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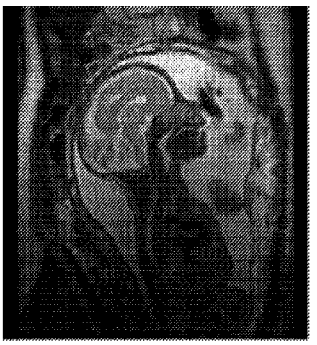
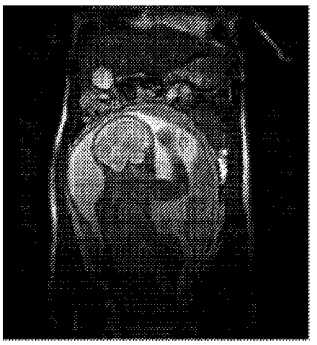
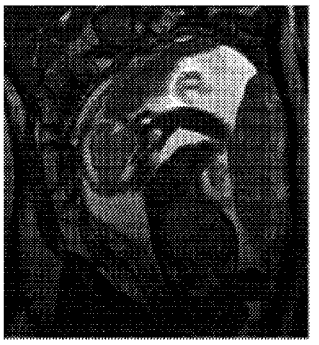
(54) **Titre : UTILISATION DE MIGALASTAT POUR LE TRAITEMENT DE LA MALADIE DE FABRY CHEZ DES PATIENTES ENCEINTES**
(54) **Title: USE OF MIGALASTAT FOR TREATING FABRY DISEASE IN PREGNANT PATIENTS**

(57) **Abrégé/Abstract:**
Provided are methods of treating a patient diagnosed with Fabry disease. Certain methods treat a pregnant patient with a therapeutically effective dose of migalastat or a salt thereof. Other methods treat a patient of childbearing potential with a therapeutically effective dose of migalastat or a salt thereof. Also described are the successful outcomes of pregnancies during which the pregnant patient is treated with migalastat.

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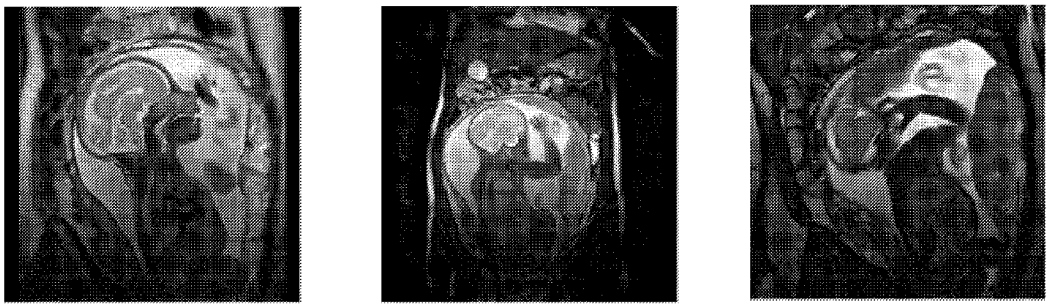

FIG. 4

(57) **Abstract:** Provided are methods of treating a patient diagnosed with Fabry disease. Certain methods treat a pregnant patient with a therapeutically effective dose of migalastat or a salt thereof. Other methods treat a patient of childbearing potential with a therapeutically effective dose of migalastat or a salt thereof. Also described are the successful outcomes of pregnancies during which the pregnant patient is treated with migalastat.

WO 2019/157047 A1

USE OF MIGALASTAT FOR TREATING FABRY DISEASE IN PREGNANT PATIENTS

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 pregnant patients or patients of childbearing potential.

[0002]

BACKGROUND

[0003] 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.

[0004] Lysosomal storage diseases (LSDs) are characterized by deficiencies of lysosomal enzymes due to mutations in the genes encoding the lysosomal enzymes. This results in the pathologic accumulation of substrates of those enzymes, which include lipids, carbohydrates, and polysaccharides.

[0005] Fabry disease is a progressive, X-linked inborn error of glycosphingolipid metabolism caused by a deficiency in the lysosomal enzyme α-galactosidase A (α-Gal A) as a

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result of mutations in the α-Gal A gene (GLA). Despite being an X-linked disorder, females can express varying degrees of clinical manifestations. Fabry is a rare disease with incidence estimated between 1 in 40,000 males to 1 in 117,000 in the general population. Moreover, there are variants of later onset phenotype of Fabry disease that can be under-diagnosed, as they do not present with classical signs and symptoms. This, and newborn screening for Fabry disease, suggests that the actual incidence of Fabry disease can be higher than currently estimated.

[0006] Untreated, life expectancy in Fabry patients is reduced and death usually occurs in the fourth or fifth decade because of vascular disease affecting the kidneys, heart and/or central nervous system. The enzyme deficiency leads to intracellular accumulation of the substrate globotriaosylceramide (GL-3) in the vascular endothelium and visceral tissues throughout the body. Gradual deterioration of renal function and the development of azotemia, due to glycosphingolipid deposition, usually occur in the third to fifth decades of life, but can occur as early as in the second decade. Renal lesions are found in both hemizygous (male) and heterozygous (female) patients.

[0007] Cardiac disease as a result of Fabry disease occurs in most males and many females. Early cardiac findings include left ventricular enlargement, valvular involvement and conduction abnormalities. Mitral insufficiency is the most frequent valvular lesion typically present in childhood or adolescence. Cerebrovascular manifestations result primarily from multifocal small-vessel involvement and can include thromboses, transient ischemic attacks, basilar artery ischemia and aneurysm, seizures, hemiplegia, hemianesthesia, aphasia, labyrinthine disorders, or cerebral hemorrhages. Average age of onset of cerebrovascular manifestations is 33.8 years. Personality change and psychotic behavior can manifest with increasing age.

[0008] Fabry disease commonly presents with dermatological symptoms, most commonly angiokeratoma (small papules that can reside on any region of the body). Angiokeratomas appear as dark red or purple skin lesions ranging in size up to several millimeters in diameter. Lesions usually appear in adolescence or young adulthood and may increase with age. Other dermatological and soft-tissue related symptoms include acroparesthesia, abnormal sweating (hypohidrosis and hyperhidrosis) and lymphedema. The

presence and extent of cutaneous vascular lesions may correlate with the severity of systemic disease.

[0009] In addition to dermatological symptoms, patients frequently experience neuropathy such as burning pain in the extremities (acroparesthesia – often hands and feet). Patients may also experience a pain crisis beginning with pain in the extremities and radiating inward which can persist for several days. Neuropathic pain is pain caused by damage to the somatosensory nervous system. Many types of sensory receptors are affected including those in skin, epithelial tissues, skeletal muscles, bones and joints, internal organs, and the cardiovascular system.

[0010] The current approved treatment for Fabry disease is enzyme replacement therapy ("ERT"). 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). These two forms of ERT are intended to compensate for a patient's inadequate α-Gal A activity with a recombinant form of the enzyme, administered intravenously. While ERT is effective in many settings, the treatment also has limitations. For example, these two α-Gal A products have not been demonstrated to decrease sufficient risk of stroke, cardiac muscle responds to treatment slowly, and GL-3 elimination from some of the cell types of the kidneys is limited.

[0011] Another 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. However, successful candidates for PC therapy should have a mutation which results in the production of an enzyme that has the potential to be stabilized and folded into a conformation that permits trafficking out of the ER. Mutations which severely truncate the enzyme, such as nonsense mutations, or mutations in the catalytic domain which prevent binding of the chaperone, will not be as likely to be "rescuable" or "enhanceable" using PC therapy, *i.e.*, to respond to PC therapy.

[0012] Migalastat, also known as 1-deoxygalactonojirimycin, acts as a pharmacological chaperone for mutant α-Gal A by selectively binding to the enzyme, thereby increasing its stability and helping the enzyme fold into its correct three-dimensional shape. This stabilization of α-Gal A allows the cell's quality control mechanisms to recognize the enzyme

as properly folded so that trafficking of the enzyme to the lysosome is increased, allowing it to carry out its intended biological function, the metabolism of GL-3. As a result of restoring the proper trafficking of α-Gal A from the ER to the lysosome, migalastat hydrochloride also reduces the accumulation of misfolded protein in the ER, which can alleviate stress on cells and some inflammatory-like responses that can be contributing factors in Fabry disease. It is estimated that approximately 35-50% of global Fabry patients have mutations which are amenable to treatment with migalastat.

[0013] Multiple *in vitro* and *in vivo* preclinical studies, as well as clinical studies, of migalastat and its salt migalastat hydrochloride have been conducted. Migalastat has been shown to increase the amount of intracellular α-Gal A protein and to enhance transport of mutant enzyme to the lysosome. It has also been generally well-tolerated. However, when elevated doses were tested in pregnant rabbits, developmental toxicity was observed. Despite the fact that these doses were also maternally toxic, migalastat is not currently recommended for use during pregnancy.

[0014] Accordingly, there remains a need for therapies for the treatment of Fabry disease in pregnant patients.

SUMMARY

[0015] One aspect of the invention pertains to a method for the treatment of Fabry disease in a pregnant patient in need thereof. In various embodiments of this aspect, the method comprises administering to the patient a formulation comprising a therapeutically effective dose of about 100mg to about 150 mg free base equivalent (FBE) of migalastat or a salt thereof at a frequency of once every other day.

[0016] In one or more embodiments, the patient becomes pregnant after initiating the treatment. In some embodiments, the patient was not instructed before initiating the treatment to use effective birth control during the treatment. In some embodiments, the patient does not use effective birth control during the treatment.

[0017] In one or more embodiments, the patient is pregnant before initiating the treatment. In some embodiments, the patient is known to be pregnant before initiating the treatment. In some embodiments, the patient is not known to be pregnant before initiating the treatment.

[0018] In some embodiments, the treatment is discontinued upon identification of the patient's pregnancy.

[0019] In one or more embodiments, the patient's pregnancy results in a birth of a child having a gestational age of at least 37 weeks. In some embodiments, the patient's pregnancy results in a birth of a child of normal weight based on a gestational age of the child. In some embodiments, the patient's pregnancy results in a child without a birth defect.

[0020] In one or more embodiments, the therapeutically effective dose is about 123 mg FBE of migalastat or a salt thereof. In some embodiments, the therapeutically effective dose is about 123 mg of migalastat free base. In some embodiments, the therapeutically effective dose is about 150 mg of migalastat hydrochloride.

[0021] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[0022] In one or more embodiments, the formulation is administered for at least 2 weeks. In some embodiments, the formulation is administered for at least 6 weeks. In some embodiments, the formulation is administered for at least 12 weeks.

[0023] In one or more embodiments, the formulation is administered for at least 2 weeks during the patient's pregnancy. In some embodiments, the formulation is administered for at least 6 weeks during the patient's pregnancy. In some embodiments, the formulation is administered for at least 12 weeks during the patient's pregnancy.

[0024] In one or more embodiments, the formulation is administered during a first trimester of the patient's pregnancy. In some embodiments, the formulation is administered during a second trimester of the patient's pregnancy. In some embodiments, the formulation is administered during the first 16 weeks of the patient's pregnancy.

[0025] In one or more embodiments, the formulation comprises a solid dosage form. In some embodiments, the formulation comprises an oral dosage form. In some embodiments, the oral dosage form comprises a tablet, a capsule, or a solution.

[0026] Another aspect of the invention pertains to a method for the treatment of Fabry disease in a female patient of childbearing potential. In various embodiments of this aspect, the method comprises administering to the patient a formulation comprising a therapeutically effective dose of about 100 mg to about 150 mg FBE of migalastat or a salt thereof at a frequency of once every other day, and wherein the patient is not instructed before the treatment is initiated to use effective birth control during the treatment.

[0027] In one or more embodiments, the patient becomes pregnant after initiating the treatment. In some embodiments, the patient does not use effective birth control during the treatment.

[0028] In some embodiments, the treatment is discontinued upon identification of the patient's pregnancy.

[0029] In one or more embodiments, the patient's pregnancy results in a birth of a child having a gestational age of at least 37 weeks. In some embodiments, the patient's pregnancy results in a birth of a child of normal weight based on a gestational age of the child. In some embodiments, the patient's pregnancy results in a child without a birth defect.

[0030] In one or more embodiments, the therapeutically effective dose is about 123 mg FBE of migalastat or a salt thereof. In some embodiments, the therapeutically effective dose is about 123 mg of migalastat free base. In some embodiments, the therapeutically effective dose is about 150 mg of migalastat hydrochloride.

[0031] In one or more embodiments, the salt of migalastat is migalastat hydrochloride.

[0032] In one or more embodiments, the formulation is administered for at least 2 weeks. In some embodiments, the formulation is administered for at least 6 weeks. In some embodiments, the formulation is administered for at least 12 weeks.

[0033] In one or more embodiments, the formulation is administered for at least 2 weeks during the patient's pregnancy. In some embodiments, the formulation is administered for at least 6 weeks during the patient's pregnancy. In some embodiments, the formulation is administered for at least 12 weeks during the patient's pregnancy.

[0034] In one or more embodiments, the formulation is administered during a first trimester of the patient's pregnancy. In some embodiments, the formulation is administered during a second trimester of the patient's pregnancy. In some embodiments, the formulation is administered during the first 16 weeks of the patient's pregnancy.

[0035] In one or more embodiments, the formulation comprises a solid dosage form. In some embodiments, the formulation comprises an oral dosage form. In some embodiments, the oral dosage form comprises a tablet, a capsule, or a solution.

[0036] 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

[0037] Further features of the present invention will become apparent from the following written description and the accompanying figures, in which:

[0038] FIGS. 1A-E show the full DNA sequence of the human wild-type GLA gene (SEQ ID NO: 1);

[0039] FIG. 2 shows the wild-type α-Gal A protein (SEQ ID NO: 2);

[0040] FIG. 3 shows the nucleic acid sequence encoding the wild-type α-Gal A protein (SEQ ID NO: 3); and

[0041] FIG. 4 shows a fetal magnetic resonance imaging (MRI) image of the coronal plane during a patient's pregnancy.

DETAILED DESCRIPTION

[0042] 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.

[0043] Various aspects of the invention pertain to methods of treating Fabry disease in pregnant patients. Other aspects of the invention pertain to methods of treating Fabry disease in female patients of childbearing potential. It has been surprisingly discovered that a patient treated with migalastat for the first 16 weeks of her pregnancy gave birth to a "normal" child without defect or other abnormality. By extension, it is believed that Fabry disease may be successfully treated in pregnant patients with migalastat without adverse effect to the patient or the developing child.

[0044] Definitions

[0045] 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 formulations and methods of the invention and how to make, use and perform them.

[0046] The term "Fabry disease" refers to an X-linked inborn error of glycosphingolipid catabolism due to deficient lysosomal α-galactosidase A activity. This defect

causes accumulation of globotriaosylceramide ("GL-3", also known as Gb3 or ceramide trihexoside) and related glycosphingolipids in vascular endothelial lysosomes of the heart, kidneys, skin, and other tissues.

[0047] 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.

[0048] A "patient" or "subject" refers to a female human.

[0049] 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.

[0050] 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. 1A-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. 2. The nucleic acid sequence that only includes the coding regions (i.e. exons) of SEQ ID NO: 1 is shown in FIG. 3 (SEQ ID NO: 3).

[0051] 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.

[0052] 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.

[0053] As used herein, the term "pharmacological chaperone" ("PC") refers to any molecule including a small molecule, protein, peptide, nucleic acid, carbohydrate, etc. that specifically binds to a protein and has one or more of the following effects: (i) enhances the formation of a stable molecular conformation of the protein; (ii) induces trafficking of the protein from the ER to another cellular location, preferably a native cellular location, i.e., prevents ER-associated degradation of the protein; (iii) prevents aggregation of misfolded proteins; and/or (iv) restores or enhances at least partial wild-type function and/or activity to the protein. A compound that specifically binds to e.g., α-Gal A means that it binds to and exerts a chaperone effect on the enzyme and not a generic group of related or unrelated enzymes. More specifically, this term does not refer to endogenous chaperones, such as BiP, or to non-specific agents which have demonstrated non-specific chaperone activity against various proteins, such as glycerol, DMSO or deuterated water, i.e., chemical chaperones. In the present invention, the SPC may be a reversible competitive inhibitor.

[0054] 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.

[0055] 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.

[0056] "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).

[0057] 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 SPC. An increase in hydrolysis is indicative of increased α-Gal A activity.

[0058] 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.

[0059] 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 improvement in surrogate markers, in response to contact with an SPC. Non-limiting examples of improvements in surrogate markers for Fabry are lyso-GB3 and those disclosed in US Patent Application Publication No. US 2010-0113517.

[0060] 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 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.

[0061] The dose that achieves one or more of the aforementioned responses is a "therapeutically effective dose."

[0062] 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.

[0063] 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.

[0064] 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.

[0065] The term "pregnant" refers to a female patient who has a child or other young developing within her. The period during which a patient is pregnant may be referred to as the patient's pregnancy. As noted below, the start of a patient's pregnancy will not coincide with the gestational age of the child. Accordingly, the duration of a patient's pregnancy and the gestational age of the child resulting therefrom will be different.

[0066] The term "becomes pregnant" refers to the conception of a child or other young. In humans, this is the moment when an oocyte (ovum) and spermatozoon combine to form an embryo. As noted herein, a patient may or may not be aware that they have become pregnant.

[0067] The term "patient of childbearing potential" refers to a female patient who is pregnant or capable of becoming pregnant. A patient who is utilizing effective birth control, but is otherwise capable of becoming pregnant is still referred to as a patient of childbearing potential.

[0068] The term "known to be pregnant" refers to a patient who has tested positive as being pregnant. Suitable tests for pregnancy include, but are not limited to, urinalysis, blood tests, or ultrasound examination.

[0069] The term "effective birth control" refers to methods for preventing pregnancy which rely on physical or physiological barriers to prevent a patient from becoming pregnant ("birth control") and are effective greater than or equal to about 90% of the time when used as directed. Suitable effective birth control methods include, but are not limited to, hormonal

contraceptives (pills, shots, patches, etc.), surgical methods (vasectomy or tubal ligation), intrauterine devices (IUDs), and physical barriers (condoms, diaphragms, cervical caps, etc.).

[0070] The term "gestational age" refers to a common measure of the age of a child or young during pregnancy before birth. Gestational age is typically measured from the end of the patient's last menstrual cycle. Accordingly, a child at the start of a pregnancy may be considered to already have a gestational age of approximately 2 weeks.

[0071] The term "trimester" refers to a period of pregnancy. Pregnancies are typically divided into three trimesters of approximately equal duration. In humans, the average gestational age is 280 days or 40 weeks. The term "first trimester" refers to the period from the start of pregnancy until a gestational age of about 13 weeks. The term "second trimester" refers to the period from a gestational age of about 14 weeks until a gestational age of about 27 weeks. The "third trimester" refers to the period from a gestational age of about 28 weeks to the birth of the child.

[0072] The term "normal weight" refers to a birth weight between the 10^{th} percentile and the 90^{th} percentile of birth weight based on the child's sex and gestational age at birth. Charts of birth weight percentiles are commonly known in the art as Fenton Growth Charts. As an example, a male child born with a birth weight of 2000g at a gestational age of 33 weeks would be considered to have normal weight (50^{th} percentile), regardless of the fact that the WHO standards would consider the child to have low birth weight.

[0073] The term "birth defect" refers to physical or biochemical abnormalities which result from the use of migalastat. In other terms, "birth defects" should be understood to mean teratogenic birth defects as a result of taking migalastat. "Birth defects" should not be understood to mean abnormalities which result from other environmental influences during pregnancy or any genetic abnormalities which may be inherited (e.g. α-gal A mutations).

[0074] 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.

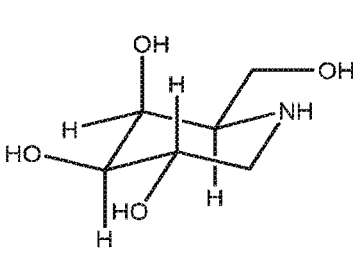
[0075] The term "migalastat" encompasses migalastat free base or a pharmaceutically acceptable salt thereof (e.g., migalastat HCl), unless otherwise indicated specifically.

[0076] Pharmacological Chaperones

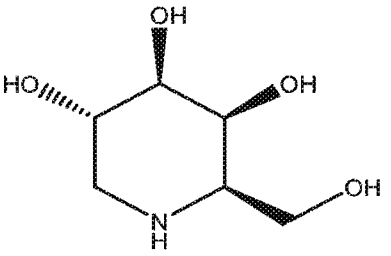
[0077] The binding of small molecule inhibitors of enzymes associated with LSDs can increase the stability of both mutant enzyme and the corresponding wild-type enzyme (see U.S. Pat. Nos. 6,274,597; 6,583,158; 6,589,964; 6,599,919; 6,916,829, and 7,141,582. In particular, administration of small molecule 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. This strategy has been shown to increase several lysosomal enzymes *in vitro* and *in vivo*, including β-glucocerebrosidase and α-glucosidase, deficiencies of which are associated with Gaucher and Pompe disease, respectively.

[0078] 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:

Date Reçue/Date Received 2023-09-28

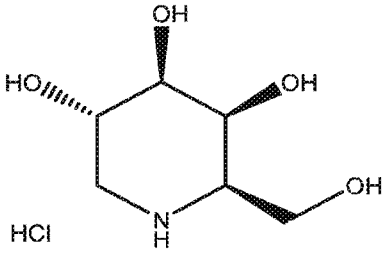


and



Migalastat free base

[0079] 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

[0080] 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.

[0081] HEK assay amenable mutations include at least those mutations listed in a pharmacological reference table (*e.g.*, the ones recited in the U.S. or International Product labels for a migalastat product such as GALAFOLD®). As used herein, "pharmacological reference table" refers to any publicly accessible written or electronic record, included in either the product label within the packaging of a migalastat product (*e.g.*, GALAFOLD®) or in a website accessible by health care providers, that conveys whether a particular mutation or variant is responsive to migalastat (*e.g.*, GALAFOLD®) PC therapy, and is not necessarily limited to written records presented in tabular form. In one embodiment of the present invention, a "pharmacological reference table" thus refers to any depository of information that includes one or more amenable mutations or variants. An exemplary pharmacological reference table for HEK assay amenable mutations can be found in the summary of product characteristics and/or prescribing information for GALAFOLD® in various countries in which GALAFOLD® is approved for use, or at a website such as www.galafoldamenabilitytable.com or www.fabrygenevariantsearch.com.

[0082] An exemplary pharmacological reference table for HEK assay amenable mutations is provided in Table 1 below. In one or more embodiments, if a double mutation is present on the same chromosome (males and females), that patient is considered HEK assay amenable if the double mutation is present in one entry in Table 1 (*e.g.*, D55V/Q57L). In some embodiments, if a double mutation is present on different chromosomes (only in females) that patient is considered HEK assay amenable if either one of the individual mutations is present in Table 1.

Table 1

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

Date Reçue/Date Received 2023-09-28

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.58G>C	c.G58C	A20P
c.59C>A	c.C59A	A20D
c.65T>G	c.T65G	V22G
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>C	c.G97C	D33H
c.97G>T	c.G97T	D33Y
c.98A>G	c.A98G	D33G
c.100A>G	c.A100G	N34D
c.100A>C	c.A100C	N34H
c.101A>C	c.A101C	N34T
c.101A>G	c.A101G	N34S
c.102T>G or c.102T>A	c.T102G or c.T102A	N34K
c.103G>C or c.103G>A	c.G103C or c.G103A	G35R
c.104G>A	c.G104A	G35E
c.104G>C	c.G104C	G35A
c.104G>T	c.G104T	G35V
c.107T>C	c.T107C	L36S
c.107T>G	c.T107G	L36W
c.108G>C or c.108G>T	c.G108C or c.G108T	L36F
c.109G>A	c.G109A	A37T
c.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.159C>G or c.159C>A	c.C159G or c.C159A	N53K
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

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
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>G	c.A170G	Q57R
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.184_185insTAG	c.184_185insTAG	S62delinsLA
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.239G>T	c.G239T	G80V
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.263A>C	c.A263C	Y88S
c.265C>T	c.C265T	L89F
c.272T>C	c.T272C	I91T
c.288G>A or c.288G>T or c.288G>C	c.G288A or c.G288T or c.G288C	M96I
c.286A>G	c.A286G	M96V
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.320A>G	c.A320G	Q107R
c.322G>A	c.G322A	A108T
c.326A>G	c.A326G	D109G
c.334C>G	c.C334G	R112G
c.335G>A	c.G335A	R112H

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.335G>T	c.G335T	R112L
c.337T>A	c.T337A	F113I
c.337T>C or c.339T>A or c.339T>G	c.T337C or c.T339A or c.T339G	F113L
c.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>G	c.T454G	Y152D
c.454T>C	c.T454C	Y152H
c.455A>G	c.A455G	Y152C
c.465T>A or c.465T>G	c.T465A or c.T465G	D155E
c.466G>T	c.G466T	A156S
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
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

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
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.567G>C or c.567G>T	c.G567C or c.G567T	L189F
c.572T>A	c.T572A	L191Q
c.580A>G	c.A580G	T194A
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.610T>G	c.T610G	W204G
c.611G>T	c.G611T	W204L
c.613C>A	c.C613A	P205T
c.613C>T	c.C613T	P205S
c.614C>T	c.C614T	P205L
c.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

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.[644A>G; 937G>T]	c.A644G/G937T	N215S/D313Y
c.646T>G	c.T646G	Y216D
c.647A>C	c.A647C	Y216S
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.682A>G	c.A682G	N228D
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.712A>G	c.A712G	S238G
c.713G>A	c.G713A	S238N
c.716T>C	c.T716C	I239T
c.717A>G	c.A717G	I239M
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.748C>A	c.C748A	Q250K
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>T	c.C770T	A257V
c.770C>G	c.C770G	A257G

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.772G>C or c.772G>A	c.G772C or c.G772A	G258R
c.773G>T	c.G773T	G258V
c.776C>A	c.C776A	P259Q
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
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

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.884T>G	c.T884G	F295C
c.886A>G	c.A886G	M296V
c.886A>T or c.886A>C	c.A886T or c.A886C	M296L
c.887T>C	c.T887C	M296T
c.888G>A or c.888G>T or c.888G>C	c.G888A or c.G888T or c.G888C	M296I
c.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
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.958A>C	c.A958C	N320H
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

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.967C>A	c.C967A	P323T
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>C	c.A989C	Q330P
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.1013A>T	c.A1013T	E338V
c.1016T>C	c.T1016C	V339A
c.1016T>A	c.T1016A	V339E
c.1027C>A	c.C1027A	P343T
c.1028C>T	c.C1028T	P343L
c.1033T>C	c.T1033C	S345P
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

Table 1

Nucleotide change	Nucleotide change	Protein sequence change
c.1124G>A	c.G1124A	G375E
c.1139C>T	c.C1139T	P380L
c.1153A>G	c.A1153G	T385A
c.1168G>A	c.G1168A	V390M
c.1171A>G	c.A1171G	K391E
c.1172A>C	c.A1172C	K391T
c.1175G>C	c.G1175C	R392T
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.1222A>T	c.A1222T	N408Y
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.1234A>C	c.A1234C	T412P
c.1235C>A	c.C1235A	T412N
c.1253A>G	c.A1253G	E418G
c.1261A>G	c.A1261G	M421V

[0083] Any PC for α-Gal A may be used in combination with any of the other embodiments of the invention, for example embodiments relating to a method of treating a patient with Fabry disease, a method of enhancing α-galactosidase A in a patient diagnosed with or suspected of having Fabry disease, use of a pharmacological chaperone for α-galactosidase A for the manufacture of a medicament for treating a patient diagnosed with Fabry disease or to a pharmacological chaperone for α-galactosidase A for use in treating a patient diagnosed with Fabry disease as well as embodiments relating to suitable doses of PCs and to the treatment of a Fabry patient who is pregnant of childbearing potential.

[0084] Formulation and Administration

[0085] 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.

[0086] The administration of migalastat or a salt of migalastat is referred to herein as "migalastat therapy".

[0087] 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.

[0088] 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 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.

[0089] 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.

[0090] 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.

[0091] 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 at least 2 weeks, such as at least 6, 12 or 16 weeks or at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 weeks. 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, 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.

[0092] 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.

[0093] 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.

[0094] In one embodiment of the invention, 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, in sterile aqueous solution for injection, or 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.

[0095] When the chaperone compound 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.

[0096] 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 monostearate and gelatin.

[0097] 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.

[0098] 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, and bicarbonate buffer, amino acids, urea, alcohols, ascorbic acid, phospholipids; proteins, such as serum albumin, collagen, and gelatin; salts such as EDTA or EGTA, and sodium chloride; liposomes; polyvinylpyrrolidone; sugars, such as dextran, mannitol, sorbitol, and glycerol; propylene glycol and polyethylene glycol (e.g., PEG-4000, PEG-6000); glycerol; glycine or other amino acids; and lipids. Buffer systems for use with the formulations include citrate; acetate; bicarbonate; and phosphate buffers. Phosphate buffer is a preferred embodiment.

[0099] 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.

[00100] 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 IV bag) or internal (e.g., a bio-erodible implant).

[00101] Embodiments relating to pharmaceutical formulations and administration may be combined with any of the other embodiments of the invention, for example embodiments relating to a method of treating a patient with Fabry disease, a method 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.

[00102] 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 lysosomal storage disorders 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).

[0100] 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.

[0101] 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.

[0102] 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.

EXAMPLES

[0103] Example 1: Patient Treated with Migalastat during Pregnancy

[0104] In October 2005, a Caucasian female was diagnosed with Fabry disease based on kidney biopsy and mutational analysis (GLA p.R112H). In 2009, the patient began treatment

for Fabry disease using agalsidase alfa (ERT). After initiation of treatment, the patient saw no progression of renal, cardiac or neurological symptoms.

[0105] In April 2012, the patient had proteinuria levels of 187 mg/24 h. In May 2012, the patient had proteinuria levels of 83 mg/24 h. Later in May 2012, the patient, now 35, began participation as part of a phase 3 clinical trial of migalastat. The patient was also taking hormonal contraceptives.

[0106] The study was a Phase 3 study of migalastat therapy in ERT-experienced Fabry patients. Eligible patients were 16-74 years old and had genetically-confirmed Fabry disease; had received ERT for ≥12 months; had a GLA mutation that resulted in a mutant protein that would respond to migalastat, based on the human embryonic kidney-293 (HEK) assay used at the time of enrollment; had an estimated glomerular filtration rate (eGFR) ≥ 30 ml/minute/1.73m^2; and had an ERT dose level and regimen that had been stable for at least 3 months.

[0107] Following eligibility-baseline assessments, the patient was randomized into a test group. The test group was planned to receive 18 months of migalastat therapy (control group continued ERT), followed by followed by an additional 12 months of migalastat therapy. The migalastat dosing regimen was 150 mg of migalastat hydrochloride every other day. The primary objective was to compare the effect of migalastat to ERT on renal function assessed by measured GFR using iohexol clearance ($mGFR_{iohexol}$) after 18 months of treatment. The secondary objectives were to compare the effect of migalastat to ERT on: renal function (assessed by eGFR and 24-hour urine protein); composite clinical outcome (assessed by time to occurrence of renal, cardiac, cerebrovascular events or death); cardiac function (assessed by echocardiography) and patient reported outcomes (pain and quality of life).

[0108] In February 2014 (21 months into the study), the patient had proteinuria levels of 78 mg/24 h. In May 2014, she had proteinuria levels of 2166 mg/24 h without exhibiting signs hypertension (131/68 mmHg). At that time, she tested negative for pregnancy by urinalysis.

[0109] In June 2014, continued proteinuria (>1000 mg/24 h) prompted a kidney biopsy and blood tests. Her pregnancy was confirmed by an ultrasound examination and estimated to be at approximately 18 weeks gestational age. In other words, it was estimated that the patient had been pregnant for about 16 weeks. Her pregnancy was despite taking hormonal

contraceptives. At that time, she tested positive for pregnancy by a blood serum analysis. Both migalastat and hormonal contraceptive treatments were stopped at that time.

[0110] In September 2014, a fetal MRI was performed. The results, provided in FIG. 4, show normal fetal development based on gestational age.

[0111] In October 2014, the child was delivered via caesarean section. The child was a female, 45 cm in length and 2.29 kg without any reported birth defects. The child had a wild-type GLA gene. The pregnancy was uneventful. In September 2015, the patient restarted ERT using agalsidase alfa by home infusion.

[0112] Summary and conclusions

[0113] As shown in the above example, a patient taking migalastat for at least the first 16 weeks of pregnancy can have an uneventful pregnancy and deliver a child of normal weight based on gestational age. This shows that patients treated with migalastat may be able to become pregnant and give birth to normal children during treatment.

[0114] The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art.

[0115] 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.

Date Reçue/Date Received 2023-09-28

What is claimed is:

1. Use of a therapeutically effective dose of about 100 mg to about 150 mg free base equivalent (FBE) of migalastat or a salt thereof at a frequency of once every other day for the treatment of Fabry disease in a pregnant patient in need.

2. The use of claim 1, further comprising administration to the patient the formulation at a frequency of once every other day during a pre-pregnancy treatment period before the patient becomes pregnant.

3. The use of claim 2, wherein the patient was not instructed to use effective birth control during the pre-pregnancy treatment period.

4. The use of claim 2, wherein the patient was not utilizing effective birth control during the pre-pregnancy treatment period.

5. The use of claim 1, wherein the patient is pregnant before initiating the treatment.

6. The use of claim 5, wherein the patient is not known to be pregnant before initiating the treatment.

7. The use of claim 1, wherein the treatment is discontinued upon identification of the patient's pregnancy.

8. The use of claim 5, wherein the patient is known to be pregnant before initiating the treatment.

9. The use of claim 1, wherein the patient's pregnancy results in a birth of a child having a gestational age of at least 37 weeks.

10. The use of claim 1, wherein the patient's pregnancy results in a birth of a child of normal weight based on a gestational age of the child.

11. The use of claim 1, wherein the patient's pregnancy results in a child without a birth defect.

12. The use of claim 1, wherein the therapeutically effective dose is about 123 mg free base equivalent (FBE) of migalastat or a salt thereof.

Date Reçue/Date Received 2023-09-28

13. The use of claim 1, wherein the therapeutically effective dose is about 123 mg of migalastat free base.

14. The use of claim 1, wherein the salt of migalastat is migalastat hydrochloride.

15. The use of claim 14, wherein the therapeutically effective dose is about 150 mg of migalastat hydrochloride.

16. The use of claim 1, wherein the formulation is for administration for at least 6 weeks during the pregnancy.

17. The use of claim 1, wherein the formulation is for administration during a first trimester of the patient's pregnancy.

18. The use of claim 1, wherein the formulation is for administration during a second trimester of the patient's pregnancy.

19. The use of claim 1, wherein the formulation is for administration during the first 16 weeks of the patient's pregnancy.

20. The use of claim 3, wherein the patient was not utilizing effective birth control during the pre-pregnancy treatment period.

Date Reçue/Date Received 2023-09-28

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cttagccctgtgacattgggtaaattacacttttttttttttttttttttgagacgggg     2880
```

FIG. 1A

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FIG. 1B

```
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```

FIG. 1C

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FIG. 1D

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```

FIG. 1E

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ANYVHSKGLK LGIYADVGNK TCAGFPGSFG YYDIDAQTFA DWGVDLLKFD GCYCDSLENL  180
ADGYKHMSLA LNRTGRSIVY SCEWPLYMWP FQKPNYTEIR QYCNHWRNFA DIDDSWKSIK  240
SILDWTSFNQ ERIVDVAGPG GWNDPDMLVI GNFGLSWNQQ VTQMALWAIM AAPLFMSNDL  300
RHISPQAKAL LQDKDVIAIN QDPLGKQGYQ LRQGDNFEVW ERPLSGLAWA VAMINRQEIG  360
GPRSYTIAVA SLGKGVACNP ACFITQLLPV KRKLGFYEWT SRLRSHINPT GTVLLQLENT  420
MQMSLKDLL                                                          429
```

FIG. 2

```
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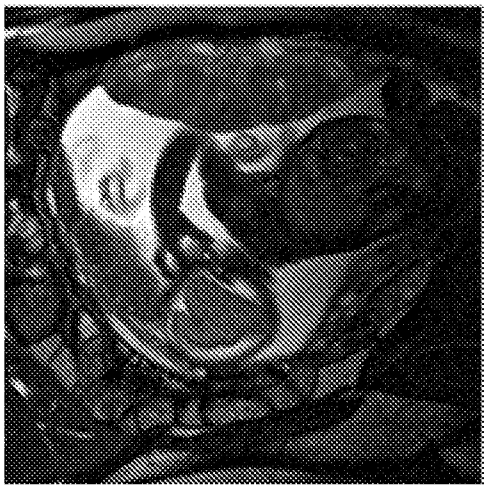
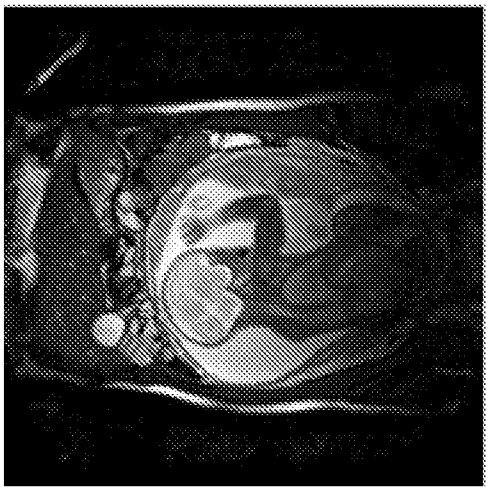
FIG. 3





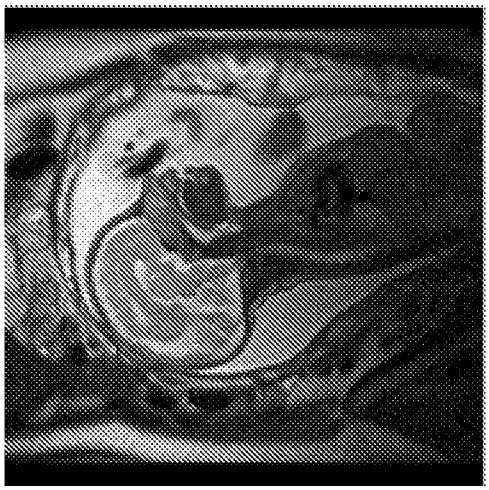


FIG. 4