1. NAME OF THE MEDICINAL PRODUCT

Galafold 123 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains migalastat hydrochloride equivalent to 123 mg migalastat.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule with an opaque blue cap and opaque white body printed with "A1001" .

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Galafold 123 mg is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in section 5.1).

4.2 Posology and method of administration

Treatment with Galafold 123 mg should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease. Galafold 123 mg is not intended for concomitant use with enzyme replacement therapy (see section 4.4).

Posology

The recommended dosage regimen in adults and adolescents 16 years and older is 123 mg migalastat (1 capsule) once every other day at the same time of day.

Missed dose
Galafold 123 mg should not be taken on 2 consecutive days. If a dose is missed entirely for the day, the patient should take the missed dose of Galafold 123mg only if it is within 12 hours of the normal time the dose is taken. If more than 12 hours has passed the patient should resume taking Galafold 123 mg at the next planned dosing day and time according to the every other day dosing schedulec

Paediatric population
The safety and efficacy of Galafold 123 mg in children aged 0 to 15 years has not yet been established. No data are available.

Special populations

Elderly population
No dosage adjustment is required based on age (see section 5.2).

Renal impairment
Galafold 123 mg is not recommended for use in patients with Fabry disease who have estimated GFR less than 30 mL/min/1.73 m^2 (see section 5.2).

Hepatic impairment
No dosage adjustment of Galafold 123 mg is required in patients with hepatic impairment (see section 5.2).

Method of administration

For oral use. Galafold 123 mg exposure is decreased by approximately 40% when taken with food and therefore should not be consumed at least 2 hours before ~~or~~ and 2 hours after taking Galafold 123mg to give a minimum 4 hours fast. Clear liquids, including carbonated drinks, can be consumed during this period. Galafold123 mg should be taken every other day at the same time of day to ensure optimal benefits to the patient.

Capsules must be swallowed whole. The capsules must not be cut, crushed, or chewed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

It is advised to periodically monitor renal function, echocardiographic parameters and biochemical markers (every 6 months) in patients initiated on or switched to Galafold123 mg. In case of meaningful clinical deterioration, further clinical evaluation or discontinuation of treatment with Galafold 123 mg should be considered.

Galafold 123 mg is not indicated for use in patients with non-amenable mutations (see section 5.1).

No reduction in proteinuria was observed in patients treated with Galafold.

Galafold 123 mg is not recommended for use in patients with severe renal insufficiency, defined as estimated GFR less than 30 mL/min/1.73m^2 (see section 5.2).

Limited data suggest that co-administration of a single dose of Galafold 123 mg and a standard enzyme replacement therapy infusion results in an increased exposure to agalsidase of up to 5-fold. This study also indicated that agalsidase has no effect on the pharmacokinetics of migalastat. Galafold 123 mg is not intended for concomitant use with enzyme replacement therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Based upon *in vitro* data, migalastat is not an inducer of CYP1A2, 2B6, or 3A4. Furthermore, migalastat is not an inhibitor or a substrate of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5. Migalastat is not a substrate for MDR1 or BCRP, nor is it an inhibitor of BCRP, MDR1, or BSEP human efflux transporters. In addition, migalastat is not a substrate for MATE1, MATE2-K, OAT1, OAT3, or OCT2, nor is it an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K human uptake transporters.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
Galafold 123 mg is not recommended in women of childbearing potential not using contraception.

Pregnancy
There are limited data from the use of Galafold 123 mg in pregnant women. In rabbits, developmental toxicity was observed only at maternally toxic doses (see section 5.3). Galafold 123 mg is not recommended during pregnancy.

Breast-feeding
It is not known whether Galafold 123 mg is secreted in human milk. However, migalastat has been shown to be expressed in the milk of lactating rats. Accordingly, a risk of migalastat exposure to the breast-feeding infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Galafold, 123 mg taking into account the benefit of breast-feeding for the child relative to the benefit of therapy for the mother.

Fertility
The effects of Galafold 123 mg on fertility in humans have not been studied. Transient and fully reversible infertility in male rats was associated with migalastat treatment at all doses assessed. Complete reversibility was seen after 4 weeks off-dose. Similar findings have been noted pre-clinically following treatment with other iminosugars (see section 5.3). Migalastat did not affect fertility in female rats.

4.7 Effects on ability to drive and use machines

Galafold 123 mg has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reaction was headache, which was experienced by approximately 10% of patients who received Galafold 123 mg.

Tabulated list of adverse reactions
Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing frequency within each System Organ Class.

Table 1: Adverse reactions with Galafold 123 mg in clinical trials

System Organ Class	Very common	Common
Psychiatric disorders		Depression
Nervous system disorders	Headache	Paraesthesia Dizziness Hypoaesthesia
Ear and labyrinth disorders		Vertigo
Cardiac disorders		Palpitations
Respiratory, thoracic, and mediastinal disorders		Dyspnoea Epistaxis

Gastrointestinal disorders		Diarrhoea Nausea Abdominal pain Constipation Dry mouth Defaecation urgency Dyspepsia
Skin and subcutaneous tissue disorders		Rash Pruritus
Musculoskeletal and connective tissue disorders		Muscle spasms Myalgia Torticollis Pain in extremity
Renal and urinary disorders		Proteinuria
General disorders and administration site conditions		Fatigue Pain
Investigations		Blood Creatine Phosphokinase increased Weight increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

4.9 Overdose

In case of overdose, general medical care is recommended. Headache and dizziness were the most common adverse reactions reported at doses of Galafold 123 mg of up to 1250 mg and 2000 mg, respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: { Various alimentary tract and metabolism products };
ATC code: { A16AX14 }

Fabry disease is a progressive X-linked lysosomal storage disorder which affects males and females. Fabry disease-causing mutations in the *GLA* gene result in a deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A) that is required for glycosphingolipid substrate (e.g., GL-3, lyso-Gb_3) metabolism. Reduced α-Gal A activity is, therefore, associated with the progressive accumulation of substrate in vulnerable organs and tissues, which leads to the morbidity and mortality associated with Fabry disease.

Mechanism of action

Certain *GLA* mutations can result in the production of abnormally folded and unstable mutant forms of α-Gal A. Migalastat is a pharmacological chaperone that is designed to selectively and reversibly bind with high affinity to the active sites of certain mutant forms of α-Gal A, the genotypes of which are referred to as amenable mutations. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum and facilitates their proper trafficking to lysosomes. Once in lysosomes dissociation of migalastat restores α-Gal A activity, leading to the catabolism of GL-3 and related substrates.

The *GLA* mutations amenable and not amenable to treatment with Galafold 123 mg are listed in Table 2 and Table 3 respectively below.

The nucleotide changes listed represent potential DNA sequence changes that result in the amino acid mutation. The amino acid mutation (protein sequence change) is most relevant when determining amenability. If a double mutation is present on the same chromosome (males and females), that patient is amenable if the double mutation is present in one entry in Table 2 (e.g., D55V/Q57L). If a double mutation is present on different chromosomes (only in females) that patient is amenable if either one of the individual mutations is present in Table 2.

Table 2: Galafold 123 mg **(migalastat) amenability table**

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
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

Table 2: Galafold 123 mg **(migalastat) amenability table**

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 2: Galafold 123 mg **(migalastat) amenability table**

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 2: Galafold 123 mg **(migalastat) amenability table**

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 2: Galafold 123 mg **(migalastat) amenability table**

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 2: Galafold 123 mg **(migalastat) amenability table**

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 2: Galafold 123 mg **(migalastat) amenability table**

Nucleotide change	Nucleotide change	Protein sequence change
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
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

Table 2: Galafold 123 mg **(migalastat) amenability table**

Nucleotide change	Nucleotide change	Protein sequence change
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

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The mutations not amenable to treatment with Galafold 123 mg are listed in Table 3 below.

UNKNOWN in the column of 'protein sequence change' indicate that the changes to the protein sequence caused by the mutations cannot be readily deduced from the nucleotide changes and need to be experimentally determined. In these cases, the question marks in the accompanying parentheses indicate that the changes provided therein have not been experimentally confirmed and may not be correct.

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.1A>C or c.1A>T	c.A1C or c.A1T	M1L
c.1A>G	c.A1G	M1V
c.2T>G	c.T2G	M1R
c.2T>C	c.T2C	M1T
c.2T>A	c.T2A	M1K
c.3G>A or c.3G>T or c.3G>C	c.G3A or c.G3T or c.G3C	M1I
c.19G>T	c.G19T	E7X
c.41T>C	c.T41C	L14P
c.43G>C	c.G43C	A15P
c.44C>A	c.C44A	A15E
c.46C>G	c.C46G	L16V
c.47T>A	c.T47A	L16H
c.47T>C	c.T47C	L16P
c.47T>G	c.T47G	L16R
c.53T>C	c.T53C	F18S
c.56T>A	c.T56A	L19Q
c.56T>C	c.T56C	L19P
c.59C>T	c.C59T	A20V
c.61C>T	c.C61T	L21F
c.62T>C	c.T62C	L21P
c.62T>G	c.T62G	L21R
c.71G>A or c.72G>A	c.G71A or c.G72A	W24X

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.92C>T	c.C92T	A31V
c.109G>C	c.G109C	A37P
c.118C>G	c.C118G	P40A
c.118C>T	c.C118T	P40S
c.119C>A	c.C119A	P40H
c.119C>G	c.C119G	P40R
c.119C>T	c.C119T	P40L
c.127G>C	c.G127C	G43R
c.127G>A	c.G127A	G43S
c.128G>A	c.G128A	G43D
c.128G>T	c.G128T	G43V
c.131G>A or c.132G>A	c.G131A or c.G132A	W44X
c.132G>T or c.132G>C	c.G132T or c.G132C	W44C
c.134T>C	c.T134C	L45P
c.134T>G	c.T134G	L45R
c.134_138delTGCACinsGCTCG	c.134_138delTGCACinsGCTCG	L45R/H46S
c.136C>T	c.C136T	H46Y
c.137A>T	c.A137T	H46L
c.137A>G	c.A137G	H46R
c.[138C>G; 153G>T; 167G>T]	c.C138G/G153T/G167T	H46Q/M51I/C56F
c.139T>C or c.139T>A	c.T139C or c.T139A	W47R
c.139T>G	c.T139G	W47G
c.140G>A or 141G>A	c.G140A or G141A	W47X
c.140G>T	c.G140T	W47L
c.141G>C or c.141G>T	c.G141C or c.G141T	W47C
c.142G>A	c.G142A	E48K
c.144G>T or c.144G>C	c.G144T or c.G144C	E48D
c.145C>T	c.C145T	R49C
c.145C>A	c.C145A	R49S
c.145C>G	c.C145G	R49G
c.146G>C	c.G146C	R49P
c.146G>T	c.G146T	R49L
c.149T>G	c.T149G	F50C
c.154T>G	c.T154G	C52G
c.154T>C	c.T154C	C52R
c.154T>A or c.155G>C	c.T154A or c.G155C	C52S
c.155G>A	c.G155A	C52Y
c.156C>A	c.C156A	C52X
c.156C>G	c.C156G	C52W
c.166T>G	c.T166G	C56G
c.166T>A or c.167G>C	c.T166A or c.G167C	C56S
c.168C>A	c.C168A	C56X
c.187T>C	c.T187C	C63R
c.188G>A	c.G188A	C63Y
c.187T>A or c.188G>C	c.T187A or c.G188C	C63S
c.194G>C (putative splicing site)	c.G194C (putative splicing site)	UNKNOWN (S65T)
c.194G>T (putative splicing site)	c.G194T (putative splicing site)	UNKNOWN (S65I)
c.196G>C	c.G196C	E66Q
c.[196G>C; 1061T>A]	c.G196C/T1061A	E66Q/I354K

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.202C>T	c.C202T	L68F
c.206T>C	c.T206C	F69S
c.208A>G	c.A208G	M70V
c.215T>G	c.T215G	M72R
c.218C>A	c.C218A	A73E
c.227T>G	c.T227G	M76R
c.228G>C or c.228G>A or c.228G>T	c.G228C or c.G228A or c.G228T	M76I
c.233C>G or c.233C>A	c.C233G or c.C233A	S78X
c.235G>T	c.G235T	E79X
c.241T>C or c.241T>A	c.T241C or c.T241A	W81R
c.242G>A or c.243G>A	c.G242A or c.G243A	W81X
c.242G>C	c.G242C	W81S
c.243G>T or c.243G>C	c.G243T or c.G243C	W81C
c.244A>T	c.A244T	K82X
c.256T>G	c.T256G	Y86D
c.256T>C	c.T256C	Y86H
c.257A>G	c.A257G	Y86C
c.258T>G or c.258T>A	c.T258G or c.T258A	Y86X
c.262T>G	c.T262G	Y88D
c.266T>A	c.T266A	L89H
c.266T>C	c.T266C	L89P
c.266T>G	c.T266G	L89R
c.268T>C	c.T268C	C90R
c.269G>A	c.G269A	C90Y
c.270C>A	c.C270A	C90X
c.274G>C	c.G274C	D92H
c.274G>A	c.G274A	D92N
c.274G>T	c.G274T	D92Y
c.275A>G	c.A275G	D92G
c.275A>T	c.A275T	D92V
c.277G>A	c.G277A	D93N
c.277G>T	c.G277T	D93Y
c.278A>G	c.A278G	D93G
c.278A>T	c.A278T	D93V
c.279C>G or c.279C>A	c.C279G or c.C279A	D93E
c.280T>G	c.T280G	C94G
c.280T>A or c.281G>C	c.T280A or c.G281C	C94S
c.[280T>A; 281G>C]	c.T280A/G281C	C94T
c.281G>A	c.G281A	C94Y
c.281G>T	c.G281T	C94F
c.283T>G	c.T283G	W95G
c.284G>A or c.285G>A	c.G284A or c.G285A	W95X
c.284G>T	c.G284T	W95L
c.284G>C	c.G284C	W95S
c.285G>T or c.285G>C	c.G285T or c.G285C	W95C
c.295C>T	c.C295T	Q99X
c.299G>A	c.G299A	R100K
c.299G>C	c.G299C	R100T

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.305C>G or c.305C>A	c.C305G or c.C305A	S102X
c.307G>C	c.G307C	E103Q
c.307G>T	c.G307T	E103X
c.317T>G	c.T317G	L106R
c.319C>T	c.C319T	Q107X
c.320A>T	c.A320T	Q107L
c.331C>T	c.C331T	Q111X
c.334C>T	c.C334T	R112C
c.334C>A	c.C334A	R112S
c.338T>C	c.T338C	F113S
c.347G>T	c.G347T	G116V
c.350T>G	c.T350G	I117S
c.355C>T	c.C355T	Q119X
c.354_368del15	c.354_368del15	Q119_Y123del5
c.358C>G	c.C358G	L120V
c.[358C>T; 359T>C]	c.C358T/T359C	L120S
c.359T>C	c.T359C	L120P
c.[359T>C; 361G>A]	c.T359C/G361A	L120P/A121T
c.361G>C	c.G361C	A121P
c.369T>G or c.369T>A	c.T369G or c.T369A	Y123X
c.371T>A	c.T371A	V124D
c.374A>C	c.A374C	H125P
c.379A>T	c.A379T	K127X
c.386T>C	c.T386C	L129P
c.389A>G	c.A389G	K130R
c.392T>A	c.T392A	L131Q
c.392T>C	c.T392C	L131P
c.394G>A or c.394G>C	c.G394A or c.G394C	G132R
c.395G>A	c.G395A	G132E
c.395G>C	c.G395C	G132A
c.398T>A	c.T398A	I133N
c.400T>C	c.T400C	Y134H
c.400T>G	c.T400G	Y134D
c.401A>C	c.A401C	Y134S
c.402T>G or c.402T>A	c.T402G or c.T402A	Y134X
c.406G>C	c.G406C	D136H
c.406G>T	c.G406T	D136Y
c.412G>A or c.412G>C	c.G412A or c.G412C	G138R
c.413G>A	c.G413A	G138E
c.416A>C	c.A416C	N139T
c.422C>A	c.C422A	T141N
c.422C>T	c.C422T	T141I
c.424T>C	c.T424C	C142R
c.425G>A	c.G425A	C142Y
c.426C>A	c.C426A	C142X
c.426C>G	c.C426G	C142W
c.427G>C	c.G427C	A143P
c.439G>A or c.439G>C	c.G439A or c.G439C	G147R
c.440G>A	c.G440A	G147E

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.443G>A	c.G443A	S148N
c.442A>C or c.444T>A or c.444T>G	c.A442C or c.T444A or c.T444G	S148R
c.453C>G or c.453C>A	c.C453G or c.C453A	Y151X
c.456C>A or c.456C>G	c.C456A or c.C456G	Y152X
c.463G>C	c.G463C	D155H
c.467C>A	c.C467A	A156D
c.469C>T	c.C469T	Q157X
c.484T>C or c.484T>A	c.T484C or c.T484A	W162R
c.485G>A or c.486G>A	c.G485A or c.G486A	W162X
c.485G>T	c.G485T	W162L
c.486G>C or c.486G>T	c.G486C or c.G486T	W162C
c.488G>T	c.G488T	G163V
c.491T>G	c.T491G	V164G
c.493G>T	c.G493T	D165Y
c.494A>T	c.A494T	D165V
c.500T>A	c.T500A	L167Q
c.500T>C	c.T500C	L167P
c.503A>G	c.A503G	K168R
c.504A>C or c.504A>T	c.A504C or c.A504T	K168N
c.508G>A	c.G508A	D170N
c.508G>C	c.G508C	D170H
c.509A>G	c.A509G	D170G
c.509A>T	c.A509T	D170V
c.511G>C	c.G511C	G171R
c.511G>T	c.G511T	G171C
c.512G>A	c.G512A	G171D
c.514T>G	c.T514G	C172G
c.514T>C	c.T514C	C172R
c.514T>A or c.515G>C	c.T514A or c.G515C	C172S
c.515G>T	c.G515T	C172F
c.515G>A	c.G515A	C172Y
c.516T>G	c.T516G	C172W
c.519C>A or c.519C>G	c.C519A or c.C519G	Y173X
c.522T>A	c.T522A	C174X
c.523G>A	c.G523A	D175N
c.530T>A	c.T530A	L177X
c.547G>A (putative splicing site)	c.G547A (putative splicing site)	UNKNOWN (G183S)
c.548G>T	c.G548T	G183V
c.552T>A or c.552T>G	c.T552A or c.T552G	Y184X
c.553A>T	c.A553T	K185X
c.557A>C	c.A557C	H186P
c.560T>G	c.T560G	M187R
c.572T>C	c.T572C	L191P
c.588A>T or c.588A>C	c.A588T or c.A588C	R196S
c.601T>C	c.T601C	S201P
c.604T>C	c.T604C	C202R
c.605G>A	c.G605A	C202Y
c.606T>G	c.T606G	C202W

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.607G>A	c.G607A	E203K
c.610T>C or c.610T>A	c.T610C or c.T610A	W204R
c.611G>A or 612G>A	c.G611A or G612A	W204X
c.612G>T or c.612G>C	c.G612T or c.G612C	W204C
c.614C>G	c.C614G	P205R
c.617T>C	c.T617C	L206P
c.620A>G	c.A620G	Y207C
c.626G>A	c.G626A	W209X
c.634C>T	c.C634T	Q212X
c.639G>A (putative splicing site)	c.G639A (putative splicing site)	UNKNOWN
c.[644A>G; 811G>A]	c.A644G/G811A	N215S/G271S
c.[644A>G; 811G>A; 937G>T]	c.A644G/G811A/G937T	N215S/G271S/D313Y
c.648T>A or c.648T>G	c.T648A or c.T648G	Y216X
c.658C>T	c.C658T	R220X
c.661C>T	c.C661T	Q221X
c.666C>A or c.666C>G	c.C666A or c.C666G	Y222X
c.667T>G	c.T667G	C223G
c.667T>C	c.T667C	C223R
c.668G>A	c.G668A	C223Y
c.670A>G	c.A670G	N224D
c.674A>G	c.A674G	H225R
c.676T>C or c.676T>A	c.T676C or c.T676A	W226R
c.677G>A or c.678G>A	c.G677A or c.G678A	W226X
c.678G>T or c.678G>C	c.G678T or c.G678C	W226C
c.679C>T	c.C679T	R227X
c.680G>A	c.G680A	R227Q
c.680G>C	c.G680C	R227P
c.688G>A	c.G688A	A230T
c.691G>A	c.G691A	D231N
c.692A>G	c.A692G	D231G
c.692A>T	c.A692T	D231V
c.695T>G	c.T695G	I232S
c.700G>T	c.G700T	D234Y
c.701A>T	c.A701T	D234V
c.702T>G or c.702T>A	c.T702G or c.T702A	D234E
c.704C>A	c.C704A	S235Y
c.704C>G	c.C704G	S235C
c.704C>T	c.C704T	S235F
c.706T>C or c.706T>A	c.T706C or c.T706A	W236R
c.707G>A or c.708G>A	c.G707A or c.G708A	W236X
c.707G>T	c.G707T	W236L
c.708G>C or c.708G>T	c.G708C or c.G708T	W236C
c.712A>C or c.714T>A or c.714T>G	c.A712C or c.T714A or c.T714G	S238R
c.718A>T	c.A718T	K240X
c.734G>A or c.735G>A	c.G734A or c.G735A	W245X
c.734G>T	c.G734T	W245L
c.739T>C	c.T739C	S247P
c.748C>T	c.C748T	Q250X

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.751G>T	c.G751T	E251X
c.755G>C	c.G755C	R252T
c.770C>A	c.C770A	A257D
c.778G>C or c.778G>A	c.G778C or c.G778A	G260R
c.782G>A	c.G782A	G261D
c.782G>T	c.G782T	G261V
c.784T>A or c.784T>C	c.T784A or c.T784C	W262R
c.785G>A or c.786G>A	c.G785A or c.G786A	W262X
c.785G>T	c.G785T	W262L
c.786G>C or c.786G>T	c.G786C or c.G786T	W262C
c.789T>A or c.789T>G	c.T789A or c.T789G	N263K
c.790G>T; c.805G>A	c.G790T/G805A	D264Y/V269M
c.791A>C	c.A791C	D264A
c.791A>T	c.A791T	D264V
c.793C>T	c.C793T	P265S
c.794C>G	c.C794G	P265R
c.796G>C	c.G796C	D266H
c.796G>T	c.G796T	D266Y
c.796G>A	c.G796A	D266N
c.797A>C	c.A797C	D266A
c.797A>G	c.A797G	D266G
c.797A>T	c.A797T	D266V
c.798T>A or c.798T>G	c.T798A or c.T798G	D266E
c.800T>G	c.T800G	M267R
c.801G>A (putative splicing site)	c.G801A (putative splicing site)	UNKNOWN (M267I)
c.803T>C	c.T803C	L268S
c.806T>A	c.T806A	V269E
c.[806T>G; 937G>T]	c.T806G/G937T	V269G/D313Y
c.808A>T	c.A808T	I270F
c.811G>T	c.G811T	G271C
c.812G>T	c.G812T	G271V
c.815A>G	c.A815G	N272S
c.816C>A or c.816C>G	c.C816A or c.C816G	N272K
c.817T>C or c.819T>A or c.819T>G	c.T817C or c.T819A or c.T819G	F273L
c.820G>A	c.G820A	G274S
c.820G>T	c.G820T	G274C
c.821G>T	c.G821T	G274V
c.823C>T	c.C823T	L275F
c.824T>A	c.T824A	L275H
c.826A>G	c.A826G	S276G
c.826A>T	c.A826T	S276C
c.830G>A or c.831G>A	c.G830A or c.G831A	W277X
c.835C>T	c.C835T	Q279X
c.835C>A	c.C835A	Q279K
c.836A>G	c.A836G	Q279R
c.837G>C or c.837G>T	c.G837C or c.G837T	Q279H
c.838C>T	c.C838T	Q280X
c.845C>A	c.C845A	T282N

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.847C>T	c.C847T	Q283X
c.848A>C	c.A848C	Q283P
c.848A>G	c.A848G	Q283R
c.853G>C	c.G853C	A285P
c.854C>A	c.C854A	A285D
c.859T>C or c.859T>A	c.T859C or c.T859A	W287R
c.859T>G	c.T859G	W287G
c.860G>A or c.861G>A	c.G860A or c.G861A	W287X
c.861G>C or c.861G>T	c.G861C or c.G861T	W287C
c.863C>A	c.C863A	A288D
c.865A>T	c.A865T	I289F
c.871G>C	c.G871C	A291P
c.874G>A	c.G874A	A292T
c.874G>C	c.G874C	A292P
c.875C>T	c.C875T	A292V
c.877C>G	c.C877G	P293A
c.877C>T	c.C877T	P293S
c.878C>A	c.C878A	P293H
c.878C>T	c.C878T	P293L
c.881T>G or c.881T>A	c.T881G or c.T881A	L294X
c.890C>G	c.C890G	S297C
c.890C>T	c.C890T	S297F
c.892A>C	c.A892C	N298H
c.894T>G or c.894T>A	c.T894G or c.T894A	N298K
c.896A>G	c.A896G	D299G
c.899T>A	c.T899A	L300H
c.901C>T	c.C901T	R301X
c.916C>T	c.C916T	Q306X
c.929T>G	c.T929G	L310R
c.931C>T	c.C931T	L311F
c.932T>C	c.T932C	L311P
c.932T>G	c.T932G	L311R
c.934C>T	c.C934T	Q312X
c.935A>C	c.A935C	Q312P
c.947T>A	c.T947A	V316E
c.949A>T	c.A949T	I317F
c.950T>A	c.T950A	I317N
c.950T>G	c.T950G	I317S
c.958A>T	c.A958T	N320Y
c.960T>G or c.960T>A	c.T960G or c.T960A	N320K
c.961C>G	c.C961G	Q321E
c.961C>T	c.C961T	Q321X
c.963_964GG>CA	c.G963C/G964A	Q321H/D322N
c.974G>A	c.G974A	G325D
c.979C>A	c.C979A	Q327K
c.982G>A or c.982G>C	c.G982A or c.G982C	G328R
c.982G>T	c.G982T	G328W
c.983G>A	c.G983A	G328E
c.983G>T	c.G983T	G328V

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.988C>T	c.C988T	Q330X
c.997C>T	c.C997T	Q333X
c.998A>G	c.A998G	Q333R
c.1012G>T	c.G1012T	E338X
c.1016T>G	c.T1016G	V339G
c.1018T>C or c.1018T>A	c.T1018C or c.T1018A	W340R
c.1019G>C	c.G1019C	W340S
c.1019G>A or c.1020G>A	c.G1019A or c.G1020A	W340X
c.1021G>A	c.G1021A	E341K
c.1021G>T	c.G1021T	E341X
c.1023A >C or c.1023A>T	c.A1023C or c.A1023T	E341D
c.1024C>G	c.C1024G	R342G
c.1024C>T	c.C1024T	R342X
c.1025G>A	c.G1025A	R342Q
c.1025G>C	c.G1025C	R342P
c.1025G>T	c.G1025T	R342L
c.1031T>C	c.T1031C	L344P
c.1034C>G or c.1034C>A	c.C1034G or c.C1034A	S345X
c.1042G>C	c.G1042C	A348P
c.1045T>C or c.1045T>A	c.T1045C or c.T1045A	W349R
c.1046G>A or c.1047G>A	c.G1046A or c.G1047A	W349X
c.1048G>C	c.G1048C	A350P
c.1054G>C	c.G1054C	A352P
c.1055C>A	c.C1055A	A352D
c.1058T>G	c.T1058G	M353R
c.1065C>A or c.1065C>G	c.C1065A or c.C1065G	N355K
c.1069C>T	c.C1069T	Q357X
c.1072G>A	c.G1072A	E358K
c.1081G>T	c.G1081T	G361X
c.1081G>A or c.1081G>C	c.G1081A or c.G1081C	G361R
c.1088G>C	c.G1088C	R363P
c.1095T>A or c.1095T>G	c.T1095A or c.T1095G	Y365X
c.1115T>A	c.T1115A	L372Q
c.1115T>C	c.T1115C	L372P
c.1115T>G	c.T1115G	L372R
c.1117G>C	c.G1117C	G373R
c.1118G>A	c.G1118A	G373D
c.1124_1129del	c.1124_1129del	G375_V376del
c.1129_1140dup	c.1129_1140dup	A377_P380dup
c.1130C>A	c.C1130A	A377D
c.1132T>C	c.T1132C	C378R
c.1133G>A	c.G1133A	C378Y
c.1144T>C	c.T1144C	C382R
c.1145G>A	c.G1145A	C382Y
c.1146C>G	c.C1146G	C382W
c.1147T>C or c.1149C>G or c.1149C>A	c.T1147C or c.C1149G or c.C1149A	F383L
c.1151T>A	c.T1151A	I384N
c.1153A>C	c.A1153C	T385P

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.1156C>T	c.C1156T	Q386X
c.1157A>C	c.A1157C	Q386P
c.1163T>C	c.T1163C	L388P
c.1165C>G	c.C1165G	P389A
c.1166C>G	c.C1166G	P389R
c.1166C>T	c.C1166T	P389L
c.1181_1183dup	c.1181_1183dup	L394_G395insV
c.1187T>A	c.T1187A	F396Y
c.1192G>T	c.G1192T	E398X
c.1193A>C	c.A1193C	E398A
c.1196G>A or c.1197G>A	c.G1196A or c.G1197A	W399X
c.1196G>C	c.G1196C	W399S
c.1202C>G or c.1202C>A	c.C1202G or c.C1202A	S401X
c.1215T>A	c.T1215A	S405R
c.1217A>G	c.A1217G	H406R
c.1219A>G	c.A1219G	I407V
c.1220T>A	c.T1220A	I407K
c.1220T>G	c.T1220G	I407R
c.1226_1231del	c.1226_1231del	p.409_410delinsR
c.1228A>C	c.A1228C	T410P
c.1229C>A	c.C1229A	T410K
c.1241T>C	c.T1241C	L414S
c.1243C>T	c.C1243T	L415F
c.1244T>C	c.T1244C	L415P
c.1246C>T	c.C1246T	Q416X
c.1247A>C	c.A1247C	Q416P
c.1247_1248CT>AA	c.C1247A/T1248A	L417K
c.1250T>G	c.T1250G	L417R
c.1250T>C	c.T1250C	L417P
c.1288T>C	c.T1288C	X430Q
g.941_5845del	c.1-179_369+577del	p.?(Exon1_2del)
g.?_?del	c.?_?	UNKNOWN (del Exon1_2?)
c.18delA	c.18delA	p.P6fs*114
c.26delA	c.26delA	p.H9Lfs*111
c.32delG	c.32delG	p.G11Afs*109
c.33delC	c.33delC	p.G11fs*109
c.34_42del	c.34_42del	p.C12_L14del
c.34_57del	c.34_57del	p.C12_L19del
c.35_47del	c.35_47del	p.C12Ffs*104
c.42_48delTGCGCTT	c.42_48delTGCGCTT	p.L14Sfs*12
c.58_72del	c.58_72del	p.A20_W24del
c.58_83del	c.58_83del	p.A20_G28delfs*2
c.85dupG	c.85dupG	p.A29Gfs*1
c.89delG	c.89delG	p.R30Kfs*89
c.123delC	c.123delC	p.T41fs*79
c.123_126dupCATG	c.123_126dupCATG	p.G43Hfs*13
c.124_125del	c.124_125del	p.M42Gfs*12
c.125_137del	c.125_137del	p.M42Tfs*74

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.147_148insCCC	c.147_148insCCC	p.49insP
c.147_148insCGC	c.147_148insCGC	p.R49ins
c.154delT	c.154delT	p.C52Afs*68
c.157_160delAACC	c.157_160delAACC	p.C52fs*67
c.162delT	c.162delT	p.L54fs*66
c.172delG	c.172delG	p.E58Kfs*61
c.181_182dupA	c.181_182dupA	p.D61Efs*5
c.184delT	c.184delT	p.S62Pfs*58
c.186delC	c.186delC	p.S62fs*58
g.2594_10904dup	c.195-2500_999+197dup	UNKNOWN
g.3422_6041delinsCG	c.194+2049_369+773del2620insCG	UNKNOWN
g.?_?del	c.195-?_547+?del	UNKNOWN (del Exon2_3?)
g.?_?dup	c.?_?dup	UNKNOWN (Exon2_4dup?)
g.2934_6378del	c.194+1561_370-891del	UNKNOWN (E66_Y123del; del Exon2?)
g.3396_6012del	c.194+2023_370-1257del	UNKNOWN (E66_Y123del; del Exon2?)
g.3260_6410del	c.194+1887_370-859del	UNKNOWN (E66_Y123del; del Exon2?)
g.2979_6442del	c.194+1606_369+1174del	UNKNOWN (E66_Y123del; del Exon2)
c.210insT	c.210insT	p.E71X
c.214delA	c.214delA	p.M72Wfs*47
c.256delT	c.256delT	p.Y88Mfs*42
g.5052_5079del28	g.5052_5079del28	UNKNOWN
g.5106_5919delins231	c.207_369+651del814ins231	UNKNOWN (del Exon2?)
c.259_276del	c.259_276del	p.87_92del
c.267_268dupCT	c.267_268dupCT	p.C90Sfs*31
c.270delC	c.270delC	p.C90X
c.281_286delinsT	c.281_286delinsT	p.C94Ffs*26
c.290delC	c.290delC	p.A97Vfs*22
c.297_298del	c.297_298del	p.Q99fs*22
c.297_300delAAGA	c.297_300delAAGA	p.Q99fs*19
c.305delC	c.305delC	p.S102X
c.317_327del	c.317_327del	p.S102fs*16
c.323_324insCAGA	c.323_324insCAGA	p.D109Rfs*14
c.336del18	c.336del18	p.113del6aa
c.354_368del	c.354_368del	p.Q119_Y123del
c.358del6	c.358del6	p.120del2aa/L120H
c.363delT	c.363delT	p.A121fs*8
g.5271_9366del4096insT	c.369+3_639+954del3129insT	UNKNOWN (del Exon3 and 4?)

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
g.6009_9741del	c.369+741_640-390del	UNKNOWN (del Exon3 and 4?)
g.6547_9783del	c.369+1279_640-348del	UNKNOWN (del Exon3 and 4?)
g.6736_11545del	c.370-533_c.1290+277del	UNKNOWN (del Exon3_7?)
g.7086_7487del	c.370-183_547+41del	UNKNOWN (del Exon3?)
g.>5.5kbdel to 3UTR	c.?_?del	UNKNOWN (delExon3_3'UTR?)
c.[374A>T; 383G>A]	c.A374T/G383A	H125L/G128E
c.402delT	c.402delT	p.Y134X
c.409delG	c.409delG	p.V137Lfs*27
c.413dupG	c.413dupG	p.G138fs*2
c.421delA	c.421delA	p.T141Pfs*23
c.426dupC	c.426dupC	p.A143Rfs*13
c.452delA	c.452delA	p.Y151Sfs*13
c.457_459del	c.457_459del	p.153delD
c.477delT	c.477delT	p.F159Lfs*5
c.486_498del	c.486_498del	p.W162Cfs*1
c.512delG	c.512delG	p.G171Vfs*19
c.516insGAC	c.516insGAC	p.152insD
c.520delT	c.520delT	p.C174Vfs*17
c.560delT	c.560delT	p.M187Sfs*3
c.568delG	c.568delG	p.A190Pfs*1
c.590delG	c.590delG	p.S197Tfs*42
c.[604T>C; 644A>G]	c.T604C/A644G	p.C202R/N215S
c.606delT	c.606delT	p.C202Wfs*37
c.613_621del	c.613_621del	p.205_207del
c.614delC	c.614delC	p.P205Lfs*34
c.618_619del	c.618_619del	p.L206fs*24
c.621dupT	c.621dupT	p.M208Yfs*24
g.?_?del	c.?_?del	UNKNOWN (del Exon5_7?)
g.[10237_11932del; 11933_12083inv; 12084_12097del]	g.[10237_11932del; 11933_12083inv; 12084_12097del]	UNKNOWN
c.646dupT	c.646dupT	p.Y216Lfs*15
c.646delT	c.646delT	p.Y216Ifs*23
c.650_663dup14	c.650_663dup14	p.Q221fs*23
c.672_673ins37	c.672_673ins37	p.H225Tfs*18
c.674_732del	c.674_732del	p.H225Lfs*5
c.678delG	c.678delG	p.A230Lfs*9
c.700_702del	c.700_702del	p.D234del
c.715_717del	c.715_717del	p.delI239
c.716dupT	c.716dupT	p.I239fs*10
c.718_719del	c.718_719del	p.K240Efs*8
c.719dupA	c.719dupA	p.K240fs*9
c.722delG	c.722delG	p.S241Ifs*27

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.723dupT	c.723dupT	p. I242Yfs*8
c.736_739delinsCAA	c.736_739delinsCAA	p.T246Qfs*21
c.732delC	c.732delC	p.D244fs*24
c.741ins9	c.741ins9	p.247ins3
c.744delT	c.744delT	p.F248Lfs*20
c.744_745del	c.744_745del	p.F248Lfs*6
c.746_747del	c.746_747del	p.N249Tfs*5
c.756delA	c.756delA	p.I253Vfs*14
c.759delT	c.759delT	p.I253Mfs*15
c.760dupG	c.760dupG	p.V254Gfs*1
c.761_762del	c.761_762del	p.V254Gfs*9
c.774_775del	c.774_775del	p.G258fx*5
c.777delA	c.777delA	p.P259fs*9
c.782dupG	c.782dupG	p.G261fs*3
c.802-2_802-3delCA	c.802-2_802-3delCA	UNKNOWN
c.803_806delTAGT	c.803_806delTAGT	p.L268X
c.807delG	c.807delG	p.V269fs*12
c.833dupA	c.833dupA	p.N278Kfs*20
c.833delA	c.833delA	p.N278Ifs*3
c.833_845del	c.833_845del	p.W277fs*34
c.838_849del	c.838_849del	p.Q280_283del
c.841_844delGTAA	c.841_844delGTAA	p.Q280fs*34
c.842_844del	c.842_844del	p.V281AdelT282
c.848_851delAGAT	c.848_851delAGAT	Q283Rfs*33
c.858_863delinsTTGG	c.858_863delinsTTGG	p.W287fs*9
c.863delC	c.863delC	p.A288Vfs*29
c.881delT	c.881delT	p.L294Yfs*22
c.891dupT	c.891dupT	p.N298X
c.892_893insT	c.892_893insT	p.N298Ifs*1
c.893_894insG	c.893_894insG	p.N298Kfs*1
c.902dupG	c.902dupG	p.R301fs*13
c.909_918del	c.909_918del	p.I303Mfx*10
c.914delC	c.914delC	p.P305Lfs*11
c.931delC	c.931delC	p.L311Ffs*5
c.941_961del	c.941_961del	p.D315_Q321del
c.946delG	c.946delG	p.V316X
c.946_954dup	c.946_954dup	p.V316_A318dup
c.950_954dupTTGCC	c.950_954dupTTGCC	p.A318fs*31
c.972delG	c.972delG	p.G325Afs*21
c.974dupG	c.974dupG	p.G325fs*7
c.986delA	c.986delA	p.Y329Sfs*18
c.988delC	c.988delC	p.Q330Sfs*17
c.946_966del	c.946_966del	p.V316_D322del
c.994delA	c.994delA	p.R332Dfs*15
c.994dupA	c.994dupA	p.R332Kfs*5
c.996_999del	c.996_999del	p.R332fs*14
c.997dupC	c.997dupC	p.Q333Pfs*5
c.1011_1029del	c.1011_1029del	p.F337fs*4
c.1017_1020delins24	c.1017_1020delins24	p.V339fs*7

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.1017_1027del	c.1017_1027del	p.V339fs*5
c.1021delG	c.1021delG	p.E341Nfs*6
c.1025delG	c.1025delG	p.R342Hfs*5
c.1028delC	c.1028delC	p.343Lfs*3
c.1029_1030delTC	c.1029_1030delTC	p.P343fs*29
c.1030_1031insT	c.1030_1031insT	p.L344fs*30
c.1033_1034del	c.1033_1034del	p.S345Rfs*28
c.1037delG	c.1037delG	p.G346Afs*1
c.1040dupT	c.1040dupT	p.L347Ffs*27
c.1041dupA	c.1041dupA	p.L347fs*27
c.1042dupG	c.1042dupG	p.A348Gfs*26
c.1043_1044insG	c.1043_1044insG	p.A348fs*26
c.1049delC	c.1049delC	p.A350Vfs*1
c.1055_1056delCT	c.1055_1056delCT	p.A352Dfs*20
c.1055_1057dup	c.1055_1057dup	p.353insT
c.1057_1058del	c.1057_1058del	p.M353Dfs*20
c.1072_1074del	c.1072_1074del	p.358delE
c.1074_1075del	c.1074_1075del	p.E358Dfs*15
c.1077delT	c.1077delT	p.I359Mfs*31
c.1081_1100del	c.1081_1100del	p.G360fs*7
c.1086_1098del	c.1086_1098del	p.P362fs*24
c.1088delG	c.1088delG	p.R363Pfs*27
c.1091_1092del	c.1091_1092del	p.S364Lfs*9
c.1093dupT	c.1093dupT	p.Y365Lfs*9
c.1095delT	c.1095delT	p.Y365X
c.1096_1100del	c.1096_1100del	p.Y365fs*7
c.1102delG	c.1102delG	p.A368Qfs*21
c.1102delGinsTTATAC	c.1102delGinsTTATAC	p.A368delinsFYfs*23
c.1114_1115insTCCC	c.1114_1115insTCCC	p.G373Pfs*1
c.1122_1125del	c.1122_1125del	p.K374fs*15
c.1123_1175del	c.1123_1175del	p.G375_R392del
c.1139delC	c.1139delC	p.380Lfs*10
c.1145_1149del	c.1145_1149del	p.C382Yfs*14
c.1146_1148del	c.1146_1148del	p.383delF
c.1151_1152delinsAT	c.1151_1152delinsAT	p.I384N
c.1156_1157del	c.1156_1157del	p.Q386Afs*10
c.1167dupT	c.1167dupT	p.P389fs*9
c.1168insT	c.1168insT	p.V390fs*9
c.1176_1179del	c.1176_1179del	p.R392Sfs*1
c.1177_1178del	c.1177_1178del	p.K393Afs*4
c.1181_1192del	c.1181_1192del	p.L394_E398delinsQ
c.1187dupT	c.1187dupT	p.F396fs*2
c.1187delT	c.1187delT	p.F396Sfs*7
c.1188delC	c.1188delC	p.F396fs*7
c.1193_1196delAATG	c.1193_1196delAATG	p.E398Gfs*3
c.1201dupT	c.1201dupT	p.S401Ffs*49
c.1202dupC	c.1202dupC	p.R402Kfs*48
c.1208delT	c.1208delT	p.L403X
c.1208ins21	c.1208ins21	UNKNOWN

Table 3: Mutations not amenable to Galafold 123 mg **(migalastat)**

Nucleotide change	Nucleotide change	Protein Sequence change
c.1209_1211del	c.1209_1211del	p.404delR
c.1223delA	c.1223delA	p.N408Ifs*9
c.1235_1236del	c.1235_1236del	p.T412Sfs*37
c.1277_1278del	c.1277_1278del	p.K426Rfs*23
c.1281_1282insCTTA	c.1281_1282insCTTA	p.L429Ifs*21
c.1284_1287del	c.1284_1287del	p.L428Ffs*23
IVS1+2T>C	c.194+2T>C	UNKNOWN
IVS1+39delAT	c.194+39delAT	UNKNOWN
IVS1-1G>A	c.195-1G>A	UNKNOWN
IVS1-1G>T	c.195-1G>T	UNKNOWN
IVS1-2A>G	c.195-2A>G	UNKNOWN
IVS1-2A>G; IVS1-49T>C	c.[195-2A>G; 195-49T>C]	UNKNOWN
IVS2+1G>A	c.369+1G>A	UNKNOWN
IVS2+1G>T	c.369+1G>T	UNKNOWN
IVS2+2T>G	c.369+2T>G	UNKNOWN
IVS2-2A>G	c.370-2A>G	UNKNOWN
IVS3+1G>A	c.547+1G>A	UNKNOWN
IVS3+1G>C	c.547+1G>C	UNKNOWN
IVS3-162A>T	c.548-162A>T	UNKNOWN
IVS3-2A>G	c.548-2A>G	UNKNOWN
IVS3-1G>A	c.548-1G>A	UNKNOWN
IVS3-1G>C	c.548-1G>C	UNKNOWN
IVS3-1G>T	c.548-1G>T	UNKNOWN
IVS4+1G>A	c.639+1G>A	UNKNOWN
IVS4+1G>C	c.639+1G>C	UNKNOWN
IVS4+4A>T	c.639+4A>T	UNKNOWN
IVS4+861C>T	c.639+861C>T	UNKNOWN
IVS4+919G>A	c.639+919G>A	UNKNOWN
IVS4-859C>T	c.640-859C>T	UNKNOWN
IVS4-11T>A	c.640-11T>A	UNKNOWN
IVS4-3C>G	c.640-3C>G	UNKNOWN
IVS4-2A>T	c.640-2A>T	UNKNOWN
IVS4-1G>A	c.640-1G>A	UNKNOWN
IVS4-1G>T	c.640-1G>T	UNKNOWN
IVS5+2T>C	c.801+2T>C	UNKNOWN
IVS5+3A>G	c.801+3A>G	UNKNOWN
IVS5+3A>T	c.801+3A>T	UNKNOWN
IVS5+4A>G	c.801+4A>G	UNKNOWN
IVS5-2A>G	c.802-2A>G	UNKNOWN
IVS6+1G>T	c.999+1G>T	UNKNOWN
IVS6+2T>C	c.999+2T>C	UNKNOWN
IVS6-2A>G	c.1000-2A>G	UNKNOWN
IVS6-2A>T	c.1000-2A>T	UNKNOWN
IVS6-1G>A	c.1000-1G>A	UNKNOWN
IVS6-1G>C	c.1000-1G>C	UNKNOWN
IVS6-10G>A; IVS6-22C>T	c.[1000-10G>A; 1000-22C>T]	UNKNOWN

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Not all mutations have been tested.

Pharmacodynamic effects

Treatment with Galafold 123 mg in Phase 2 pharmacodynamic trials generally resulted in increases in endogenous α-Gal A activity in WBCs, as well as in skin and kidney for the majority of patients. In patients with amenable mutations, GL-3 levels tended to decrease in urine and in kidney interstitial capillaries.

Clinical efficacy and safety

The clinical efficacy and safety of Galafold 123 mg have been evaluated in two Phase 3 pivotal trials and an open-label extension (OLE) trial. All patients received the recommended dosage of 123 mg Galafold 123 mg every other day.

The first Phase 3 trial (ATTRACT) was a randomised open-label active comparator trial that evaluated the efficacy and safety of Galafold 123 mg compared to enzyme replacement therapy (ERT) (agalsidase beta, agalsidase alfa) in 52 male and female patients with Fabry disease who were receiving ERT prior to trial entry and who have amenable mutations (ERT-experienced trial). The study was structured in two periods. During the first period (18-months) ERT-experienced patients were randomised to switch from ERT to Galafold 123 mg or continue with ERT. The second period was an optional 12-month open-label extension in which all subjects received Galafold.

The second Phase 3 trial (FACETS) was a 6-month randomised double-blind placebo-controlled trial (through month 6) with an 18-month open-label period to evaluate the efficacy and safety of Galafold 123 mg in 50 male and female patients with Fabry disease who were naïve to ERT, or had previously been on ERT and had stopped for at least 6 months and who have amenable mutations (ERT-naïve trial).

The first OLE trial (AT1001-041) included patients from Phase 2 and Phase 3 studies and has completed. The mean extent of the marketed dose of Galafold 123mg QOD in patients completing study AT1001-041 was 3.57(±1.23) years (n=85).The maximum exposure was 5.6 years.

The second OLE trial (AT1001-042) included patients that both transferred from OLE study AT1001-041 and directly from Phase 3 study ATTRACT, and is going

Renal Function
In the ERT-experienced trial, renal function remained stable for up to 18 months of treatment with Galafold 123 mg. Mean annualised rate of change in $eGFR_{CKD-EPI}$ was -0.40 mL/min/1.73 m^2 (95% CI: -2.272, 1.478; n=34) in the Galafold 123 mg group compared to -1.03 mL/min/1.73 m^2 (95% CI: -3.636, 1.575; n=18) in the ERT group. The mean annualised rate of change from baseline in $eGFR_{CKD-EPI}$ in patients treated for 30 months with Galafold 123 mg was -1.72 mL/min/1.73 m^2 (95% CI: -2.653, -0.782; n=31).

In the ERT- naïve trial and open label extension, renal function remained stable forup to 5 years of treatment with Galafold 123 mg. After an average of 3.4 years of treatment, the mean annualised rate of change in $eGFR_{CKD-EPI}$ was ~~-0.81~~ 0.74 mL/min/1.73 m^2 (95% CI: -1.89, 40; n=41). No clinically significant differences were observed during the initial 6-month placebo-controlled period.

Left Ventricular Mass Index (LVMi)
In the ERT-experienced trial, following 18 months of treatment with Galafold 123 mg there was a statistically significant decrease in LVMi ($p< 0.05$). The baseline values were 95.3 g/m^2 for the Galafold 123 mg arm and 92.9 g/m^2 for the ERT arm and the mean change from baseline in LVMi at Month 18 was -6.6 (95% CI: -11.0, -2.1; n=31) for Galafold 123 mg and -2.0 (95% CI: -11.0, 7.0; n=13) for ERT. The change from baseline to Month 18 in LVMi (g/m^2) in patients with left ventricular

hypertrophy (females with baseline LVMi > 95 g/m^2 and males with baseline LVMi > 115 g/m^2) was -8.4 (95% CI: -15.7, 2.6; n=13) for migalastat and 4.5 (95% CI: -10.7, 18.4; n=5) for ERT. After 30 months treatment with Galafold 123 mg, the mean change from baseline in LVMi was -3.8 (95% CI: -8.9, 1.3; n=28) and the mean change from baseline in LVMi in patients with left ventricular hypertrophy at baseline was -10.0 (95% CI: -16.6, -3.3; n=10).

In the ERT-naïve trial, Galafold 123 mg resulted in a statistically significant decrease in LVMi ($p< 0.05$); the mean change from baseline in LVMi at Month 18 to 24 was -7.7 (95% CI: -15.4, -0.01; n=27). After follow up in the OLE, the mean change from baseline in LVMi at Month 36 was -8.3(95% CI: -17.1,0.4 ; n= 25 at Month 48was -9.1(95% CI:-20.3; n=18) The mean change from baseline in LVMi at Month 18 to 24 in patients with left ventricular hypertrophy at baseline (females with baseline LVMi > 95 g/m^2 or males with baseline LVMi > 115 g/m^2) was -18.6 (95% CI: -38.2, 1.0; n=8). After follow up in the OLE, the mean change from baseline in LVMi in patients with left ventricular hypertrophy at baseline at Month 36 was -30.0 (95% CI: -57.9, -2.2; n=4 and at Month 48was -33.1(CI:-60.9,-5.4: n=4). No clinically significant differences in LVMi were observed during the initial 6-month placebo-controlled period.

Disease Substrate
In the ERT-experienced trial, plasma lyso-Gb_3 levels slightly increased but remained low in patients with amenable mutations treated with Galafold 123 mg for the 30 month duration of the study. Plasma lyso- Gb3 levels also remained low in patients on ERT for up to 18 months.

In the ERT- naïve trial, Galafold 123 mg showed statistically significant reductions in plasma lyso-Gb_3 concentrations and kidney interstitial capillary GL-3 inclusions in patients with amenable mutations. Patients randomised to Galafold 123 mg in Stage 1 demonstrated statistically significant greater reduction (±SEM) in mean interstitial capillary GL-3 deposition (-0.25±0.10; -39%) at month 6 compared to placebo (+0.07 ± 0.13; +14%) (p=0.008). Patients randomised to placebo in Stage 1 and switched to Galafold 123 mg at month 6 (Stage 2) also demonstrated statistically significant decreases in interstitial capillary GL-3 inclusions at month 12 (-0.33±0.15; -58%) (p=0.014). Qualitative reductions in GL-3 levels were observed in multiple renal cell types: podocytes, mesangial cells, and glomerular endothelial cells, respectively, over 12 months of treatment with Galafold 123 mg.

Composite Clinical Outcomes
In the ERT-experienced trial, an analysis of a composite clinical outcome composed of renal, cardiac, and cerebrovascular events, or death, showed that the frequency of events observed in the Galafold 123 mg treatment group was 29% compared to 44% in the ERT group over 18 months. The frequency of events in patients treated with Galafold 123 mg over 30 months (32%) was similar to the 18 month period.

Patient-Reported Outcome - Gastrointestinal Symptoms Rating Scale
In the ERT-naïve trial, analyses of the Gastrointestinal Symptoms Rating Scale demonstrated that treatment with Galafold 123 mg was associated with statistically significant ($p<0.05$) improvements versus placebo from baseline to month 6 in the diarrhoea domain, and in the reflux domain for patients with symptoms at baseline. During the open-label extension, statistically significant ($p<0.05$) improvements from baseline were observed in the diarrhoea and indigestion domains, with a trend of improvement in the constipation domain.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability (AUC) for a single oral 150 mg migalastat hydrochloride dose or a single 2-hour 150 mg intravenous infusion was approximately 75%. Following a single oral dose of 150 mg migalastat hydrochloride solution, the time to peak plasma concentration was approximately 3 hours.

Plasma migalastat exposure ($AUC_{0-\infty}$) and C_{max} demonstrated dose-proportional increases at migalastat hydrochloride oral doses from 50 mg to 1,250 mg.

Migalastat administered with a high-fat meal, or 1 hour before a high-fat or light meal, or 1 hour after a light meal, resulted in significant reductions of 37% to 42% in mean total migalastat exposure ($AUC_{0-\infty}$) and reductions of 15% to 40% in mean peak migalastat exposure (C_{max}) compared with the fasting state. See section 4.2.

Distribution

In healthy volunteers, the volume of distribution (V_z/F) of migalastat following ascending single oral doses (25-675 mg migalastat HCl) ranged from 77 to 133 L, indicating it is well distributed into tissues and greater than total body water (42 litres). There was no detectable plasma protein binding following administration of [^{14}C]-migalastat hydrochloride in the concentration range between 1 and 100 μM.

Biotransformation

Based upon in vivo data, migalastat is a substrate for UGT, being a minor elimination pathway. Migalastat is not a substrate for P-glycoprotein (P-gP) *in vitro* and it is considered unlikely that migalastat would be subject to drug-drug interactions with cytochrome P450s. A pharmacokinetic trial in healthy male volunteers with 150 mg [^{14}C]-migalastat HCl revealed that 99% of the radiolabeled dose recovered in plasma was comprised of unchanged migalastat (77%) and 3 dehydrogenated O-glucuronide conjugated metabolites, M1to M3 (13%). Approximately 9% of the total radioactivity was unassigned.

Elimination

A pharmacokinetic trial in healthy male volunteers with 150 mg [^{14}C]-migalastat hydrochloride revealed that approximately 77% of the radiolabeled dose was recovered in urine of which 55% of was excreted as unchanged migalastat and 4% as combined metabolites M1, M2 and M3. Approximately 5% of the total sample radioactivity was unassigned components. Approximately 20% of the total radiolabeled dose was excreted in faeces, with unchanged migalastat being the only measured component.

Following ascending single oral doses (25-675 mg migalastat hydrochloride), no trends were found for clearance, CL/F). At the 150 mg dose, CL/F was approximately 11 to 14 L/hr. Following administration of the same doses, the mean elimination half-life ($t_{1/2}$) ranged from approximately 3 to 5 hours.

Special populations

Patients with renal impairment
Galafold 123 mg has not been studied in patients with Fabry disease who have a GFR less than 30 mL/min/1.73 m^2. In a single dose study with Galafold 123 mg in non-Fabry subjects with varying degrees of renal insufficiency, exposures were increased by 4.3-fold in subjects with severe renal impairment (GFR < 30 mL/min/1.73 m^2).

Patients with hepatic impairment
No studies have been carried out in subjects with impaired hepatic function. From the metabolism and excretion pathways, it is not expected that a decreased hepatic function may affect the pharmacokinetics of migalastat.

Elderly (> 65 years)
Clinical studies of Galafold 123 mg included small number of patients aged 65 and over. The effect of age was evaluated in a population pharmacokinetic analysis on plasma migalastat clearance in the

ERT-naïve study population. The difference in clearance between Fabry patients ≥ 65 years and those < 65 years was 20%, which was not considered clinically significant.

Gender

The pharmacokinetic characteristics of migalastat were not significantly different between females and males in either healthy volunteers or in patients with Fabry disease.

5.3 Preclinical safety data

Non-clinical studies suggest no specific hazard for humans on the basis of single-and repeat-dose studies, with the exception of transient and fully reversible infertility in male rats associated with migalastat treatment. The infertility associated with migalastat treatment was reported at clinically relevant exposures. Complete reversibility was seen after 4 weeks off-dose. Similar findings have been noted pre-clinically following treatment with other iminosugars. In the rabbit embryo-foetal toxicity study, findings including embryo-foetal death, a reduction in mean foetal weight, retarded ossification, and slightly increased incidences of minor skeletal abnormalities were observed only at doses associated with maternal toxicity.

In a rat 104-week carcinogenicity study, there was an increased incidence of pancreatic islet cell adenomas in males at a dose level 19-fold higher than the exposure (AUC) at the clinically efficacious dose. This is a common spontaneous tumour in *ad libitum*-fed male rats. In the absence of similar findings in females, no findings in the genotoxicity battery or in the carcinogenicity study with Tg.rasH2 mice, and no pre-neoplastic pancreatic findings in the rodents or monkeys, this observation in male rats is not considered related to treatment and its relevance to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Starch, pregelatinised
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide
Indigotine FD&C Blue2

Printing ink
Shellac
Black iron oxide
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC / PCTFE / PVC/Al blister.
Pack size of 14 capsules.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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