	-	1549 (59.3%)
48	48h	1	322	8.70	334 (38.2%)
24	24h	2	569	-	770 (26.5%)
48	48h	2	260	8.70	334 (38.2%)

[00289] As seen from Table 5, C_{48} concentration, although increased by 49%, remains similar to Example 1 non-Fabry subjects with moderate renal impairment. C_{max} has increased by 33%, but remains similar to Example 1. C_{24} is similar to Example 1 for moderate renal impairment. $eGFR_{MDRD}$ remains within range for moderate impairment as well (32 mL/min).

[00290] The percentages in parentheses are coefficients of variation, which are relatively high, corresponding to variability in the time 0h or time 48h concentrations. This result is likely due to the fact that half of the subjects from Example 1 with moderate renal impairment had low concentrations and half of them high concentrations.

[00291] The concentrations at 48 hours are higher than at 0 hours for P1 (third and fourth columns), but for a person with moderate impairment from Example 1, the concentration at 48 hours is the same as at 0 hours. This is because separate blood samples were taken at times 0 and 48 in P1. However, repeat dose modeling simulation outputs from single dose data were used in Example 1, therefore the values are one in the same.

[00292] Similar trends can be seen from Table 6. Accordingly, Tables 5 and 6 confirm similar pharmacokinetics of migalastat in Fabry and non-Fabry patients having similar renal impairment.

[00293] FIG. 4 shows the Fabry patients' plasma migalastat trough concentrations (C_{48}) versus the renal impairment study of Example 1. FIG. 5 shows the mean (SD) renal impairment study exposures versus Fabry patient estimated AUCs. As seen from the figure, P1 and P2 followed the general trend of the renal impairment study results in non-Fabry patients.

[00294] Table 7 below shows the Lyso-GB_3/eGFR for P1.

Table 7

Visits	Lyso-Gb_3 (nM/L)	eGFR (MDRD), IDMS Traceable
18 Month Visit	11.1	42
24 Month Visit	13.1	37
30 Month Visit	10.8	Unavailable
34-Month Visit	9.3	32

[00295] Despite continued decline in renal function to eGFR of 32 mL/min/1.73 m2, plasma lyso-GB_3 has not shown clinically relevant changes from previous visits, and plasma migalastat concentrations remain similar to those observed in non-Fabry patients with moderate renal impairment.

[00296] This study demonstrates that the renal impairment and pharmacokinetic trends in Fabry patients correlates with the trends of non-Fabry patients.

[00297] Example 4: Additional Simulations on Renal Impairment Subjects

[00298] This example provides additional computer simulations of migalastat dosing of the renal impairment subjects of Example 1.

[00299] FIGS. 6A-D show simulated median and observed migalastat concentration versus time in normal, severe, mild and moderate renal impairment subjects, respectively. Table 8 below shows the data:

Table 8

Renal Function Group (CL_{CR} range mL/min), N	**C_{max} [a] (ng/ml)**	**$AUC_{0-\infty}$ [a] (hr*ng/ml)**	**AUC Ratio**	**$t_{1/2}$ [c] (hr)**
Normal (>=90), 8	2270 (37.6)	12808 (31.3)	-	6.2 (1.6)
Mild (>=60-<90), 8	2278 (22.5)	15359 (25.2)	1.2	8.0 (2.8)
Moderate (>=30-<60), 8	2058 (47.1)	23897 (38.9)	1.9	23.0 (13.3)
Severe (<30), 4	2122 (29.1)	61208 (23.1)	4.8	32.5 (2.4)

[a] Geometric mean (CV%)

[c] Mean (SD)

[00300] FIGS. 7A-D show simulated C_{max}, AUC, C_{min} and C_{48}, respectively, for normal, mild, moderate and severe renal impairment subjects.

[00301] FIGS. 8A-D show the steady state prediction for QOD. The dashed line is the mean value from the QT study. FIGS. 9A-D show C_{max}, AUC, C_{min} and C_{48}, respectively for the same simulation.

[00302] Example 5: Clinical Results of Migalastat Therapy in Fabry Patients with Renal Impairment and/or Elevated Proteinuria

[00303] As described above, several studies were conducted using 150 mg of migalastat hydrochloride every other day (QOD) in Fabry patients. One study was a 24-month trial, including a 6-month double-blind, placebo-controlled period, in 67 ERT-naïve patients. The other study was an active-controlled, 18-month trial in 57 ERT-experienced patients with a 12-month open-label extension (OLE). Both the ERT-naïve and ERT-experienced studies included Fabry patients having an eGFR of $\geq$30mL/min/1.73m^2. The study designs for these studies are shown in FIGS. 10A-B.

[00304] In the ERT-experienced study, the primary efficacy parameters were the annualized changes (mL/min/1.73m^2/yr) from baseline through month 18 in measured GFR using iohexol clearance ($mGFR_{iohexol}$) and eGFR using the Chronic Kidney Disease

Epidemiology Collaboration (CKD-EPI) formula ($eGFR_{CKD-EPI}$). Annualized change in eGFR using the Modification of Diet in Renal Disease ($eGFR_{MDRD}$) was also calculated.

[00305] In the ERT-naïve study, the primary efficacy parameter was GL-3 inclusions per kidney interstitial capillary. Renal function was also evaluated by $mGFR_{iohexol}$, $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$.

[00306] A post-hoc analysis of data from the ERT-naïve study examined $eGFR_{CKD-EPI}$ annualized rate of change in subgroups based on eGFR at baseline for amenable patients with moderate renal impairment (30 to <60 mL/min/1.73 m^2), mild renal impairment (60 to <90 mL/min/1.73 m^2), and normal renal function (≥90 mL/min/1.73 m^2). The annualized rate of change of $eGFR_{CKD-EPI}$ from baseline to 18/24 months is shown in FIG. 11. As can be seen from FIG. 11, patients with moderate renal impairment had a mean ± SEM annualized rate of change of $eGFR_{CKD-EPI}$ of -0.7 ± 3.97 mL/min/1.73 m^2/year, patients with mild renal impairment had a mean annualized rate of change of $eGFR_{CKD-EPI}$ of -0.8 ± 1.01 mL/min/1.73 m^2/year, and patients with normal renal function had a mean annualized rate of change of $eGFR_{CKD-EPI}$ of 0.2 ± 0.90 mL/min/1.73 m^2/year. This data shows a stabilization of renal function with migalastat treatment was observed regardless of baseline eGFR.

[00307] A post-hoc analysis of data from the ERT-experienced study examined $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ annualized rate of change in subgroups based on eGFR at baseline for patients with mild/moderate renal impairment (30 to <90 mL/min/1.73 m^2) and normal renal function (≥90 mL/min/1.73 m^2). The annualized rates of change from baseline to 18 months for patients on migalastat therapy (patients with amenable mutations) and ERT is shown in FIGS. 12A-B for $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$, respectively. As can be seen from FIG. 12A, patients with normal renal function had a mean annualized rate of change of $eGFR_{CKD-EPI}$ of -0.4 mL/min/1.73 m^2/year on migalastat therapy and -1.03 mL/min/1.73 m^2/year on ERT. Patients with mild or moderate renal impairment had a mean annualized rate of change of $eGFR_{CKD-EPI}$ of -3.33 mL/min/1.73 m^2/year on migalastat therapy and -9.05 mL/min/1.73 m^2/year on ERT. As can be seen from FIG. 12B, patients with normal renal function had a mean annualized rate of change $mGFR_{iohexol}$ of -4.35 mL/min/1.73 m^2/year on migalastat therapy and -3.24 mL/min/1.73 m^2/year on ERT. Patients with mild or moderate renal impairment had a mean annualized rate of change $mGFR_{iohexol}$ of -3.51 mL/min/1.73 m^2/year on migalastat therapy and -7.96 mL/min/1.73 m^2/year on ERT. This data shows that

migalastat therapy and ERT had comparable favorable effects on renal function using both GFR methods.

[00308] Another post-hoc analysis of data from the ERT-experienced study examined $eGFR_{CKD\text{-}EPI}$ annualized rate of change in subgroups based on eGFR at baseline for patients with moderate renal impairment (30 to <60 mL/min/1.73 m^2), mild renal impairment (60 to <90 mL/min/1.73 m^2), and normal renal function (≥90 mL/min/1.73 m^2). The annualized rates of change from baseline to 18 months for patients on migalastat therapy (patients with amenable mutations) and ERT is shown in FIG. 13. As can be seen from FIG. 13, patients with normal renal function had a mean ± SE annualized rate of change of $eGFR_{CKD\text{-}EPI}$ of -2.0 ± 0.57 mL/min/1.73 m^2/year on migalastat therapy and -2.1 ± 1.60 mL/min/1.73 m^2/year on ERT. Patients with mild renal impairment had a mean ± SE annualized rate of change of $eGFR_{CKD\text{-}EPI}$ of -0.2 ± 1.25 mL/min/1.73 m^2/year on migalastat therapy and -7.3 ± 6.01 mL/min/1.73 m^2/year on ERT. Patients with moderate renal impairment had a mean ± SE annualized rate of change of $eGFR_{CKD\text{-}EPI}$ of -4.5 ± 2.68 mL/min/1.73 m^2/year on migalastat therapy and 1.3 mL/min/1.73 m^2/year on ERT. This data shows that migalastat stabilized renal function regardless of whether the patient had normal renal function or mild renal impairment. Although the number of patients with moderate renal impairment included in this analysis is two (compared to three for the ERT-naïve study), the data supports the efficacy of migalastat when administered to patients with some form of renal impairment.

[00309] A further analysis of data from these studies examined annualized change in $eGFR_{CKD\text{-}EPI}$, LVMi, WBC α-Gal A activity and plasma lyso-Gb_3 levels based on renal function at baseline. The results for each renal subgroup are shown in Table 9 below, with the ERT-naïve study subgroups based on $eGFR_{MDRD}$ and the ERT-experienced study subgroups based on $mGFR_{iohexol}$.

Table 9

Treatment	Renal Subgroup	Change from Baseline, mean ± SE [n]			
		Annualized Change in $eGFR_{CKD-EPI}$ mL/min/1.73 m^2	LVMi, g/m^2	WBC α-Gal A Activity, 4MU/hr/mg (males only)	Plasma lyso-Gb_3, nmol/L (SD instead of SE)
ERT-Naïve					
Migalastat→ Migalastat 0-24 months	30 to <60	+3.2 ± 1.1 [2]	-5.5 ± 10.0 [2]	+1.4 [1]	-29.0 (41.5) [2]
	≥60	-0.7 ± 0.6 [20]	-9.2 ± 5.8 [14]	+1.6 ± 1.5 [3]	-7.7 (24.5) [14]
Placebo→ Migalastat 6-24 months	30 to <60	-2.8 ± 2.8 [2]	-21.0 ± 14.1 [2]	+4.0 ± 3.0 [2]	—
	≥60	+0.1 ± 0.7 [17]	-3.2 ± 5.6 [10]	+5.2 1.4 [5]	-20.0 (28.7) [13]
ERT-Experienced					
Migalastat 0-18 months	30 to <60	-4.2 ± 2.7 [2]	-10.2 ± 2.4 [2]	+4.6 ± 2.3 [2]	+0.5 (0.6) [3]
	≥60	-0.4 ± 0.8 [32]	-4.8 ± 2.3 [24]	+5.5 ± 1.4 [12]	1.9 (5.8) [28]

[00310] As can be seen from Table 9, in the ERT-naïve study, plasma lyso-Gb_3 and LVMi decreased and WBC α-Gal A activity increased with migalastat at month 24 in both renal subgroups. Moreover, regardless of renal function, in the ERT-naïve study, there was a reduction in kidney interstitial capillary GL-3 inclusions from baseline to month 6 with migalastat (eGFR <60 mL/min/1.73 m^2, -0.39, n=3; eGFR ≥60 mL/min/1.73 m^2, -0.30, n=22) but not placebo (<60, 0.04, n=2; ≥60, 0.07, n=18). Table 9 also shows that in the ERT-experienced study, LVMi decreased, WBC α-Gal A activity increased, and lyso-Gb_3 remained low and stable during 18 months of treatment with migalastat in both renal subgroups. Table 9 also shows that renal function was stabilized in patients with a baseline eGFR ≥60 mL/min/1.73 m^2 in both the ERT-naïve and the ERT experienced study. This data further supports the efficacy of migalastat when administered to patients with some form of renal impairment.

[00311] In addition to the studies described above, other patients also received migalastat therapy in other studies such as dose-finding studies and/or long-term extension

studies. Patients that completed the some studies were eligible to continue open-label migalastat HCl 150 mg every other day in a separate extension study.

[00312] 12 patients that completed multiple studies were further analyzed. Linear regression was used to calculate the annualized rate of change in $eGFR_{CKD-EPI}$ from baseline. At the time of this analysis, mean time on migalastat for these 12 patients was 8.2 (standard deviation [SD], 0.83) years, the median time on treatment was 8.4 (range, 6.3-9.3) years, and 11 patients received migalastat HCl 150 mg QOD for ≥17 months. The baseline demographics for these 12 patients is shown in Table 10 below:

Table 10

Patient	**Age (years)**	**Sex**	**eGFR (mL/min/1.73 m^2)**
1	37	M	100.9
2	39	M	114.4
3	42	M	87.1
4	49	M	84.4
5	24	M	126.2
6	39	M	121.7
7	55	M	92.0
8	47	M	135.7
9	62	F	90.1
10	59	F	76.4
11	36	F	100.6
12	43	F	116.0
Mean (SD)	44.3 (10.7)	--	103.8 (18.7)
Median (min, max)	42.5 (24, 62)	--	100.8 (76, 136)

[00313] The annualized change in $eGFR_{CKD-EPI}$ for these patients is shown in Table 11 below:

Table 11

Patient	Annualized Rate of Change in $eGFR_{CKD-EPI}$, mL/min/1.72 m^2 [a]
1	-0.853
2	0.584
3	-2.838
4	0.488
5	0.001
6	-2.179
7	-0.704
8	-1.09
9	-0.443
10	0.219
11	-0.342
12	-0.871
Mean (95% CI)	-0.67 (-1.32, -0.02)

[a]Includes the entire duration of migalastat treatment, including periods when patients received various dosing regimens of migalastat and periods when patients received migalastat HCl 150 mg every other day

[00314] As can be seen from Table 11, among these 12 patients, renal function remained stable (annualized mean change in $eGFR_{CKD-EPI}$, -0.67 mL/min/1.72 m^2 [95% CI -1.32, -0.02]) during the entire migalastat treatment period (mean exposure, 8.2 years). Renal function also remained stable (annualized mean change in $eGFR_{CKD-EPI}$, 0.24 mL/min/1.72 m^2 [95% CI -1.7, 2.2]) in an analysis of the 11 patients who received migalastat HCl 150 mg QOD for ≥17 months (mean exposure, 4-5 years). The renal outcomes for these 11 patients based on sex and baseline proteinuria levels are shown in Table 12 below:

Table 12

Sex	Baseline 24-hour Urine Protein (mg/24 h) Category[a]	n	Annualized Rate of Change in eGFR $_{CKD-EPI}$, mL/min/1.73 m^2, Mean (95%CI)
All	All	11	+0.3 [-1.7, 2.2]
Males	<100	3	+0.4 [-4.1, 4.9]
Males	100-1000	4	+2.4 [-4.0, 8.8]
Females	<100	2	-1.6 [-2.4, -0.9]
Females	100-1000	2	-1.7 [-2.0, -1.3]

[00315] These results show stabilization of renal function was demonstrated in male and female patients with Fabry disease and amenable mutations treated with migalastat for up to 9 years. The effects were observed over a wide baseline proteinuria range.

[00316] Another analysis was performed on patients who participated in multiple studies for the use of migalastat. Annualized change rate in $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ were calculated for patients based on proteinuria at baseline (<100, 100-1000, >1000 mg/24 h). A total of 52 ERT-naive patients with amenable mutations received migalastat HCl 150 mg QOD for ≥17 months were analyzed. Table 13 below shows the baseline proteinuria and duration of migalastat treatment for these patients.

Table 13

	Males		Females	
Baseline 24 h urine protein, mg/24 h	n	Duration, years, Median (min, max)	n	Duration, years, Median (min, max)
<100	3	4.8 (4.8, 4.8)	9	4.2 (2.0, 5.3)
100-1000	16	4.3 (1.5, 4.9)	19	3.5 (1.5, 5.0)
>1000	2	3.6 (3.0, 4.3)	3	3.7 (1.5, 4.1)

[00317] As can be seen from Table 13, most patients (67%) had proteinuria levels between 100-1000 mg/24 h at baseline; 23% of patients had baseline proteinuria levels <100 mg/24 h, and 10% had levels >1000 mg/24 h. Median treatment duration ranged from 3.5 to 4.8 years (maximum, 5.3 years) across baseline proteinuria subgroups.

[00318] The annualized mean change in $eGFR_{CKD-EPI}$ with migalastat treatment by baseline proteinuria for these patients is shown in Table 14 below.

Table 14

	Males		Females	
Baseline 24 h urine protein, mg/24 h	**n**	**Annualized $eGFR_{CKD-EPI}$ Change Rate, mL/min/1.73 m^2, Mean (SE)**	**n**	**Annualized $eGFR_{CKD-EPI}$ Change Rate, mL/min/1.73 m^2, Mean (SE)**
<100	3	0.4 (1.0)	9	–0.9 (0.4)
100-1000	16	0.2 (0.8)	19	–0.3 (1.0)
>1000	2	–5.1 (0.1)	3	–2.2 (1.3)

[00319] As can be seen from Table 14, $eGFR_{CKD-EPI}$ remained stable in most patients with baseline proteinuria ≤1000 mg/24 h during migalastat treatment. Declines in $eGFR_{CKD-EPI}$ were observed in patients with proteinuria levels >1000 mg/24 h at baseline.

[00320] Results for $eGFR_{MDRD}$ were compared with changes in $eGFR_{MDRD}$ reported in the literature for untreated patients with Fabry disease (natural history cohort; Schiffmann R et al. Nephrol Dial Transplant. 2009;24:2102-11) and are shown in Table 15 below:

Table 15

	Males		Females	
Baseline 24h urine protein, mg/24 h	**n**	**Annualized eGFR Rate of Change, mL/min/m^2, Mean (SEM)**	**n**	**Annualized eGFR Rate of Change, mL/min/m^2, Mean (SEM)**
Migalastat cohort				
<100	3	1.2 (1.2)	9	-0.9 (0.5)
100-1000	16	0.9 (1.0)	19	1.3 (1.5)
>1000	2	-4.3 (0.1)	3	-1.7 (1.1)
Natural history cohort (Schiffmann et al. 2009)				
<100	18	-1.6 (1.5)	7	-0.6 (2.6)
100-1000	21	-3.3 (1.8)	17	-2.2 (2.2)
>1000	22	-6.9 (1.5)	5	-4.6 (2.3)

[00321] As shown in Table 15, mean annualized change in eGFR was smaller overall in patients treated with migalastat versus that observed in the natural history cohort across proteinuria categories. While mean eGFR declined in all untreated subgroups, increases were seen with migalastat in patients with baseline proteinuria <100 mg/24 h (males) and 100-1000 mg/24 h (males and females). Regardless of treatment, eGFR decreased in patients with baseline proteinuria >1000 mg/24 h; however, patients treated with migalastat had smaller decreases compared to the natural history cohort. Thus, long-term migalastat treatment was generally associated with stable renal function in patients with Fabry disease and amenable mutations, regardless of baseline proteinuria levels.

[00322] The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

[00323] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

What is claimed is:

1. A method of stabilizing renal function in a patient diagnosed with Fabry disease and having renal impairment, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE) and wherein the administration of the migalastat or salt thereof is effective to stabilize renal function in the patient.

2. The method of claim 1, wherein the patient has mild or moderate renal impairment.

3. The method of claim 1, wherein the patient has mild renal impairment.

4. The method of claim 1, wherein the patient has moderate renal impairment.

5. The method of claim 1, wherein the patient has severe renal impairment.

6. The method of any one of claims 1-5, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

7. The method of any one of claims 1-5, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

8. The method of any one of claims 1-7, wherein the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

9. The method of any one of claims 1-7, wherein the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

10. The method of any one of claims 1-7, wherein the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

11. The method of any one of claims 1-10, wherein the migalastat or salt thereof is in a solid dosage form.

12. The method of any one of claims 1-11, wherein the migalastat or salt thereof is administered orally.

13. The method of any one of claims 1-12, wherein the migalastat or salt thereof is administered for at least 28 days.

14. The method of any one of claims 1-13, wherein the migalastat or salt thereof is administered for at least 6 months.

15. The method of any one of claims 1-14, wherein the migalastat or salt thereof is administered for at least 12 months.

16. The method of any one of claims 1-15, wherein administration of the effective amount of the migalastat or salt thereof to a group of patients having mild or moderate renal impairment provides a mean annualized rate of change in $eGFR_{CKD-EPI}$ of greater than -1.0 mL/min/1.73 m^2.

17. The method of any one of claims 1-16, wherein administration of the effective amount of the migalastat or salt thereof to a group of patients having mild renal impairment provides a mean annualized rate of change in $eGFR_{CKD-EPI}$ of greater than -1.0 mL/min/1.73 m^2.

18. The method of any one of claims 1-17, wherein administration of the effective amount of the migalastat or salt thereof to a group of patients having moderate renal impairment provides a mean annualized rate of change in $eGFR_{CKD-EPI}$ of greater than -1.0 mL/min/1.73 m^2.

19. The method of any one of claims 1-18, wherein the effective amount is about 123 mg FBE.

20. The method of any one of claims 1-19, wherein the effective amount is about 123 mg of migalastat free base.

21. The method of any one of claims 1-19, wherein the effective amount is about 150 mg of migalastat hydrochloride.

22. The method of any one of claims 1-21, wherein the patient has a HEK assay amenable mutation in α-galactosidase A.

23. A method of treating Fabry disease in a patient diagnosed with Fabry disease and having renal impairment, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE).

24. The method of claim 23, wherein the patient has mild or moderate renal impairment.

25. The method of claim 23, wherein the patient has mild renal impairment.

26. The method of claim 23, wherein the patient has moderate renal impairment.

27. The method of claim 23, wherein the patient has severe renal impairment.

28. The method of any one of claims 23-27, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

29. The method of any one of claims 23-27, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

30. The method of any one of claims 23-29, wherein the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

31. The method of any one of claims 23-29, wherein the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

32. The method of any one of claims 23-29, wherein the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

33. The method of any one of claims 23-32, wherein the migalastat or salt thereof is in a solid dosage form.

34. The method of any one of claims 23-33, wherein the migalastat or salt thereof is administered orally.

35. The method of any one of claims 23-34, wherein the migalastat or salt thereof is administered for at least 28 days.

36. The method of any one of claims 23-35, wherein the migalastat or salt thereof is administered for at least 6 months.

37. The method of any one of claims 23-36, wherein the migalastat or salt thereof is administered for at least 12 months.

38. The method of any one of claims 23-37, wherein the administration of the migalastat or salt thereof is effective to increase α-galactosidase A (α-Gal A) activity in the patient.

39. The method of claim 38, wherein the α-Gal A activity is white blood cell (WBC) α-Gal A activity.

40. The method of any one of claims 23-39, wherein the administration of the migalastat or salt thereof is effective to reduce left ventricular mass index (LVMi) in the patient.

41. The method of any one of claims 23-40, wherein the administration of the migalastat or salt thereof is effective to stabilize plasma globotriaosylsphingosine (lyso-Gb_3) in the patient.

42. The method of any one of claims 23-41, wherein the administration of the migalastat or salt thereof is effective to stabilize renal function in the patient.

43. The method of any one of claims 23-42, wherein the effective amount is about 123 mg FBE.

44. The method of any one of claims 23-43, wherein the effective amount is about 123 mg of migalastat free base.

45. The method of any one of claims 23-43, wherein the effective amount is about 150 mg of migalastat hydrochloride.

46. The method of any one of claims 23-45 wherein the patient has a HEK assay amenable mutation in α-galactosidase A.

47. A method of stabilizing plasma globotriaosylsphingosine (lyso-Gb_3) in a patient diagnosed with Fabry disease and having renal impairment, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE) and wherein the administration of the migalastat or salt thereof is effective to stabilize plasma lyso-Gb_3 in the patient.

48. The method of claim 47, wherein the patient has mild or moderate renal impairment.

49. The method of claim 47, wherein the patient has mild renal impairment.

50. The method of claim 47, wherein the patient has moderate renal impairment.

51. The method of claim 47, wherein the patient has severe renal impairment.

52. The method of any one of claims 47-50, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

53. The method of any one of claims 47-51, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

54. The method of any one of claims 47-53, wherein the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

55. The method of any one of claims 47-53, wherein the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

56. The method of any one of claims 47-53, wherein the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

57. The method of any one of claims 47-56, wherein the migalastat or salt thereof is in a solid dosage form.

58. The method of any one of claims 47-57, wherein the migalastat or salt thereof is administered orally.

59. The method of any one of claims 47-58, wherein the migalastat or salt thereof is administered for at least 28 days.

60. The method of any one of claims 47-59, wherein the migalastat or salt thereof is administered for at least 6 months.

61. The method of any one of claims 47-60, wherein the migalastat or salt thereof is administered for at least 12 months.

62. The method of any one of claims 47-61, wherein administration of the effective amount of the migalastat or salt thereof to a group of ERT-naïve patients having moderate renal impairment provides a mean reduction of plasma lyso-Gb_3 of at least about 5 nmol/L after 24 months of the administration of the migalastat or salt thereof.

63. The method of any one of claims 47-62, wherein the effective amount is about 123 mg FBE.

64. The method of any one of claims 47-63, wherein the effective amount is about 123 mg of migalastat free base.

65. The method of any one of claims 47-64, wherein the effective amount is about 150 mg of migalastat hydrochloride.

66. The method of any one of claims 47-65, wherein the patient has a HEK assay amenable mutation in α-galactosidase A.

67. A method of reducing left ventricular mass index (LVMi) in a patient diagnosed with Fabry disease and having renal impairment, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE) and wherein the administration of the migalastat or salt thereof is effective to reduce the patient's LVMi.

68. The method of claim 67, wherein the patient has mild or moderate renal impairment.

69. The method of claim 67, wherein the patient has mild renal impairment.

70. The method of claim 67, wherein the patient has moderate renal impairment.

71. The method of claim 67, wherein the patient has severe renal impairment.

72. The method of any one of claims 67-71, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

73. The method of any one of claims 67-71, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

74. The method of any one of claims 67-73, wherein the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

75. The method of any one of claims 67-73, wherein the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

76. The method of any one of claims 67-73, wherein the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

77. The method of any one of claims 67-76, wherein the migalastat or salt thereof is in a solid dosage form.

78. The method of any one of claims 67-77, wherein the migalastat or salt thereof is administered orally.

79. The method of any one of claims 67-78, wherein the migalastat or salt thereof is administered for at least 28 days.

80. The method of any one of claims 67-79, wherein the migalastat or salt thereof is administered for at least 6 months.

81. The method of any one of claims 67-80, wherein the migalastat or salt thereof is administered for at least 12 months.

82. The method of any one of claims 67-81, wherein administration of the effective amount of the migalastat or salt thereof to a group of ERT-naïve patients having moderate renal impairment provides a mean reduction of LVMi of at least about 2 g/m^2 after 24 months of the administration of the migalastat or salt thereof.

83. The method of any one of claims 67-82, wherein administration of the effective amount of the migalastat or salt thereof to a group of ERT-experienced patients having moderate renal impairment provides a mean reduction of LVMi of at least about 2 g/m^2 after 18 months of the administration of the migalastat or salt thereof.

84. The method of any one of claims 67-83, wherein the effective amount is about 123 mg FBE.

85. The method of any one of claims 67-84, wherein the effective amount is about 123 mg of migalastat free base.

86. The method of any one of claims 67-84, wherein the effective amount is about 150 mg of migalastat hydrochloride.

87. The method of any one of claims 67-86, wherein the patient has a HEK assay amenable mutation in α-galactosidase A.

88. A method of increasing white blood cell (WBC) α-galactosidase A (α-Gal A) activity in a patient diagnosed with Fabry disease and having renal impairment, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE) and wherein the administration of the migalastat or salt thereof is effective to increase WBC α-Gal A activity in the patient.

89. The method of claim 88, wherein the patient has mild or moderate renal impairment.

90. The method of claim 88, wherein the patient has mild renal impairment.

91. The method of claim 88, wherein the patient has moderate renal impairment.

92. The method of claim 88, wherein the patient has severe renal impairment.

93. The method of any one of claims 88-92, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

94. The method of any one of claims 88-92, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

95. The method of any one of claims 88-94, wherein the patient has a proteinuria level of less than 100 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

96. The method of any one of claims 88-94, wherein the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

97. The method of any one of claims 88-94, wherein the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

98. The method of any one of claims 88-97, wherein the migalastat or salt thereof is in a solid dosage form.

99. The method of any one of claims 88-98, wherein the migalastat or salt thereof is administered orally.

100. The method of any one of claims 88-99, wherein the migalastat or salt thereof is administered for at least 28 days.

101. The method of any one of claims 88-100, wherein the migalastat or salt thereof is administered for at least 6 months.

102. The method of any one of claims 88-101, wherein the migalastat or salt thereof is administered for at least 12 months.

103. The method of any one of claims 88-102, wherein administration of the effective amount of the migalastat or salt thereof to a group of ERT-naïve patients having moderate renal impairment provides a mean increase in WBC α-Gal A activity of at least about 1 4MU/hr/mg after 24 months of the administration of the migalastat or salt thereof.

104. The method of any one of claims 88-103, wherein administration of the effective amount of the migalastat or salt thereof to a group of ERT-experienced patients having

moderate renal impairment provides a mean increase in WBC α-Gal A activity of at least about 1 4MU/hr/mg after 18 months of the administration of the migalastat or salt thereof.

105. The method of any one of claims 88-104, wherein the effective amount is about 123 mg FBE.

106. The method of any one of claims 88-105, wherein the effective amount is about 123 mg of migalastat free base.

107. The method of any one of claims 88-105, wherein the effective amount is about 150 mg of migalastat hydrochloride.

108. The method of any one of claims 88-107, wherein the patient has a HEK assay amenable mutation in α-galactosidase A.

109. A method of stabilizing renal function in a patient diagnosed with Fabry disease and having elevated proteinuria, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE) and wherein the administration of the migalastat or salt thereof is effective to stabilize renal function in the patient.

110. The method of claim 109, wherein the patient has renal impairment.

111. The method of claim 110, wherein the patient has mild renal impairment.

112. The method of claim 110, wherein the patient has moderate renal impairment.

113. The method of claim 110, wherein the patient has severe renal impairment.

114. The method of any one of claims 109-113, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

115. The method of any one of claims 109-113, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

116. The method of any one of claims 109-115, wherein the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

117. The method of any one of claims 109-115, wherein the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

118. The method of any one of claims 109-117, wherein the migalastat or salt thereof is in a solid dosage form.

119. The method of any one of claims 109-118, wherein the migalastat or salt thereof is administered orally.

120. The method of any one of claims 109-119, wherein the migalastat or salt thereof is administered for at least 28 days.

121. The method of any one of claims 109-120, wherein the migalastat or salt thereof is administered for at least 6 months.

122. The method of any one of claims 109-121, wherein the migalastat or salt thereof is administered for at least 12 months.

123. The method of any one of claims 109-122, wherein administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD-EPI}$ of greater than -2.0 mL/min/1.73 m^2.

124. The method of any one of claims 109-123, wherein administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD-EPI}$ of greater than -5.0 mL/min/1.73 m^2.

125. The method of any one of claims 109-124, wherein the effective amount is about 123 mg FBE.

126. The method of any one of claims 109-125, wherein the effective amount is about 123 mg of migalastat free base.

127. The method of any one of claims 109-125, wherein the effective amount is about 150 mg of migalastat hydrochloride.

128. The method of any one of claims 109-127, wherein the patient has a HEK assay amenable mutation in α-galactosidase A.

129. A method of treating Fabry disease in a patient diagnosed with Fabry disease and having elevated proteinuria, the method comprising administering to the patient an effective amount of migalastat or salt thereof at a frequency of once every other day, wherein the effective amount is about 100 mg to about 150 mg free base equivalent (FBE).

130. The method of claim 129, wherein the patient has renal impairment.

131. The method of claim 130, wherein the patient has mild renal impairment.

132. The method of claim 130, wherein the patient has moderate renal impairment.

133. The method of claim 130, wherein the patient has severe renal impairment.

134. The method of any one of claims 129-133, wherein the patient is an enzyme replacement therapy (ERT)-experienced patient.

135. The method of any one of claims 129-133, wherein the patient is an enzyme replacement therapy (ERT)-naïve patient.

136. The method of any one of claims 129-134, wherein the patient has a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

137. The method of any one of claims 129-134, wherein the patient has a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof.

138. The method of any one of claims 129-137, wherein the migalastat or salt thereof is in a solid dosage form.

139. The method of any one of claims 129-138, wherein the migalastat or salt thereof is administered orally.

140. The method of any one of claims 129-139, wherein the migalastat or salt thereof is administered for at least 28 days.

141. The method of any one of claims 129-140, wherein the migalastat or salt thereof is administered for at least 6 months.

142. The method of any one of claims 129-141, wherein the migalastat or salt thereof is administered for at least 12 months.

143. The method of any one of claims 129-142, wherein administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of 100 to 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ of greater than -2.0 mL/min/1.73 m^2.

144. The method of any one of claims 129-143, wherein administration of the effective amount of the migalastat or salt thereof to a group of patients having a proteinuria level of greater than 1,000 mg/24hr prior to initiating the administration of the migalastat or salt thereof provides a mean annualized rate of change in $eGFR_{CKD\text{-}EPI}$ of greater than -5.0 mL/min/1.73 m^2.

145. The method of any one of claims 129-144, wherein the effective amount is about 123 mg FBE.

146. The method of any one of claims 129-145, wherein the effective amount is about 123 mg of migalastat free base.

147. The method of any one of claims 129-146, wherein the effective amount is about 150 mg of migalastat hydrochloride.

148. The method of any one of claims 129-147, wherein the patient has a HEK assay amenable mutation in α-galactosidase A.