ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.
Size 2 hard capsule (6.4x18.0 mm) with an opaque blue cap and opaque white body with “A1001” printed in black, containing white to pale brown powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Galafold 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 should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease. Galafold 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 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 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 at the next planned dosing day and time according to the every other day dosing schedule.

Paediatric population
The safety and efficacy of Galafold 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 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 is required in patients with hepatic impairment (see section 5.2).

Method of administration

For oral use. Galafold exposure is decreased by approximately 40% when taken with food and therefore food should not be consumed at least 2 hours before and 2 hours after taking Galafold to give a minimum 4 hours fast. Clear liquids, including carbonated drinks, can be consumed during this period. Galafold 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 Galafold. In case of meaningful clinical deterioration, further clinical evaluation or discontinuation of treatment with Galafold should be considered.

Galafold 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 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 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 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 is not recommended in women of childbearing potential not using contraception.

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

Breast-feeding
It is not known whether Galafold 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, 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 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 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.

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 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 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 are listed in Table 2 and Table 3 respectively below. The GLA mutations are also accessible by health care providers at www.galafoldamenabilitytable.com.

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 (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.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>C	c.A100C	N34H
c.100A>G	c.A100G	N34D
c.101A>C	c.A101C	N34T
c.101A>G	c.A101G	N34S
c.102T>G or c.102T>A	c.T102G or c.T102A	N34K
c.103G>C or c.103G>A	c.G103C or c.G103A	G35R
c.104G>A	c.G104A	G35E
c.104G>C	c.G104C	G35A
c.104G>T	c.G104T	G35V
c.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

Table 2: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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>C; 158A>T]	c.A157C/A158T	N53L
c.157A>G	c.A157G	N53D
c.159C>G or c.159C>A	c.C159G or c.C159A	N53K
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>A	c.G167A	C56Y
c.167G>T	c.G167T	C56F
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.[253G>A; 254G>A]	c.G253A/G254A	G85N
c.[253G>A; 254G>T; 255T>G]	c.G253A/G254T/T255G	G85M
c.254G>A	c.G254A	G85D
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.286A>G	c.A286G	M96V
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

Table 2: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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
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>C	c.T454C	Y152H
c.454T>G	c.T454G	Y152D
c.455A>G	c.A455G	Y152C
c.465T>A or c.465T>G	c.T465A or c.T465G	D155E
c.466G>A	c.G466A	A156T
c.466G>T	c.G466T	A156S
c.467C>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.496_497delinsTC	c.496_497delinsTC	L166S
c.496C>G	c.C496G	L166V
c.[496C>G; 497T>G]	c.C496G/T497G	L166G
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 or c.540G>T	c.G540C or c.G540T	L180F

Table 2: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
c.548G>A	c.G548A	G183D
c.548G>C	c.G548C	G183A
c.550T>A	c.T550A	Y184N
c.551A>G	c.A551G	Y184C
c.553A>G	c.A553G	K185E
c.559_564dup	c.559_564dup	p.M187_S188dup
c.559A>G	c.A559G	M187V
c.560T>C	c.T560C	M187T
c.561G>T or c.561G>A or c.561G>C	c.G561T or c.G561A or c.G561C	M187I
c.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>A	c.C602A	S201Y
c.602C>T	c.C602T	S201F
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>G; 937G>T]	c.A644G/G937T	N215S/D313Y
c.644A>T	c.A644T	N215I
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

Table 2: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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 or c.761-763del	c.760_762delGTT or c.761_763del	p.V254del
c.769G>C	c.G769C	A257P
c.770C>G	c.C770G	A257G
c.770C>T	c.C770T	A257V
c.772G>C or c.772G>A	c.G772C or c.G772A	G258R
c.773G>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

Table 2: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
c.805G>A	c.G805A	V269M
c.806T>C	c.T806C	V269A
c.809T>C	c.T809C	I270T
c.810T>G	c.T810G	I270M
c.811G>A	c.G811A	G271S
c.[811G>A; 937G>T]	c.G811A/G937T	G271S/D313Y
c.812G>A	c.G812A	G271D
c.823C>G	c.C823G	L275V
c.827G>A	c.G827A	S276N
c.829T>G	c.T829G	W277G
c.831G>T or c.831G>C	c.G831T or c.G831C	W277C
c.832A>T	c.A832T	N278Y
c.835C>G	c.C835G	Q279E
c.838C>A	c.C838A	Q280K
c.840A>T or c.840A>C	c.A840T or c.A840C	Q280H
c.844A>G	c.A844G	T282A
c.845C>T	c.C845T	T282I
c.850A>G	c.A850G	M284V
c.851T>C	c.T851C	M284T
c.860G>T	c.G860T	W287L
c.862G>C	c.G862C	A288P
c.866T>G	c.T866G	I289S
c.868A>C or c.868A>T	c.A868C or c.A868T	M290L
c.869T>C	c.T869C	M290T
c.870G>A or c.870G>C or c.870G>T	c.G870A or c.G870C or c.G870T	M290I
c.871G>A	c.G871A	A291T
c.877C>A	c.C877A	P293T
c.881T>C	c.T881C	L294S
c.884T>G	c.T884G	F295C
c.886A>G	c.A886G	M296V
c.886A>T or c.886A>C	c.A886T or c.A886C	M296L
c.887T>C	c.T887C	M296T
c.888G>A or c.888G>T or c.888G>C	c.G888A or c.G888T or c.G888C	M296I
c.893A>G	c.A893G	N298S
c.897C>G or c.897C>A	c.C897G or c.C897A	D299E
c.898C>T	c.C898T	L300F
c.899T>C	c.T899C	L300P
c.901C>G	c.C901G	R301G
c.902G>A	c.G902A	R301Q
c.902G>C	c.G902C	R301P
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

Table 2: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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
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>A	c.T1016A	V339E
c.1016T>C	c.T1016C	V339A
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

Table 2: Galafold (migalastat) amenability table

Nucleotide change	Nucleotide change	Protein sequence change
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.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>A	c.C1225A	P409T
c.1225C>G	c.C1225G	P409A
c.1225C>T	c.C1225T	P409S
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

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The mutations not amenable to treatment with Galafold 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 (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>A	c.T2A	M1K
c.2T>C	c.T2C	M1T
c.2T>G	c.T2G	M1R
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
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>A	c.G127A	G43S
c.127G>C	c.G127C	G43R
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.136C>T	c.C136T	H46Y
c.137A>G	c.A137G	H46R
c.137A>T	c.A137T	H46L
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>A	c.C145A	R49S
c.145C>G	c.C145G	R49G

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.145C>T	c.C145T	R49C
c.146G>C	c.G146C	R49P
c.146G>T	c.G146T	R49L
c.148T>C or c.150C>G or c.150C>A	c.T148C or c.C150G or c.C150A	F50L
c.149T>G	c.T149G	F50C
c.154T>A or c.155G>C	c.T154A or c.G155C	C52S
c.154T>C	c.T154C	C52R
c.154T>G	c.T154G	C52G
c.155G>A	c.G155A	C52Y
c.155G>T	c.G155T	C52F
c.156C>A	c.C156A	C52X
c.156C>G	c.C156G	C52W
c.166T>A or c.167G>C	c.T166A or c.G167C	C56S
c.166T>G	c.T166G	C56G
c.168C>A	c.C168A	C56X
c.187T>A or c.188G>C	c.T187A or c.G188C	C63S
c.187T>C	c.T187C	C63R
c.188G>A	c.G188A	C63Y
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; 334C>T]	c.G196C/C334T	E66Q/R112C
c.[196G>C; 1061T>A]	c.G196C/T1061A	E66Q/I354K
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.254G>T	c.G254T	G85V
c.256T>C	c.T256C	Y86H
c.256T>G	c.T256G	Y86D
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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.270C>A	c.C270A	C90X
c.274G>A	c.G274A	D92N
c.274G>C	c.G274C	D92H
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>A or c.281G>C	c.T280A or c.G281C	C94S
c.[280T>A; 281G>C]	c.T280A/G281C	C94T
c.280T>G	c.T280G	C94G
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>C	c.G284C	W95S
c.284G>T	c.G284T	W95L
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
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>A	c.C334A	R112S
c.334C>T	c.C334T	R112C
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.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.[374A>T; 383G>A]	c.A374T/G383A	H125L/G128E
c.379A>T	c.A379T	K127X
c.383G>T	c.G383T	G128V
c.386T>C	c.T386C	L129P
c.388A>G	c.A388G	K130E

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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
c.442A>C or c.444T>A or c.444T>G	c.A442C or c.T444A or c.T444G	S148R
c.443G>A	c.G443A	S148N
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.497T>C	c.T497C	L166P
c.500T>A	c.T500A	L167Q
c.500T>C	c.T500C	L167P
c.502A>C	c.A502C	K168Q
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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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>A or c.515G>C	c.T514A or c.G515C	C172S
c.514T>C	c.T514C	C172R
c.514T>G	c.T514G	C172G
c.515G>A	c.G515A	C172Y
c.515G>T	c.G515T	C172F
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.550T>G	c.T550G	Y184D
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.[604T>C; 644A>G]	c.T604C/A644G	p.C202R/N215S
c.605G>A	c.G605A	C202Y
c.606T>G	c.T606G	C202W
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>A or c.668G>C	c.T667A or c.G668C	C223S
c.667T>C	c.T667C	C223R
c.667T>G	c.T667G	C223G
c.668G>A	c.G668A	C223Y
c.668G>T	c.G668T	C223F
c.670A>G	c.A670G	N224D

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.680G>T	c.G680T	R227L
c.688G>A	c.G688A	A230T
c.691G>A	c.G691A	D231N
c.691G>T	c.G691T	D231Y
c.692A>C	c.A692C	D231A
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>G	c.A701G	D234G
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.706T>G	c.T706G	W236G
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
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; 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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.796G>A	c.G796A	D266N
c.796G>C	c.G796C	D266H
c.796G>T	c.G796T	D266Y
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.815A>T	c.A815T	N272I
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.834T>G or c.834T>A	c.T834G or c.T834A	N278K
c.835C>A	c.C835A	Q279K
c.835C>T	c.C835T	Q279X
c.836A>G	c.A836G	Q279R
c.[836A>T; 902G>A]	c.A836T/902G>A	Q279L/R301Q
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
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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.980A>G	c.A980G	Q327R
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
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>A or c.1020G>A	c.G1019A or c.G1020A	W340X
c.1019G>C	c.G1019C	W340S
c.1021G>A	c.G1021A	E341K
c.1021G>T	c.G1021T	E341X
c.1022A>G	c.A1022G	E341G
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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.[1067G>A; 1078G>C]	c.G1067A/G1078C	R356Q/G360R
c.1069C>T	c.C1069T	Q357X
c.1072G>A	c.G1072A	E358K
c.1081G>A or c.1081G>C	c.G1081A or c.G1081C	G361R
c.1081G>T	c.G1081T	G361X
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.1124G>T	c.G1124T	G375V
c.1130C>A	c.C1130A	A377D
c.1132T>C	c.T1132C	C378R
c.1133G>A	c.G1133A	C378Y
c.1133G>C	c.G1133C	C378S
c.1133G>T	c.G1133T	C378F
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
c.1156C>T	c.C1156T	Q386X
c.1157A>C	c.A1157C	Q386P
c.1160T>C	c.T1160C	L387P
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.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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.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.1247_1248CT>AA	c.C1247A/T1248A	L417K
c.1247A>C	c.A1247C	Q416P
c.1250T>C	c.T1250C	L417P
c.1250T>G	c.T1250G	L417R
c.1288T>C	c.T1288C	X430Q
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.123_126dupCATG	c.123_126dupCATG	p.G43Hfs*13
c.123delC	c.123delC	p.T41fs*79
c.124_125del	c.124_125del	p.M42Gfs*12
c.125_137del	c.125_137del	p.M42Tfs*74
c.134_138delTGCACinsGCTCG	c.134_138delTGCACinsGCTCG	L45R/H46S
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
c.210insT	c.210insT	p.E71X
c.214delA	c.214delA	p.M72Wfs*47
c.256delT	c.256delT	p.Y88Mfs*42
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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.354_368del15	c.354_368del15	Q119_Y123del5
c.358del6	c.358del6	p.120del2aa/L120H
c.363delT	c.363delT	p.A121fs*8
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.428dupC	c.428dupC	p.G144Qfs*12
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.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
c.646delT	c.646delT	p.Y216Ifs*23
c.646dupT	c.646dupT	p.Y216Lfs*15
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.719delA	c.719delA	p.K240Rfs*29
c.719dupA	c.719dupA	p.K240fs*9
c.722delG	c.722delG	p.S241Ifs*27
c.723dupT	c.723dupT	p.I242Yfs*8
c.732delC	c.732delC	p.D244fs*24
c.736_739delinsCAA	c.736_739delinsCAA	p.T246Qfs*21
c.741ins9	c.741ins9	p.247ins3
c.744_745del	c.744_745del	p.F248Lfs*6

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
c.744delT	c.744delT	p.F248Lfs*20
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.833_845del	c.833_845del	p.W277fs*34
c.833delA	c.833delA	p.N278Ifs*3
c.833dupA	c.833dupA	p.N278Kfs*20
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.931dupC	c.931dupC	p.L311Pfs*4
c.941_961del	c.941_961del	p.D315_Q321del
c.946_954dup	c.946_954dup	p.V316_A318dup
c.946_966del	c.946_966del	p.V316_D322del
c.946delG	c.946delG	p.V316X
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.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
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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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.1124_1129del	c.1124_1129del	G375_V376del
c.1129_1140dup	c.1129_1140dup	A377_P380dup
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_1183dup	c.1181_1183dup	L394_G395insV
c.1181_1192del	c.1181_1192del	p.L394_E398delinsQ
c.1187delT	c.1187delT	p.F396Sfs*7
c.1187dupT	c.1187dupT	p.F396fs*2
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
c.1209_1211del	c.1209_1211del	p.404delR
c.1223delA	c.1223delA	p.N408Ifs*9
c.1226_1231del	c.1226_1231del	p.409_410delinsR

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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
g.941_5845del	c.1-179_369+577del	p.?(Exon1_2del)
g.2594_10904dup	c.195-2500_999+197dup	UNKNOWN
g.2934_6378del	c.194+1561_370-891del	UNKNOWN (E66_Y123del; del Exon2?)
g.2979_6442del	c.194+1606_369+1174del	UNKNOWN (E66_Y123del; del Exon2)
g.3260_6410del	c.194+1887_370-859del	UNKNOWN (E66_Y123del; del Exon2?)
g.3396_6012del	c.194+2023_370-1257del	UNKNOWN (E66_Y123del; del Exon2?)
g.3422_6041delinsCG	c.194+2049_369+773del2620insCG	UNKNOWN
g.5052_5079del28	g.5052_5079del28	UNKNOWN
g.5106_5919delins231	c.207_369+651del814ins231	UNKNOWN (del Exon2?)
g.5271_9366del4096insT	c.369+3_639+954del3129insT	UNKNOWN (del Exon3 and 4?)
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.[10237_11932del; 11933_12083inv; 12084_12097del]	g.10237_11932del/11933_12083inv/12084_12097del	UNKNOWN
g.>5.5kbdel to 3UTR	c.?_?del	UNKNOWN (delExon3_3'UTR?)
g.?_?del	c.?_?	UNKNOWN (del Exon1_2?)
g.?_?del	c.195-?_547+?del	UNKNOWN (del Exon2_3?)
g.?_?del	c.?_?del	UNKNOWN (del Exon5_7?)
g.?_?dup	c.?_?dup	UNKNOWN (Exon2_4dup?)
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

Table 3: Mutations not amenable to Galafold (migalastat)

Nucleotide change	Nucleotide change	Protein Sequence change
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+1G>T	c.547+1G>T	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
IVS3-2A>G	c.548-2A>G	UNKNOWN
IVS3-162A>T	c.548-162A>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
IVS4-1G>A	c.640-1G>A	UNKNOWN
IVS4-1G>T	c.640-1G>T	UNKNOWN
IVS4-2A>T	c.640-2A>T	UNKNOWN
IVS4-3C>G	c.640-3C>G	UNKNOWN
IVS4-4A>C	c.640-4A>C	UNKNOWN
IVS4-11T>A	c.640-11T>A	UNKNOWN
IVS4-859C>T	c.640-859C>T	UNKNOWN
IVS5+1G>T	c.801+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
IVS6-1G>A	c.1000-1G>A	UNKNOWN
IVS6-1G>C	c.1000-1G>C	UNKNOWN
IVS6-2A>G	c.1000-2A>G	UNKNOWN
IVS6-2A>T	c.1000-2A>T	UNKNOWN
IVS6-10G>A; IVS6-22C>T	c.1000-10G>A/1000-22C>T	UNKNOWN

NP GAL 0719

Not all mutations have been tested.

Pharmacodynamic effects

Treatment with Galafold 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 have been evaluated in two Phase 3 pivotal trials and two open-label extension (OLE) trials. All patients received the recommended dosage of 123 mg Galafold 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 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 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 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 exposure to the marketed dose of Galafold 123 mg 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 ongoing.*Renal Function*
In the ERT-experienced trial, renal function remained stable for up to 18 months of treatment with Galafold. 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 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 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 for up to 5 years of treatment with Galafold. After an average of 3.4 years of treatment, the mean annualised rate of change in $eGFR_{CKD-EPI}$ was -0.74 mL/min/1.73 m^2 (95% CI: -1.89, 0.40; 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 there was a statistically significant decrease in LVMi ($p< 0.05$). The baseline values were 95.3 g/m^2 for the Galafold 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 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, 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 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) and at Month 48 was -9.1 (95% CI: -20.3, 2.0; 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 48

was -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 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 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 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 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.

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 treatment group was 29% compared to 44% in the ERT group over 18 months. The frequency of events in patients treated with Galafold 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 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Galafold in one or more subsets of the paediatric population in the treatment of Fabry disease (see section 4.2 for information on paediatric use).

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 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 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 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
Pregelatinised starch (maize)
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide (E171)
Indigotine (E132)

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

This medicinal product does not require any special temperature storage conditions. 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. MARKETING AUTHORISATION HOLDER

Amicus Therapeutics UK Ltd
Phoenix House,
Oxford Road,
Tatling End,
Gerrards Cross,
Buckinghamshire
SL9 7AP
United Kingdom
tel +44 1753 888 567
fax +44 1753 437 192
e-mail info@amicusrx.co.uk

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1082/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 May 2016

10. DATE OF REVISION OF THE TEXT

DD month YYYY

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Almac Pharma Services Limited
Seagoe Industrial Estate
Portadown, Craigavon
BT63 5UA
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Galafold 123 mg hard capsules
migalastat

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains migalastat hydrochloride equivalent to 123 mg migalastat

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not eat food at least 2 hours before and 2 hours after taking your medicine to give a minimum 4 hours fast. Take at the same time each day.
Swallow the capsule whole. Do not cut, crush, or chew the capsule.
Read the package leaflet before use.
Oral use.

Take Galafold capsule every other day and punch out the perforated circle on the blister sleeve on the days you are not taking Galafold.

Instructions to open

1. PRESS and hold tab at the left
2. PULL out card on the right
3. PUSH capsule through the foil
4. PUSH card back into holder

To access the package leaflet, scan the code below.
QR code to be included + www.galafoldsmpc.co.uk

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amicus Therapeutics UK Ltd
Phoenix House,
Oxford Road,
Tatling End,
Gerrards Cross,
Buckinghamshire
SL9 7AP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1082/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

galafold 123 mg hard capsules

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING

BLISTER SLEEVE

1. NAME OF THE MEDICINAL PRODUCT

Galafold 123 mg hard capsules
migalastat

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amicus Therapeutics UK, Ltd

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

LOT:

5. OTHER

See package leaflet for further instructions.

Punch out the perforated circles on days you are not taking Galafold.

Galafold is to be taken every other day.

Starting date:

MINIMUM PARTICULARS TO APPEAR ON INTERMEDIATE PACKAGING

BLISTER FOIL

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

LOT:

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Galafold 123 mg hard capsules
Migalastat

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Galafold is and what it is used for

Galafold contains the active substance migalastat.

This medicine is used for the long-term treatment of Fabry disease in adults and adolescents aged 16 years and older who have certain genetic mutations (changes).

Fabry disease is caused by the lack of or a faulty enzyme called alpha-galactosidase A (α–Gal A). Depending upon the kind of mutation (change) in the gene that produces α–Gal A, the enzyme does not work properly or is completely absent. This enzyme defect leads to abnormal deposits of a fatty substance known as globotriaosylceramide (GL-3) in kidneys, heart, and other organs, leading to the symptoms of Fabry disease.

This medicine works by stabilising the enzyme that your body produces naturally, so that it can work better to reduce the amount of GL-3 that has accumulated in your cells and tissues.

2. What you need to know before you take Galafold

Do not take Galafold if you:
- are allergic to migalastat or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor before taking Galafold if you are currently taking enzyme replacement therapy. You should not take Galafold if you are also receiving enzyme replacement therapy.

Your doctor will monitor your condition and whether your medicine is working every 6 months while you are taking Galafold. If your condition worsens, your doctor may evaluate you further or may discontinue your treatment with Galafold.

Children and adolescents
This medicine has not been studied in children and adolescents under the age of 16 years; therefore, the safety and efficacy in this age group has not been established.

Other medicines and Galafold
Tell your doctor, pharmacist or nurse if you are taking, have recently taken, or might take any other medicines because certain other medicines may increase or decrease the amount of Galafold in your body.

Pregnancy, breast-feeding, and fertility

Pregnancy
There is very limited experience with the use of this medicine in pregnant women. If you are pregnant, think you may be pregnant, or are planning to have a baby, do not take this medicine until you have checked with your doctor, pharmacist, or nurse. While taking Galafold you should use effective birth control.

Breast-feeding
Do not take this medicine if you are breast-feeding, until you have spoken with your doctor, pharmacist, or nurse. It is not yet known whether this medicine passes into breast milk. Your doctor will decide whether you need to stop breast-feeding or temporarily stop your medicine.

Fertility in men
It is not yet known if this medicine affects fertility in men. The effects of Galafold on fertility in humans have not been studied.

Fertility in women
It is not yet known if this medicine affects fertility in women.

If you are planning to have a baby, ask your doctor, pharmacist, or nurse for advice.

Driving and using machines

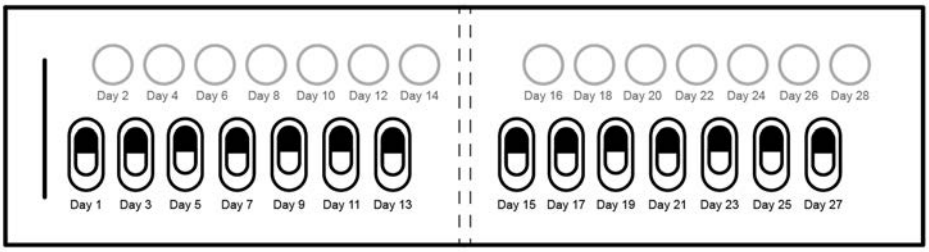
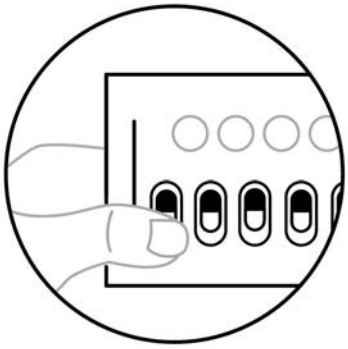
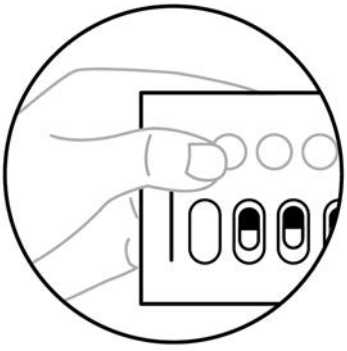
It is unlikely that this medicine will affect your ability to drive and use machines.

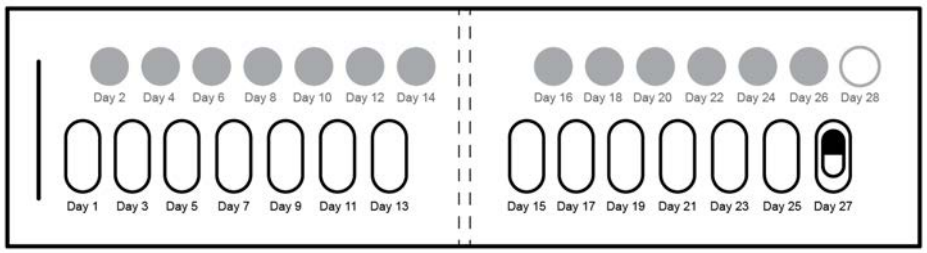
3. How to take Galafold

Always take this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor, pharmacist, or nurse if you are not sure.

Take one capsule every other day at the same time of the day. Do not take Galafold on two consecutive days.
. Do not eat food at least 2 hours before and 2 hours after taking your medicine. This minimum 4 hours fast around taking your medicine is needed to allow your medicine to be fully absorbed. Clear liquids, including carbonated drinks, can be consumed during this period.

Swallow the capsule whole. Do not cut, crush, or chew the capsule.

<table>
<tr><td colspan="2"> 
</td></tr>
<tr><td colspan="2">One Galafold blister sleeve = 14 hard capsules = 28 days of therapy</td></tr>
<tr><td>  </td><td>On your first day of taking this medicine from a new blister sleeve, record the date on the blister sleeve.</td></tr>
<tr><td>  </td><td>Then, punch out the left-most capsule labelled Day 1.</td></tr>
<tr><td>  </td><td>On the next day, punch out the perforated white circle labelled Day 2. This will help you remember which day you did not take the medicine. You should only take Galafold once every other day.</td></tr>
</table>



After Day 2, continue moving right on the blister sleeve.
Alternate daily between taking the capsule on odd numbered days and
punching out the perforated white circles on even numbered days, up to and including day 28.

If you take more Galafold than you should
If you take more capsules than you should, then you should stop taking the medicine and contact your doctor. You may get a headache and feel dizzy.

If you forget to take Galafold
If you forget to take your capsule at the usual time but remember later, you can take the capsule only if it is within 12 hours of your normal dosing time. If more than 12 hours has passed you should resume taking Galafold at the next planned dosing day and time according to your every other day dosing schedule.. Do not take two capsules to make up for your missed dose.

If you stop taking Galafold
Do not stop taking this medicine without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common: may affect more than 1 in 10 people
- Headache

Common: may affect up to 1 in 10 people

- Palpitations (the feeling of a pounding heart)
- Sensation of spinning (vertigo)
- Diarrhoea
- Feeling sick (nausea)
- Stomach ache
- Constipation
- Dry mouth
- Sudden need to defecate
- Indigestion (dyspepsia)
- Tiredness
- raised levels of creatine phosphokinase in blood tests
- Weight gain
- Muscle spasms
- Muscle pain (myalgia)
- Painful stiff neck (torticollis)
- Tingling in extremities (paraesthesia)
- Dizziness
- Reduced sense of touch or sensation (hypoaesthesia)
- Depression
- Protein in the urine (proteinuria)
- Shortness of breath (dyspnoea)
- Nose bleed (epistaxis)
- Rash
- Persistent itch (pruritus)
- Pain

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Galafold

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Galafold contains

- The active substance is migalastat. Each capsule contains migalastat hydrochloride equivalent to 123 mg migalastat
- The other ingredients are:
  Capsule contents: Pregelatinised maize starch and magnesium stearate
  Capsule shell: Gelatin, titanium dioxide, and indigotine
  Printing ink: Shellac, black iron oxide, and potassium hydroxide

What Galafold looks like and contents of the pack

Opaque, blue, and white hard capsules, marked with “A1001” in black ink, containing white to pale brown powder.

Galafold is available in a blister pack containing 14 capsules.

Marketing Authorisation Holder

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder (if you cannot reach your Amicus representative by phone please contact via the email address listed below):

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.