PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]GALAFOLD®

Migalastat capsules

Capsules, 123 mg migalastat (as migalastat hydrochloride), Oral

Alpha-galactosidase A (alpha-Gal A) pharmacological chaperone

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RECENT MAJOR LABEL CHANGES

1 Indications, 1.1 Pediatrics	03/2023
4 Dosage and Administration, 4.1 Dosing Considerations	03/2023
4 Dosage and Administration, 4.2 Recommended Dosage and Dose Adjustment	03/2023
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

GALAFOLD (migalastat capsules) is indicated for:

- long-term treatment of adults and adolescents aged 12 years and older with a confirmed diagnosis of Fabry disease [deficiency of α-galactosidase (α-Gal A)] and who have an α-Gal A mutation determined to be amenable by an in vitro assay (see 10.1 Mechanism of Action - Table 5).

1.1 Pediatrics

12 to < 18 years of age: Based on the data submitted and reviewed by Health Canada, the safety and efficacy of GALAFOLD in pediatric patients 12 to < 18 years and weighing ≥ 45 kg have been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2 Recommended Dose and Dose Adjustment, Pediatrics, 7.1.3 WARNINGS AND PRECAUTIONS, Pediatrics and 14.2 Study Results, Pediatric Population).

< 12 years of age: GALAFOLD has not been authorized for use in pediatric patients less than 12 years of age.

1.2 Geriatrics

> 65 years of age: Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

Migalastat is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment with GALAFOLD should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Fabry disease. GALAFOLD treatment is only indicated for adults and adolescents aged 12 years and older with Fabry disease who have an amenable *GLA* mutation that is interpreted by the specialist physician as causing Fabry disease (pathogenic, likely pathogenic) in the clinical context of the patient. Consultation with a clinical genetics' specialist is strongly recommended in cases where the amenable *GLA* mutation/variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease) (see 10.1 Mechanism of Action).
- GALAFOLD is not indicated and should not be used in patients with non-amenable mutations (see 10.1 Mechanism of Action). Efficacy was not demonstrated in these patients. GALAFOLD may result in a net loss of α-Gal A activity in patients with non-amenable mutations, potentially worsening the disease condition.
- Clinical data supporting the effectiveness of GALAFOLD for the treatment of Fabry disease patients

with amenable mutations are limited (see 14 CLINICAL TRIALS). In clinical trials, individual response to GALAFOLD treatment varied considerably among patients with amenable mutations. Patients should be assessed for treatment response or failure when initiating GALAFOLD, and monitored periodically thereafter (every 6 months or more frequently) throughout the treatment (see 7 WARNINGS AND PRECAUTIONS - Monitoring and Laboratory Tests).

- GALAFOLD should not be used concomitantly with enzyme replacement therapy (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage regimen of GALAFOLD in patients ≥ 12 years and weighing ≥ 45 kg is 123 mg migalastat (1 capsule) taken once every other day at the same time of day. A higher dose or shorter dosing interval may result in a loss of efficacy, potentially worsening the disease condition (see 10.2 Pharmacodynamics - Clinical Studies).

Elderly population (> 65 years of age)
No dosage adjustment is expected in this population (see 10.3 Special Populations and Conditions - Geriatrics).

Patients with Renal Impairment
GALAFOLD should not be used in patients with severe renal insufficiency defined as an eGFR less than 30 mL/min/1.73 m^2 (see 7 WARNINGS AND PRECAUTIONS - Renal and 10.3 Pharmacokinetics - Special Populations and Conditions - Renal Insufficiency).

Patients with Hepatic Impairment
No dosing adjustment of GALAFOLD is expected in these patients (see 7 WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics - Special Populations and Conditions - Hepatic Insufficiency).

Pediatrics
Adolescents aged ≥ 12 years and weighing ≥ 45 kg
123 mg migalastat (1 capsule) taken once every other day at the same time of the day (see 10.3 Pharmacokinetics).

Children < 12 years or adolescents weighing < 45 kg
The safety and efficacy of GALAFOLD in children aged < 12 years or in adolescents weighing < 45 kg have not yet been established. No data are available in this age group.

4.4 Administration

For oral use.

GALAFOLD exposure is decreased by approximately 40% when taken with food and 60% when taken with caffeine (see 9.5 Drug-Food Interactions and 10.3 Pharmacokinetics – Absorption), therefore, it should be taken on an empty stomach. Food and caffeine should not be consumed for at least 2 hours before and 2 hours after taking GALAFOLD, to give a minimum of 4 hours fast.

Water (plain, flavored, sweetened), fruit juices without pulp, and caffeine-free carbonated beverages can be consumed during the 4-hour fasting 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.

4.5 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 that the dose should have been taken. If more than 12 hours have passed, the patient should resume taking GALAFOLD at the next planned dosing day and time, according to the every other day dosing schedule.

5 OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Immediate release hard capsule / 123 mg migalastat (equivalent to 150 mg migalastat hydrochloride)	black printing ink, gelatin, indigo carmine (FD&C blue 2), magnesium stearate, pregelatinized maize starch (maize), and titanium dioxide.

GALAFOLD is an oral immediate release, size 2 hard capsule with an opaque blue cap and opaque white body with the identifying code “A1001” printed in black.

GALAFOLD® is provided in a quantity of 14 capsules packaged in a blister strip comprised of polyvinylchloride (PVC) / polychlorotrifluoroethylene (PCTFE) and an aluminium foil lidding with a vinyl acrylic heat seal coating. Blister strips are encased in a paperboard secondary pack forming a blister card.

7 WARNINGS AND PRECAUTIONS

General

GALAFOLD is not indicated and should not be used in patients with non-amenable mutations (see 10.1 Mechanism of Action). GALAFOLD may result in a net loss of α-Gal A activity in patients with non-amenable mutations, potentially worsening the disease condition.

The patient should be advised to carefully adhere to the recommended dosing regimen of GALAFOLD [one 123 mg migalastat capsule every other day]. A higher dose or shorter dosing interval may result in a loss of efficacy, potentially worsening the disease condition (see 4 DOSAGE AND ADMINISTRATION).

GALAFOLD should not be used concomitantly with enzyme replacement therapy (see 9.4 Drug-Drug Interactions). Limited data suggest that co-administration of a single dose of GALAFOLD and a standard enzyme replacement therapy infusion results in increased exposure to agalsidase of up to 5-fold (see 9.4 Drug-Drug Interactions).

Hepatic/Biliary/Pancreatic

The safety and efficacy of GALAFOLD have not been studied in subjects with impaired hepatic function. No dosing adjustment of GALAFOLD is expected in this population (see 4.2 Recommended Dose and Dosage Adjustment - Patients with Hepatic Impairment and 10.3 Pharmacokinetics - Special Populations and Conditions - Hepatic Insufficiency).

Monitoring and Laboratory Tests

Assessment of renal function is recommended prior to the initiation of GALAFOLD treatment. GALAFOLD should not be used in patients with severe renal insufficiency, defined as an eGFR less than 30 mL/min/1.73 m^2.

In clinical trials, individual response to GALAFOLD varied considerably among patients with amenable mutations. Therefore, it is recommended to monitor renal function, echocardiographic parameters, and biochemical markers (plasma Lyso-Gb_3 or urine GL-3) prior to and periodically (every 6 months or more frequently) following the initiation of GALAFOLD. An increase in plasma lyso-Gb_3 or urine GL-3 during treatment with GALAFOLD may be a sign of treatment failure. In case of meaningful clinical deterioration, GALAFOLD treatment should be stopped, further clinical assessment should be initiated and other treatment options should be considered.

Renal

GALAFOLD should not be used in patients with severe renal insufficiency, defined as having an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2, due to a significant increase in the exposure to and prolonged half-life of migalastat. This may result in a net loss of α-Gal A activity, potentially worsening the disease condition (see 4.2 Recommended Dose and Dosage Adjustment - Patients with Renal Impairment and 10.3 Pharmacokinetics-Special Populations and Conditions - Renal Insufficiency).

In clinical studies, no reduction in proteinuria was observed in patients treated with GALAFOLD.

Reproductive Health: Female and Male Potential

- **Fertility**

  The effects of GALAFOLD on fertility in humans have not been studied. Infertility in male rats was associated with migalastat treatment at exposures below clinically relevant exposures. Complete reversibility was seen after a 4-week non-dosing recovery period (see 16 NON-CLINICAL TOXICOLOGY). GALAFOLD did not affect fertility in female rats.

7.1 Special Populations

7.1.1 Pregnant Women

GALAFOLD should not be used by pregnant women and is not recommended in women of childbearing potential not using contraception.

In nonclinical studies in pregnant rats, it has been shown that migalastat can penetrate the placental:blood barrier.

In pregnant rabbits, developmental toxicity was observed at maternally toxic doses and was evidenced as a dose-related increase in embryo-fetal death, a reduction in mean fetal weights, retarded ossification and slightly increased incidences of other minor skeletal abnormalities (see 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

GALAFOLD should not be used in breast-feeding women. It is unknown if GALAFOLD is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

In nonclinical studies, migalastat has been shown to be excreted into the milk of lactating rats. Accordingly, a risk of migalastat exposure to the breast-feeding infant cannot be excluded.

7.1.3 Pediatrics

No data are available to Health Canada for children aged 0 to 11 years or in patients ≥ 12 years who weigh < 45 kg; therefore, Health Canada has not authorized an indication for children aged less than 12 years or for adolescents who weigh < 45 kg. See 1 INDICATIONS and 10.3 Pharmacokinetics, Special Populations and Conditions – Pediatrics.

7.1.4 Geriatrics

Clinical studies of GALAFOLD included a small number of patients aged 65 and over.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reaction reported from clinical trials of migalastat was headache, which was experienced by ≥ 10% of patients who received GALAFOLD.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety profile of GALAFOLD was assessed in two Phase 3 clinical trials:

- A double-blind, randomized, placebo-controlled study in patients with Fabry disease and predicted to have migalastat-responsive *GLA* mutations (based on a preliminary in vitro assay) and who were naïve to enzyme replacement therapy (ERT-naïve trial) (Table 2)
- A randomized, open-label study in patients with Fabry disease predicted to have migalastat-responsive *GLA* mutations and who were previously treated with enzyme replacement therapy (ERT-experienced trial) (Table 3).

Table 2 Incidence of Adverse Drug Reactions Reported in ≥ 1% of Patients Treated with GALAFOLD *Versus* Placebo for up to 6 Months in a Double-Blind Study (Enzyme Replacement Therapy-Naïve Trial)

System Organ Class/ Preferred Term	GALAFOLD 123 mg every other day† N = 34 n (%)‡	Placebo† N = 33 n (%)‡
Ear and labyrinth disorders		
Vertigo	1 (2.9%)	1 (3.0%)
Gastrointestinal disorders		
Diarrhea	2 (5.9%)	0
Dry mouth	2 (5.9%)	1 (3.0%)
Nausea	2 (5.9%)	0
Constipation	1 (2.9%)	1 (3.0%)
Defecation urgency	1 (2.9%)	0
General disorders and administration site conditions		
Inflammation	1 (2.9%)	0
Infections and infestations		
Nasopharyngitis	6 (18%)	2 (6.0%)
Injury, poisoning, and procedural complications		
Overdose	1 (2.9%)	0
Investigations		
Weight increased	2 (5.9%)	0
Blood pressure increased	1 (2.9%)	0
Musculoskeletal and connective tissue disorders		
Torticollis	2 (5.9%)	0
Muscle spasms	1 (2.9%)	1 (3.0%)
Myalgia	1 (2.9%)	0
Nervous system disorders		
Paresthesia	2 (5.9%)	0
Dizziness	1 (2.9%)	0
Headache	1 (2.9%)	3 (9.1%)
Hyperesthesia	1 (2.9%)	0
Hypoesthesia	1 (2.9%)	0

System Organ Class/ Preferred Term	GALAFOLD 123 mg every other day† N = 34 n (%)‡	Placebo† N = 33 n (%)‡
Psychiatric disorders		
Depression	1 (2.9%)	0
Insomnia	1 (2.9%)	1 (3.0%)
Respiratory, thoracic, and mediastinal disorders		
Epistaxis	2 (5.9%)	1 (3.0%)
Cough	3 (9%)	0
Skin and subcutaneous tissue disorders		
Rash	1 (2.9%)	0

†Once every other day

‡Percentages are calculated based on the total number of patients treated with the same dose/regimen

Table 3 Incidence of Adverse Drug Reactions Reported in ≥ 1% of Patients Treated with GALAFOLD *Versus* Enzyme-Replacement Therapy (ERT) for up to 18 Months in an Open-Label Study (Enzyme Replacement Therapy Experienced Trial)

System Organ Class/ Preferred Term	GALAFOLD 123 mg every other day† N = 36 n (%)‡	Enzyme Replacement Therapy N = 21 n (%)‡
Cardiac disorders		
Palpitations	1 (2.8%)	0
Eye disorders		
Eye pruritus	1 (2.8%)	0
Gastrointestinal disorders		
Diarrhea	3 (8.3%)	0
Abdominal pain	2 (5.6%)	0
Dyspepsia	2 (5.6%)	0
Nausea	2 (5.6%)	0
Change of bowel habit	1 (2.8%)	0
Dry mouth	1 (2.8%)	1 (4.8%)
Irritable bowel syndrome	1 (2.8%)	0

System Organ Class/ Preferred Term	GALAFOLD 123 mg every other day† N = 36 n (%)‡	Enzyme Replacement Therapy N = 21 n (%)‡
General disorders and administration site conditions		
Fatigue	1 (2.8%)	1 (4.8%)
Influenza like illness	1 (2.8%)	0
Local swelling	1 (2.8%)	0
Edema peripheral	1 (2.8%)	0
Pyrexia	1 (2.8%)	0
Investigations		
Blood creatine phosphokinase increased	2 (5.6%)	0
Blood bilirubin increased	1 (2.8%)	0
Body temperature increased	1 (2.8%)	0
Liver function test abnormal	1 (2.8%)	0
Weight decreased	1 (2.8%)	0
Weight increased	1 (2.8%)	0
White blood cell count decreased	1 (2.8%)	0
Metabolism and nutrition disorders		
Hypoglycemia	1 (2.8%)	0
Musculoskeletal and connective tissue disorders		
Flank pain	1 (2.8%)	0
Musculoskeletal chest pain	1 (2.8%)	0
Myalgia	1 (2.8%)	0
Pain in extremity	1 (2.8%)	0
Nervous system disorders		
Headache	6 (16.7%)	0
Dizziness	2 (5.6%)	0
Ataxia	1 (2.8%)	0
Paresthesia	1 (2.8%)	0
Psychiatric disorders		

System Organ Class/ Preferred Term	GALAFOLD 123 mg every other day† N = 36 n (%)‡	Enzyme Replacement Therapy N = 21 n (%)‡
Sleep disorder	1 (2.8%)	0
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	1 (2.8%)	0
Rhinorrhea	1 (2.8%)	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	1 (2.8%)	0
Night sweats	1 (2.8%)	0
Pruritus	1 (2.8%)	0
Psoriasis	1 (2.8%)	0
Rash	1 (2.8%)	0

†Once every other day

‡Percentages are calculated based on the total number of patients treated with the same dose/regimen.

Patients who completed the 18-month treatment period in the ERT-experienced trial were eligible to receive treatment with GALAFOLD in an optional 12-month open-label extension period. Eleven adverse drug reactions were newly reported between Month 18 and Month 30 of the study in the 51 patients who continued to receive GALAFOLD or switched from ERT to GALAFOLD during the 12-month open-label extension period: abdominal discomfort, feeling hot, hunger, migraine, muscle spasms, neuralgia, pain, proteinuria, tremor, vomiting, and vertigo; all reported in one patient (2%) except for muscle spasms which was reported in two patients (4%). There were generally no significant changes in the nature or frequency of adverse reactions observed between 18 and 30 months.

Adverse drug reactions reported during long-term treatment with GALAFOLD (mean duration of treatment of approximately 43 months, n = 85) were generally in line with those reported during short-term treatment. In addition to the adverse drug reactions listed in Table 2, Table 3, and the 12-month open-label extension of the ERT-experienced trial, the following adverse drug reactions were reported: abdominal pain upper, aggression, alopecia, arthralgia, atrial fibrillation, back pain, bile duct stones, biliary dilatation, chest discomfort, chest pain, goitre, glomerular filtration rate decreased, hematochezia, hot flush, impatience, movement disorder, mucosal dryness, muscular weakness, myocardial ischemia, sneezing, urinary tract infection, vitamin D deficiency, and vitiligo; all reported in one patient (1% each) except for glomerular filtration rate decreased, urinary tract infection, and vitamin D deficiency which were reported in two patients (2% each).

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

The safety assessment in 21 adolescents (12 to < 18 years of age and weighing ≥45 kg) is based on 1-year safety data from the open label AT1001-020 trial in which patients received the same dosage regimen as adults (see 14.2 Study Results). The adverse reactions observed in the adolescent patients were similar to those observed in trials with adult patients.

8.3 Less Common Clinical Trial Adverse Reactions

Clinical trial adverse drug reactions reported in less than 1% of patients in a combined analysis of patients treated with GALAFOLD from the two Phase 3 clinical trials (the ERT-naïve trial and the ERT-experienced) for up to 24 months and not reported in either Table 2 or Table 3 were:

Eye disorders: eye pruritus, visual acuity reduced

Gastrointestinal disorders: abdominal discomfort, abdominal pain upper, fecal incontinence, vomiting

General disorders and administration site conditions: feeling hot, hunger, pain

Hepatobiliary disorders: hepatocellular injury

Investigations: blood calcium decreased, blood cholesterol increased

Metabolism and nutrition disorders: decreased appetite

Musculoskeletal and connective tissue disorders: muscle twitching

Nervous system disorders: balance disorder, memory impairment, migraine, neuralgia, somnolence, tremor

Renal and urinary disorders: pollakiuria

Skin and subcutaneous tissue disorders: erythema

Vascular disorders: systolic hypertension

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Blood Creatine Phosphokinase increased, Liver Function Test abnormal, Blood Bilirubin increased, Blood Cholesterol increased, Blood Calcium decreased, White Blood Cell Count decreased, all occurred with a frequency of ≥ 1%.

8.5 Post-Market Adverse Reactions

The following adverse reaction has been identified during post-market use. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Angioedema

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

GALAFOLD is not intended for concomitant use with enzyme replacement therapy.

GALAFOLD increased exposure to agalsidase by up to 5-fold.

9.3 Drug Behavioural Interactions

The effect of GALAFOLD on the ability to drive and use machines has not been established.

The effects of smoking, diet, and alcohol use on the pharmacokinetics of GALAFOLD have not been studied.

9.4 Drug-Drug Interactions

The drugs listed in Table 4 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e. those identified as contraindicated).

Table 4 Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
agalsidase	CT	Single dose of GALAFOLD increased exposure to agalsidase by up to 5-fold. Agalsidase had no effect on the pharmacokinetics of migalastat.	GALAFOLD is not intended for concomitant use with enzyme replacement therapy.

CT = Clinical Trial

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, OCT2, MATE1, or MATE2-K human uptake transporters.

9.5 Drug-Food Interactions

Food consumption affects the pharmacokinetics of migalastat. GALAFOLD exposure is decreased by approximately 40% when taken with food (see 10.3 Pharmacokinetics - Absorption - Effect of Food).

Co-administration of GALAFOLD with caffeine decreases migalastat systemic exposure (AUC and C_{max}) which may reduce GALAFOLD efficacy (see 10.3 Pharmacokinetics – Absorption – Effect of Beverages). Avoid co-administration of GALAFOLD with caffeine at least 2 hours before and 2 hours after taking

GALAFOLD (see 4.4 Administration).

9.6 Drug-Herb Interactions

The effects of herbal products on the pharmacokinetics of migalastat have not been studied.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the gene encoding lysosomal hydrolase α-galactosidase A (α-Gal A). More than 800 different mutations in the α-Gal A gene have been reported in Fabry disease patients. Of these, more than 60% are missense mutations that result in a single amino acid substitution. Many of the mutated proteins are fully or partially catalytically competent but are structurally unstable, resulting in reduced levels in the lysosomes for breaking down GL-3 and other lipid substrates. Protein instability varies significantly among different mutant forms of α-Gal A proteins.

Migalastat, an analog of the terminal galactose of GL-3, is a specific potent reversible competitive inhibitor of human α-Gal A. It is also a specific structural stabilizer for the wild-type and many mutant forms of α-Gal A. The net biochemical and clinical effects of migalastat in Fabry disease patients initially involves intracellular accumulation of migalastat-stabilized and inhibited α-Gal A enzyme, followed by the recovery of activity of accumulated α-Gal A after migalastat drops to a sub-inhibitory level due to pharmacokinetic elimination. The efficacy of migalastat depends on a net increase of α-Gal A activity resulting from a sufficiently high level of accumulation of the migalastat-inhibited enzyme and an adequate duration for recovery of enzyme activity during the dosing interval.

The genotype of α-Gal A determines the nature and extent of the clinical response to GALAFOLD in Fabry disease patients. For amenable genotypes, the extent of the migalastat-induced accumulation of the α-Gal A protein can vary significantly. Therefore, response to GALAFOLD can differ according to the specific amenable mutation. For non-amenable genotypes, GALAFOLD may result in a net loss of α-Gal A activity, potentially worsening the disease condition.

GALAFOLD is only indicated in patients with Fabry disease who have an amenable mutation as listed in Table 5. A mutation is determined to be amenable by a Good Laboratory Practice (GLP)-validated in vitro assay (see 10.2 Pharmacodynamics - Variants Amenable to GALAFOLD).

Predictability of the extent of clinical outcome based on the GLP HEK-293 assay is limited. The inclusion of *GLA* mutations in Table 5 does not reflect the interpretation of their clinical significance in Fabry disease. Whether a certain amenable *GLA* mutation in a patient with Fabry disease is disease-causing or not should be determined prior to treatment initiation by a clinical genetics' specialist experienced in the diagnosis and treatment of Fabry disease. Consultation with a clinical genetics' specialist is strongly recommended in cases where the amenable *GLA* mutation/variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease) (see 4.1 Dosing Considerations).

Phase 3 clinical studies were conducted in patients with Fabry disease having 43 of the amenable

mutations listed in Table 5.

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 5 (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 5.

Table 5 *GLA* Variants Amenable to GALAFOLD Based on the In Vitro Assay

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.7C>G	c.C7G	p.(L3V)
c.8T>C	c.T8C	p.(L3P)
c.[11G>T; 620A>C]	c.G11T/A620C	p.(R4M/Y207S)
c.13A>G	c.A13G	p.(N5D)
c.15C>G	c.C15G	p.(N5K)
c.16C>A	c.C16A	p.(P6T)
c.16C>T	c.C16T	p.(P6S)
c.17C>A	c.C17A	p.(P6Q)
c.17C>G	c.C17G	p.(P6R)
c.17C>T	c.C17T	p.(P6L)
c.19G>A	c.G19A	p.(E7K)
c.20A>T	c.A20T	p.(E7V)
c.21A>T	c.A21T	p.(E7D)
c.22C>A	c.C22A	p.(L8I)
c.23T>A	c.T23A	p.(L8Q)
c.23T>C	c.T23C	p.(L8P)
c.25C>T	c.C25T	p.(H9Y)
c.26A>G	c.A26G	p.(H9R)
c.26A>T	c.A26T	p.(H9L)
c.27T>A	c.T27A	p.(H9Q)
c.28C>A	c.C28A	p.(L10M)
c.28C>G	c.C28G	p.(L10V)
c.29T>A	c.T29A	p.(L10Q)
c.29T>C	c.T29C	p.(L10P)
c.29T>G	c.T29G	p.(L10R)
c.31G>A	c.G31A	p.(G11S)
c.31G>C	c.G31C	p.(G11R)
c.31G>T	c.G31T	p.(G11C)
c.32G>A	c.G32A	p.(G11D)
c.32G>T	c.G32T	p.(G11V)
c.34T>A	c.T34A	p.(C12S)
c.34T>C	c.T34C	p.(C12R)
c.34T>G	c.T34G	p.(C12G)
c.35G>A	c.G35A	p.(C12Y)
c.37G>A	c.G37A	p.(A13T)
c.37G>C	c.G37C	p.(A13P)
c.38C>A	c.C38A	p.(A13E)
c.38C>G	c.C38G	p.(A13G)
c.40C>G	c.C40G	p.(L14V)
c.40C>T	c.C40T	p.(L14F)
c.41T>A	c.T41A	p.(L14H)
c.43G>A	c.G43A	p.(A15T)
c.44C>G	c.C44G	p.(A15G)
c.49C>A	c.C49A	p.(R17S)
c.49C>G	c.C49G	p.(R17G)
c.49C>T	c.C49T	p.(R17C)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.50G>A	c.G50A	p.(R17H)
c.50G>C	c.G50C	p.(R17P)
c.52T>A	c.T52A	p.(F18I)
c.53T>G	c.T53G	p.(F18C)
c.54C>G	c.C54G	p.(F18L)
c.58G>C	c.G58C	p.(A20P)
c.59C>A	c.C59A	p.(A20D)
c.59C>G	c.C59G	p.(A20G)
c.62T>A	c.T62A	p.(L21H)
c.64G>A	c.G64A	p.(V22I)
c.64G>C	c.G64C	p.(V22L)
c.64G>T	c.G64T	p.(V22F)
c.65T>C	c.T65C	p.(V22A)
c.65T>G	c.T65G	p.(V22G)
c.67T>A	c.T67A	p.(S23T)
c.67T>C	c.T67C	p.(S23P)
c.70T>C or c.70T>A	c.T70C or c.T70A	p.(W24R)
c.[70T>A; 1255A>G]	c.T70A/A1255G	p.(W24R/N419D)
c.70T>G	c.T70G	p.(W24G)
c.71G>C	c.G71C	p.(W24S)
c.72G>C or c.72G>T	c.G72C or c.G72T	p.(W24C)
c.73G>C	c.G73C	p.(D25H)
c.77T>A	c.T77A	p.(I26N)
c.79C>A	c.C79A	p.(P27T)
c.79C>G	c.C79G	p.(P27A)
c.79C>T	c.C79T	p.(P27S)
c.80C>T	c.C80T	p.(P27L)
c.82G>C	c.G82C	p.(G28R)
c.82G>T	c.G82T	p.(G28W)
c.83G>A	c.G83A	p.(G28E)
c.85G>C	c.G85C	p.(A29P)
c.86C>A	c.C86A	p.(A29D)
c.86C>G	c.C86G	p.(A29G)
c.86C>T	c.C86T	p.(A29V)
c.88A>G	c.A88G	p.(R30G)
c.94C>A	c.C94A	p.(L32M)
c.94C>G	c.C94G	p.(L32V)
c.95T>A	c.T95A	p.(L32Q)
c.95T>C	c.T95C	p.(L32P)
c.95T>G	c.T95G	p.(L32R)
c.97G>C	c.G97C	p.(D33H)
c.97G>T	c.G97T	p.(D33Y)
c.98A>C	c.A98C	p.(D33A)
c.98A>G	c.A98G	p.(D33G)
c.98A>T	c.A98T	p.(D33V)
c.99C>G	c.C99G	p.(D33E)
c.100A>C	c.A100C	p.(N34H)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.100A>G	c.A100G	p.(N34D)
c.101A>C	c.A101C	p.(N34T)
c.101A>G	c.A101G	p.(N34S)
c.102T>G or c.102T>A	c.T102G or c.T102A	p.(N34K)
c.103G>C or c.103G>A	c.G103C or c.G103A	p.(G35R)
c.104G>A	c.G104A	p.(G35E)
c.104G>C	c.G104C	p.(G35A)
c.104G>T	c.G104T	p.(G35V)
c.106T>A	c.T106A	p.(L36M)
c.106T>G	c.T106G	p.(L36V)
c.107T>C	c.T107C	p.(L36S)
c.107T>G	c.T107G	p.(L36W)
c.108G>C or c.108G>T	c.G108C or c.G108T	p.(L36F)
c.109G>A	c.G109A	p.(A37T)
c.109G>T	c.G109T	p.(A37S)
c.110C>A	c.C110A	p.(A37E)
c.110C>G	c.C110G	p.(A37G)
c.110C>T	c.C110T	p.(A37V)
c.112A>G	c.A112G	p.(R38G)
c.112A>T	c.A112T	p.(R38W)
c.113G>T	c.G113T	p.(R38M)
c.114G>C	c.G114C	p.(R38S)
c.115A>G	c.A115G	p.(T39A)
c.115A>T	c.A115T	p.(T39S)
c.116C>A	c.C116A	p.(T39K)
c.116C>G	c.C116G	p.(T39R)
c.116C>T	c.C116T	p.(T39M)
c.121A>G	c.A121G	p.(T41A)
c.122C>A	c.C122A	p.(T41N)
c.122C>G	c.C122G	p.(T41S)
c.122C>T	c.C122T	p.(T41I)
c.124A>C or c.124A>T	c.A124C or c.A124T	p.(M42L)
c.124A>G	c.A124G	p.(M42V)
c.125T>A	c.T125A	p.(M42K)
c.125T>C	c.T125C	p.(M42T)
c.125T>G	c.T125G	p.(M42R)
c.126G>A or c.126G>C or c.126G>T	c.G126A or c.G126C or c.G126T	p.(M42I)
c.128G>C	c.G128C	p.(G43A)
c.133C>A	c.C133A	p.(L45M)
c.133C>G	c.C133G	p.(L45V)
c.136C>A	c.C136A	p.(H46N)
c.136C>G	c.C136G	p.(H46D)
c.137A>C	c.A137C	p.(H46P)
c.138C>G	c.C138G	p.(H46Q)
c.142G>C	c.G142C	p.(E48Q)
c.143A>C	c.A143C	p.(E48A)
c.149T>A	c.T149A	p.(F50Y)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.151A>G	c.A151G	p.(M51V)
c.152T>A	c.T152A	p.(M51K)
c.152T>C	c.T152C	p.(M51T)
c.152T>G	c.T152G	p.(M51R)
c.153G>A or c.153G>T or c.153G>C	c.G153A or c.G153T or c.G153C	p.(M51I)
c.157A>C	c.A157C	p.(N53H)
c.[157A>C; 158A>T]	c.A157C/A158T	p.(N53L)
c.157A>G	c.A157G	p.(N53D)
c.157A>T	c.A157T	p.(N53Y)
c.158A>C	c.A158C	p.(N53T)
c.158A>G	c.A158G	p.(N53S)
c.158A>T	c.A158T	p.(N53I)
c.159C>G or c.159C>A	c.C159G or c.C159A	p.(N53K)
c.160C>G	c.C160G	p.(L54V)
c.160C>T	c.C160T	p.(L54F)
c.161T>A	c.T161A	p.(L54H)
c.161T>C	c.T161C	p.(L54P)
c.161T>G	c.T161G	p.(L54R)
c.163G>C	c.G163C	p.(D55H)
c.163G>T	c.G163T	p.(D55Y)
c.164A>C	c.A164C	p.(D55A)
c.164A>G	c.A164G	p.(D55G)
c.164A>T	c.A164T	p.(D55V)
c.[164A>T; 170A>T]	c.A164T/A170T	p.(D55V/Q57L)
c.165C>G	c.C165G	p.(D55E)
c.167G>A	c.G167A	p.(C56Y)
c.167G>T	c.G167T	p.(C56F)
c.168C>G	c.C168G	p.(C56W)
c.170A>G	c.A170G	p.(Q57R)
c.170A>T	c.A170T	p.(Q57L)
c.172G>A	c.G172A	p.(E58K)
c.175G>A	c.G175A	p.(E59K)
c.175G>C	c.G175C	p.(E59Q)
c.176A>C	c.A176C	p.(E59A)
c.176A>G	c.A176G	p.(E59G)
c.176A>T	c.A176T	p.(E59V)
c.177G>C	c.G177C	p.(E59D)
c.178C>A	c.C178A	p.(P60T)
c.178C>G	c.C178G	p.(P60A)
c.178C>T	c.C178T	p.(P60S)
c.179C>A	c.C179A	p.(P60Q)
c.179C>G	c.C179G	p.(P60R)
c.179C>T	c.C179T	p.(P60L)
c.182A>T	c.A182T	p.(D61V)
c.183T>A	c.T183A	p.(D61E)
c.184_185insTAG	c.184_185insTAG	p.(S62delinsLA)
c.184T>C	c.T184C	p.(S62P)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.184T>G	c.T184G	p.(S62A)
c.185C>A	c.C185A	p.(S62Y)
c.185C>G	c.C185G	p.(S62C)
c.185C>T	c.C185T	p.(S62F)
c.190A>C	c.A190C	p.(I64L)
c.190A>G	c.A190G	p.(I64V)
c.193A>G	c.A193G	p.(S65G)
c.193A>T	c.A193T	p.(S65C)
c.195T>A	c.T195A	p.(S65R)
c.196G>A	c.G196A	p.(E66K)
c.197A>G	c.A197G	p.(E66G)
c.197A>T	c.A197T	p.(E66V)
c.198G>C	c.G198C	p.(E66D)
c.199A>C	c.A199C	p.(K67Q)
c.199A>G	c.A199G	p.(K67E)
c.200A>C	c.A200C	p.(K67T)
c.200A>T	c.A200T	p.(K67M)
c.201G>C	c.G201C	p.(K67N)
c.202C>A	c.C202A	p.(L68I)
c.205T>A	c.T205A	p.(F69I)
c.206T>A	c.T206A	p.(F69Y)
c.207C>A or c.207C>G	c.C207A or c.C207G	p.(F69L)
c.208A>T	c.A208T	p.(M70L)
c.209T>A	c.T209A	p.(M70K)
c.209T>G	c.T209G	p.(M70R)
c.210G>C	c.G210C	p.(M70I)
c.211G>C	c.G211C	p.(E71Q)
c.212A>C	c.A212C	p.(E71A)
c.212A>G	c.A212G	p.(E71G)
c.212A>T	c.A212T	p.(E71V)
c.213G>C	c.G213C	p.(E71D)
c.214A>G	c.A214G	p.(M72V)
c.214A>T	c.A214T	p.(M72L)
c.215T>C	c.T215C	p.(M72T)
c.216G>A or c.216G>T or c.216G>C	c.G216A or c.G216T or c.G216C	p.(M72I)
c.217G>A	c.G217A	p.(A73T)
c.217G>T	c.G217T	p.(A73S)
c.218C>T	c.C218T	p.(A73V)
c.[218C>T; 525C>G]	c.C218T/C525G	p.(A73V/D175E)
c.220G>A	c.G220A	p.(E74K)
c.221A>G	c.A221G	p.(E74G)
c.221A>T	c.A221T	p.(E74V)
c.222G>C	c.G222C	p.(E74D)
c.223C>T	c.C223T	p.(L75F)
c.224T>C	c.T224C	p.(L75P)
c.226A>G	c.A226G	p.(M76V)
c.227T>C	c.T227C	p.(M76T)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.229G>A	c.G229A	p.(V77I)
c.229G>C	c.G229C	p.(V77L)
c.232T>C	c.T232C	p.(S78P)
c.233C>T	c.C233T	p.(S78L)
c.235G>A	c.G235A	p.(E79K)
c.235G>C	c.G235C	p.(E79Q)
c.236A>C	c.A236C	p.(E79A)
c.236A>G	c.A236G	p.(E79G)
c.236A>T	c.A236T	p.(E79V)
c.237A>T	c.A237T	p.(E79D)
c.238G>A	c.G238A	p.(G80S)
c.238G>T	c.G238T	p.(G80C)
c.239G>A	c.G239A	p.(G80D)
c.239G>C	c.G239C	p.(G80A)
c.239G>T	c.G239T	p.(G80V)
c.242G>T	c.G242T	p.(W81L)
c.244A>G	c.A244G	p.(K82E)
c.245A>C	c.A245C	p.(K82T)
c.245A>G	c.A245G	p.(K82R)
c.245A>T	c.A245T	p.(K82M)
c.246G>C	c.G246C	p.(K82N)
c.247G>A	c.G247A	p.(D83N)
c.248A>C	c.A248C	p.(D83A)
c.248A>G	c.A248G	p.(D83G)
c.248A>T	c.A248T	p.(D83V)
c.249T>A	c.T249A	p.(D83E)
c.250G>A	c.G250A	p.(A84T)
c.250G>C	c.G250C	p.(A84P)
c.250G>T	c.G250T	p.(A84S)
c.251C>A	c.C251A	p.(A84E)
c.251C>G	c.C251G	p.(A84G)
c.251C>T	c.C251T	p.(A84V)
c.253G>A	c.G253A	p.(G85S)
c.[253G>A; 254G>A]	c.G253A/G254A	p.(G85N)
c.[253G>A; 254G>T; 255T>G]	c.G253A/G254T/T255G	p.(G85M)
c.253G>C	c.G253C	p.(G85R)
c.253G>T	c.G253T	p.(G85C)
c.254G>A	c.G254A	p.(G85D)
c.254G>C	c.G254C	p.(G85A)
c.257A>T	c.A257T	p.(Y86F)
c.260A>G	c.A260G	p.(E87G)
c.261G>C or c.261G>T	c.G261C or c.G261T	p.(E87D)
c.262T>A	c.T262A	p.(Y88N)
c.262T>C	c.T262C	p.(Y88H)
c.263A>C	c.A263C	p.(Y88S)
c.263A>G	c.A263G	p.(Y88C)
c.265C>G	c.C265G	p.(L89V)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.265C>T	c.C265T	p.(L89F)
c.271A>C	c.A271C	p.(I91L)
c.271A>T	c.A271T	p.(I91F)
c.272T>C	c.T272C	p.(I91T)
c.272T>G	c.T272G	p.(I91S)
c.273T>G	c.T273G	p.(I91M)
c.286A>G	c.A286G	p.(M96V)
c.286A>T	c.A286T	p.(M96L)
c.287T>C	c.T287C	p.(M96T)
c.288G>A or c.288G>T or c.288G>C	c.G288A or c.G288T or c.G288C	p.(M96I)
c.289G>A	c.G289A	p.(A97T)
c.289G>C	c.G289C	p.(A97P)
c.289G>T	c.G289T	p.(A97S)
c.290C>A	c.C290A	p.(A97D)
c.290C>T	c.C290T	p.(A97V)
c.293C>A	c.C293A	p.(P98H)
c.293C>G	c.C293G	p.(P98R)
c.293C>T	c.C293T	p.(P98L)
c.295C>G	c.C295G	p.(Q99E)
c.296A>C	c.A296C	p.(Q99P)
c.296A>G	c.A296G	p.(Q99R)
c.296A>T	c.A296T	p.(Q99L)
c.301G>C	c.G301C	p.(D101H)
c.302A>C	c.A302C	p.(D101A)
c.302A>G	c.A302G	p.(D101G)
c.302A>T	c.A302T	p.(D101V)
c.303T>A	c.T303A	p.(D101E)
c.304T>A	c.T304A	p.(S102T)
c.304T>C	c.T304C	p.(S102P)
c.304T>G	c.T304G	p.(S102A)
c.305C>T	c.C305T	p.(S102L)
c.310G>A	c.G310A	p.(G104S)
c.311G>A	c.G311A	p.(G104D)
c.311G>C	c.G311C	p.(G104A)
c.311G>T	c.G311T	p.(G104V)
c.313A>G	c.A313G	p.(R105G)
c.314G>A	c.G314A	p.(R105K)
c.314G>C	c.G314C	p.(R105T)
c.314G>T	c.G314T	p.(R105I)
c.316C>A	c.C316A	p.(L106I)
c.316C>G	c.C316G	p.(L106V)
c.316C>T	c.C316T	p.(L106F)
c.317T>A	c.T317A	p.(L106H)
c.317T>C	c.T317C	p.(L106P)
c.319C>A	c.C319A	p.(Q107K)
c.319C>G	c.C319G	p.(Q107E)
c.320A>G	c.A320G	p.(Q107R)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.321G>C	c.G321C	p.(Q107H)
c.322G>A	c.G322A	p.(A108T)
c.323C>A	c.C323A	p.(A108E)
c.323C>T	c.C323T	p.(A108V)
c.325G>A	c.G325A	p.(D109N)
c.325G>C	c.G325C	p.(D109H)
c.325G>T	c.G325T	p.(D109Y)
c.326A>C	c.A326C	p.(D109A)
c.326A>G	c.A326G	p.(D109G)
c.327C>G	c.C327G	p.(D109E)
c.328C>A	c.C328A	p.(P110T)
c.334C>G	c.C334G	p.(R112G)
c.335G>A	c.G335A	p.(R112H)
c.335G>T	c.G335T	p.(R112L)
c.337T>A	c.T337A	p.(F113I)
c.337T>C or c.339T>A or c.339T>G	c.T337C or c.T339A or c.T339G	p.(F113L)
c.337T>G	c.T337G	p.(F113V)
c.338T>A	c.T338A	p.(F113Y)
c.341C>T	c.C341T	p.(P114L)
c.343C>A	c.C343A	p.(H115N)
c.343C>G	c.C343G	p.(H115D)
c.346G>C	c.G346C	p.(G116R)
c.350T>C	c.T350C	p.(I117T)
c.351T>G	c.T351G	p.(I117M)
c.352C>T	c.C352T	p.(R118C)
c.361G>A	c.G361A	p.(A121T)
c.362C>T	c.C362T	p.(A121V)
c.367T>A	c.T367A	p.(Y123N)
c.367T>G	c.T367G	p.(Y123D)
c.368A>C	c.A368C	p.(Y123S)
c.368A>G	c.A368G	p.(Y123C)
c.368A>T	c.A368T	p.(Y123F)
c.370G>A	c.G370A	p.(V124I)
c.371T>G	c.T371G	p.(V124G)
c.373C>A	c.C373A	p.(H125N)
c.373C>G	c.C373G	p.(H125D)
c.373C>T	c.C373T	p.(H125Y)
c.374A>G	c.A374G	p.(H125R)
c.374A>T	c.A374T	p.(H125L)
c.376A>G	c.A376G	p.(S126G)
c.376A>T	c.A376T	p.(S126C)
c.377G>T	c.G377T	p.(S126I)
c.379A>G	c.A379G	p.(K127E)
c.383G>A	c.G383A	p.(G128E)
c.383G>C	c.G383C	p.(G128A)
c.385C>G	c.C385G	p.(L129V)
c.388A>C	c.A388C	p.(K130Q)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.389A>T	c.A389T	p.(K130M)
c.390G>C	c.G390C	p.(K130N)
c.391C>G	c.C391G	p.(L131V)
c.397A>C	c.A397C	p.(I133L)
c.397A>G	c.A397G	p.(I133V)
c.397A>T	c.A397T	p.(I133F)
c.398T>C	c.T398C	p.(I133T)
c.399T>G	c.T399G	p.(I133M)
c.[399T>G; 434T>C]	c.T399G/T434C	p.(I133M/F145S)
c.403G>A	c.G403A	p.(A135T)
c.403G>T	c.G403T	p.(A135S)
c.404C>A	c.C404A	p.(A135E)
c.404C>G	c.C404G	p.(A135G)
c.404C>T	c.C404T	p.(A135V)
c.406G>A	c.G406A	p.(D136N)
c.407A>C	c.A407C	p.(D136A)
c.407A>T	c.A407T	p.(D136V)
c.408T>A or c.408T>G	c.T408A or c.T408G	p.(D136E)
c.409G>A	c.G409A	p.(V137I)
c.409G>C	c.G409C	p.(V137L)
c.410T>A	c.T410A	p.(V137D)
c.410T>C	c.T410C	p.(V137A)
c.410T>G	c.T410G	p.(V137G)
c.413G>C	c.G413C	p.(G138A)
c.415A>C	c.A415C	p.(N139H)
c.415A>T	c.A415T	p.(N139Y)
c.416A>G	c.A416G	p.(N139S)
c.416A>T	c.A416T	p.(N139I)
c.417T>A	c.T417A	p.(N139K)
c.418A>C	c.A418C	p.(K140Q)
c.418A>G	c.A418G	p.(K140E)
c.419A>C	c.A419C	p.(K140T)
c.419A>G	c.A419G	p.(K140R)
c.419A>T	c.A419T	p.(K140I)
c.420A>T	c.A420T	p.(K140N)
c.421A>T	c.A421T	p.(T141S)
c.427G>A	c.G427A	p.(A143T)
c.428C>A	c.C428A	p.(A143E)
c.428C>G	c.C428G	p.(A143G)
c.428C>T	c.C428T	p.(A143V)
c.430G>A	c.G430A	p.(G144S)
c.430G>C	c.G430C	p.(G144R)
c.430G>T	c.G430T	p.(G144C)
c.431G>A	c.G431A	p.(G144D)
c.431G>C	c.G431C	p.(G144A)
c.431G>T	c.G431T	p.(G144V)
c.433T>G	c.T433G	p.(F145V)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.434T>A	c.T434A	p.(F145Y)
c.434T>C	c.T434C	p.(F145S)
c.434T>G	c.T434G	p.(F145C)
c.435C>G	c.C435G	p.(F145L)
c.436C>A	c.C436A	p.(P146T)
c.436C>G	c.C436G	p.(P146A)
c.436C>T	c.C436T	p.(P146S)
c.437C>A	c.C437A	p.(P146H)
c.437C>G	c.C437G	p.(P146R)
c.437C>T	c.C437T	p.(P146L)
c.440G>C	c.G440C	p.(G147A)
c.442A>G	c.A442G	p.(S148G)
c.442A>T	c.A442T	p.(S148C)
c.443G>C	c.G443C	p.(S148T)
c.446T>G	c.T446G	p.(F149C)
c.449G>A	c.G449A	p.(G150E)
c.449G>T	c.G449T	p.(G150V)
c.451T>G	c.T451G	p.(Y151D)
c.452A>C	c.A452C	p.(Y151S)
c.452A>G	c.A452G	p.(Y151C)
c.454T>A	c.T454A	p.(Y152N)
c.454T>C	c.T454C	p.(Y152H)
c.454T>G	c.T454G	p.(Y152D)
c.455A>C	c.A455C	p.(Y152S)
c.455A>G	c.A455G	p.(Y152C)
c.455A>T	c.A455T	p.(Y152F)
c.457G>A	c.G457A	p.(D153N)
c.457G>C	c.G457C	p.(D153H)
c.457G>T	c.G457T	p.(D153Y)
c.458A>C	c.A458C	p.(D153A)
c.458A>T	c.A458T	p.(D153V)
c.465T>A or c.465T>G	c.T465A or c.T465G	p.(D155E)
c.466G>A	c.G466A	p.(A156T)
c.466G>T	c.G466T	p.(A156S)
c.467C>G	c.C467G	p.(A156G)
c.467C>T	c.C467T	p.(A156V)
c.469C>A	c.C469A	p.(Q157K)
c.469C>G	c.C469G	p.(Q157E)
c.470A>C	c.A470C	p.(Q157P)
c.470A>T	c.A470T	p.(Q157L)
c.471G>C or c.471G>T	c.G471C or c.G471T	p.(Q157H)
c.472A>G	c.A472G	p.(T158A)
c.472A>T	c.A472T	p.(T158S)
c.473C>A	c.C473A	p.(T158N)
c.473C>T	c.C473T	p.(T158I)
c.475T>A	c.T475A	p.(F159I)
c.475T>G	c.T475G	p.(F159V)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.476T>A	c.T476A	p.(F159Y)
c.476T>G	c.T476G	p.(F159C)
c.477T>A	c.T477A	p.(F159L)
c.478G>A	c.G478A	p.(A160T)
c.478G>T	c.G478T	p.(A160S)
c.479C>A	c.C479A	p.(A160D)
c.479C>G	c.C479G	p.(A160G)
c.479C>T	c.C479T	p.(A160V)
c.481G>A	c.G481A	p.(D161N)
c.481G>C	c.G481C	p.(D161H)
c.481G>T	c.G481T	p.(D161Y)
c.482A>T	c.A482T	p.(D161V)
c.484T>G	c.T484G	p.(W162G)
c.485G>C	c.G485C	p.(W162S)
c.490G>A	c.G490A	p.(V164I)
c.490G>T	c.G490T	p.(V164L)
c.491T>C	c.T491C	p.(V164A)
c.493G>A	c.G493A	p.(D165N)
c.493G>C	c.G493C	p.(D165H)
c.494A>C	c.A494C	p.(D165A)
c.494A>G	c.A494G	p.(D165G)
c.495T>A	c.T495A	p.(D165E)
c.496_497delinsTC	c.496_497delinsTC	p.(L166S)
c.496C>A	c.C496A	p.(L166M)
c.496C>G	c.C496G	p.(L166V)
c.[496C>G; 497T>G]	c.C496G/T497G	p.(L166G)
c.497T>A	c.T497A	p.(L166Q)
c.499C>A	c.C499A	p.(L167I)
c.499C>G	c.C499G	p.(L167V)
c.505T>A	c.T505A	p.(F169I)
c.505T>G	c.T505G	p.(F169V)
c.506T>A	c.T506A	p.(F169Y)
c.506T>C	c.T506C	p.(F169S)
c.506T>G	c.T506G	p.(F169C)
c.507T>A	c.T507A	p.(F169L)
c.511G>A	c.G511A	p.(G171S)
c.512G>C	c.G512C	p.(G171A)
c.512G>T	c.G512T	p.(G171V)
c.517T>C	c.T517C	p.(Y173H)
c.518A>C	c.A518C	p.(Y173S)
c.518A>G	c.A518G	p.(Y173C)
c.518A>T	c.A518T	p.(Y173F)
c.520T>C	c.T520C	p.(C174R)
c.520T>G	c.T520G	p.(C174G)
c.523G>C	c.G523C	p.(D175H)
c.523G>T	c.G523T	p.(D175Y)
c.524A>G	c.A524G	p.(D175G)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.524A>T	c.A524T	p.(D175V)
c.525C>G or c.525C>A	c.C525G or c.C525A	p.(D175E)
c.526A>T	c.A526T	p.(S176C)
c.528T>A	c.T528A	p.(S176R)
c.529T>A	c.T529A	p.(L177M)
c.529T>G	c.T529G	p.(L177V)
c.530T>C	c.T530C	p.(L177S)
c.530T>G	c.T530G	p.(L177W)
c.531G>C	c.G531C	p.(L177F)
c.532G>A	c.G532A	p.(E178K)
c.532G>C	c.G532C	p.(E178Q)
c.533A>C	c.A533C	p.(E178A)
c.533A>G	c.A533G	p.(E178G)
c.538T>A	c.T538A	p.(L180M)
c.538T>G	c.T538G	p.(L180V)
c.539T>C	c.T539C	p.(L180S)
c.539T>G	c.T539G	p.(L180W)
c.540G>C or c.540G>T	c.G540C or c.G540T	p.(L180F)
c.541G>A	c.G541A	p.(A181T)
c.541G>C	c.G541C	p.(A181P)
c.542C>T	c.C542T	p.(A181V)
c.544G>T	c.G544T	p.(D182Y)
c.545A>C	c.A545C	p.(D182A)
c.545A>G	c.A545G	p.(D182G)
c.545A>T	c.A545T	p.(D182V)
c.546T>A	c.T546A	p.(D182E)
c.548G>A	c.G548A	p.(G183D)
c.548G>C	c.G548C	p.(G183A)
c.550T>A	c.T550A	p.(Y184N)
c.550T>C	c.T550C	p.(Y184H)
c.551A>C	c.A551C	p.(Y184S)
c.551A>G	c.A551G	p.(Y184C)
c.551A>T	c.A551T	p.(Y184F)
c.553A>C	c.A553C	p.(K185Q)
c.553A>G	c.A553G	p.(K185E)
c.554A>C	c.A554C	p.(K185T)
c.554A>T	c.A554T	p.(K185M)
c.555G>C	c.G555C	p.(K185N)
c.556C>A	c.C556A	p.(H186N)
c.556C>G	c.C556G	p.(H186D)
c.556C>T	c.C556T	p.(H186Y)
c.557A>T	c.A557T	p.(H186L)
c.558C>G	c.C558G	p.(H186Q)
c.559_564dup	c.559_564dup	p.(M187_S188dup)
c.559A>G	c.A559G	p.(M187V)
c.559A>T	c.A559T	p.(M187L)
c.560T>C	c.T560C	p.(M187T)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.561G>T or c.561G>A or c.561G>C	c.G561T or c.G561A or c.G561C	p.(M187I)
c.562T>A	c.T562A	p.(S188T)
c.562T>C	c.T562C	p.(S188P)
c.562T>G	c.T562G	p.(S188A)
c.563C>A	c.C563A	p.(S188Y)
c.563C>G	c.C563G	p.(S188C)
c.563C>T	c.C563T	p.(S188F)
c.565T>G	c.T565G	p.(L189V)
c.566T>C	c.T566C	p.(L189S)
c.567G>C or c.567G>T	c.G567C or c.G567T	p.(L189F)
c.568G>A	c.G568A	p.(A190T)
c.568G>T	c.G568T	p.(A190S)
c.569C>A	c.C569A	p.(A190D)
c.569C>G	c.C569G	p.(A190G)
c.569C>T	c.C569T	p.(A190V)
c.571C>A	c.C571A	p.(L191M)
c.571C>G	c.C571G	p.(L191V)
c.572T>A	c.T572A	p.(L191Q)
c.574A>C	c.A574C	p.(N192H)
c.574A>G	c.A574G	p.(N192D)
c.575A>C	c.A575C	p.(N192T)
c.575A>G	c.A575G	p.(N192S)
c.576T>A	c.T576A	p.(N192K)
c.577A>G	c.A577G	p.(R193G)
c.577A>T	c.A577T	p.(R193W)
c.578G>C	c.G578C	p.(R193T)
c.578G>T	c.G578T	p.(R193M)
c.580A>C	c.A580C	p.(T194P)
c.580A>G	c.A580G	p.(T194A)
c.580A>T or c.581C>G	c.A580T or c.C581G	p.(T194S)
c.581C>A	c.C581A	p.(T194N)
c.581C>T	c.C581T	p.(T194I)
c.583G>A	c.G583A	p.(G195S)
c.583G>C	c.G583C	p.(G195R)
c.583G>T	c.G583T	p.(G195C)
c.584G>T	c.G584T	p.(G195V)
c.586A>G	c.A586G	p.(R196G)
c.587G>A	c.G587A	p.(R196K)
c.587G>C	c.G587C	p.(R196T)
c.587G>T	c.G587T	p.(R196I)
c.589A>G	c.A589G	p.(S197G)
c.589A>T	c.A589T	p.(S197C)
c.590G>A	c.G590A	p.(S197N)
c.590G>C	c.G590C	p.(S197T)
c.590G>T	c.G590T	p.(S197I)
c.593T>C	c.T593C	p.(I198T)
c.593T>G	c.T593G	p.(I198S)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.594T>G	c.T594G	p.(I198M)
c.595G>A	c.G595A	p.(V199M)
c.595G>C	c.G595C	p.(V199L)
c.596T>A	c.T596A	p.(V199E)
c.596T>C	c.T596C	p.(V199A)
c.596T>G	c.T596G	p.(V199G)
c.598T>A	c.T598A	p.(Y200N)
c.599A>C	c.A599C	p.(Y200S)
c.599A>G	c.A599G	p.(Y200C)
c.601T>A	c.T601A	p.(S201T)
c.601T>G	c.T601G	p.(S201A)
c.602C>A	c.C602A	p.(S201Y)
c.602C>G	c.C602G	p.(S201C)
c.602C>T	c.C602T	p.(S201F)
c.607G>C	c.G607C	p.(E203Q)
c.608A>C	c.A608C	p.(E203A)
c.608A>G	c.A608G	p.(E203G)
c.608A>T	c.A608T	p.(E203V)
c.609G>C or c.609G>T	c.G609C or c.G609T	p.(E203D)
c.610T>G	c.T610G	p.(W204G)
c.611G>C	c.G611C	p.(W204S)
c.611G>T	c.G611T	p.(W204L)
c.613C>A	c.C613A	p.(P205T)
c.613C>T	c.C613T	p.(P205S)
c.614C>T	c.C614T	p.(P205L)
c.616C>A	c.C616A	p.(L206I)
c.616C>G	c.C616G	p.(L206V)
c.616C>T	c.C616T	p.(L206F)
c.617T>A	c.T617A	p.(L206H)
c.617T>G	c.T617G	p.(L206R)
c.619T>C	c.T619C	p.(Y207H)
c.620A>C	c.A620C	p.(Y207S)
c.620A>T	c.A620T	p.(Y207F)
c.623T>A	c.T623A	p.(M208K)
c.623T>G	c.T623G	p.(M208R)
c.625T>A	c.T625A	p.(W209R)
c.625T>G	c.T625G	p.(W209G)
c.627G>C	c.G627C	p.(W209C)
c.628C>A	c.C628A	p.(P210T)
c.628C>T	c.C628T	p.(P210S)
c.629C>A	c.C629A	p.(P210H)
c.629C>T	c.C629T	p.(P210L)
c.631T>C	c.T631C	p.(F211L)
c.631T>G	c.T631G	p.(F211V)
c.632T>A	c.T632A	p.(F211Y)
c.632T>C	c.T632C	p.(F211S)
c.632T>G	c.T632G	p.(F211C)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.635A>C	c.A635C	p.(Q212P)
c.636A>T	c.A636T	p.(Q212H)
c.637A>C	c.A637C	p.(K213Q)
c.637A>G	c.A637G	p.(K213E)
c.638A>G	c.A638G	p.(K213R)
c.638A>T	c.A638T	p.(K213M)
c.640C>A	c.C640A	p.(P214T)
c.640C>G	c.C640G	p.(P214A)
c.640C>T	c.C640T	p.(P214S)
c.641C>A	c.C641A	p.(P214H)
c.641C>G	c.C641G	p.(P214R)
c.641C>T	c.C641T	p.(P214L)
c.643A>C	c.A643C	p.(N215H)
c.643A>G	c.A643G	p.(N215D)
c.643A>T	c.A643T	p.(N215Y)
c.644A>C	c.A644C	p.(N215T)
c.644A>G	c.A644G	p.(N215S)
c.[644A>G; 937G>T]	c.A644G/G937T	p.(N215S/D313Y†)
c.644A>T	c.A644T	p.(N215I)
c.645T>A	c.T645A	p.(N215K)
c.646T>A	c.T646A	p.(Y216N)
c.646T>C	c.T646C	p.(Y216H)
c.646T>G	c.T646G	p.(Y216D)
c.647A>C	c.A647C	p.(Y216S)
c.647A>G	c.A647G	p.(Y216C)
c.647A>T	c.A647T	p.(Y216F)
c.649A>C	c.A649C	p.(T217P)
c.649A>G	c.A649G	p.(T217A)
c.649A>T	c.A649T	p.(T217S)
c.650C>A	c.C650A	p.(T217K)
c.650C>G	c.C650G	p.(T217R)
c.650C>T	c.C650T	p.(T217I)
c.652G>A	c.G652A	p.(E218K)
c.652G>C	c.G652C	p.(E218Q)
c.653A>C	c.A653C	p.(E218A)
c.653A>G	c.A653G	p.(E218G)
c.653A>T	c.A653T	p.(E218V)
c.654A>T	c.A654T	p.(E218D)
c.655A>C	c.A655C	p.(I219L)
c.655A>T	c.A655T	p.(I219F)
c.656T>A	c.T656A	p.(I219N)
c.656T>C	c.T656C	p.(I219T)
c.656T>G	c.T656G	p.(I219S)
c.657C>G	c.C657G	p.(I219M)
c.659G>A	c.G659A	p.(R220Q)
c.659G>C	c.G659C	p.(R220P)
c.659G>T	c.G659T	p.(R220L)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.661C>A	c.C661A	p.(Q221K)
c.661C>G	c.C661G	p.(Q221E)
c.662A>C	c.A662C	p.(Q221P)
c.662A>G	c.A662G	p.(Q221R)
c.662A>T	c.A662T	p.(Q221L)
c.663G>C	c.G663C	p.(Q221H)
c.664T>A	c.T664A	p.(Y222N)
c.664T>C	c.T664C	p.(Y222H)
c.664T>G	c.T664G	p.(Y222D)
c.665A>C	c.A665C	p.(Y222S)
c.665A>G	c.A665G	p.(Y222C)
c.670A>C	c.A670C	p.(N224H)
c.671A>C	c.A671C	p.(N224T)
c.671A>G	c.A671G	p.(N224S)
c.673C>G	c.C673G	p.(H225D)
c.679C>G	c.C679G	p.(R227G)
c.682A>C	c.A682C	p.(N228H)
c.682A>G	c.A682G	p.(N228D)
c.683A>C	c.A683C	p.(N228T)
c.683A>G	c.A683G	p.(N228S)
c.683A>T	c.A683T	p.(N228I)
c.685T>A	c.T685A	p.(F229I)
c.686T>A	c.T686A	p.(F229Y)
c.686T>C	c.T686C	p.(F229S)
c.687T>A or c.687T>G	c.T687A or c.T687G	p.(F229L)
c.688G>C	c.G688C	p.(A230P)
c.689C>A	c.C689A	p.(A230D)
c.689C>G	c.C689G	p.(A230G)
c.689C>T	c.C689T	p.(A230V)
c.694A>C	c.A694C	p.(I232L)
c.694A>G	c.A694G	p.(I232V)
c.695T>C	c.T695C	p.(I232T)
c.696T>G	c.T696G	p.(I232M)
c.698A>C	c.A698C	p.(D233A)
c.698A>G	c.A698G	p.(D233G)
c.698A>T	c.A698T	p.(D233V)
c.699T>A	c.T699A	p.(D233E)
c.703T>A	c.T703A	p.(S235T)
c.703T>G	c.T703G	p.(S235A)
c.710A>T	c.A710T	p.(K237I)
c.712A>T	c.A712T	p.(S238C)
c.712A>G	c.A712G	p.(S238G)
c.713G>A	c.G713A	p.(S238N)
c.713G>C	c.G713C	p.(S238T)
c.713G>T	c.G713T	p.(S238I)
c.715A>T	c.A715T	p.(I239L)
c.716T>C	c.T716C	p.(I239T)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.717A>G	c.A717G	p.(I239M)
c.718A>G	c.A718G	p.(K240E)
c.719A>G	c.A719G	p.(K240R)
c.719A>T	c.A719T	p.(K240M)
c.720G>C or c.720G>T	c.G720C or c.G720T	p.(K240N)
c.721A>T	c.A721T	p.(S241C)
c.722G>C	c.G722C	p.(S241T)
c.722G>T	c.G722T	p.(S241I)
c.724A>C	c.A724C	p.(I242L)
c.724A>G	c.A724G	p.(I242V)
c.724A>T	c.A724T	p.(I242F)
c.725T>A	c.T725A	p.(I242N)
c.725T>C	c.T725C	p.(I242T)
c.725T>G	c.T725G	p.(I242S)
c.726C>G	c.C726G	p.(I242M)
c.727T>A	c.T727A	p.(L243M)
c.727T>G	c.T727G	p.(L243V)
c.728T>C	c.T728C	p.(L243S)
c.728T>G	c.T728G	p.(L243W)
c.729G>C or c.729G>T	c.G729C or c.G729T	p.(L243F)
c.730G>A	c.G730A	p.(D244N)
c.730G>C	c.G730C	p.(D244H)
c.730G>T	c.G730T	p.(D244Y)
c.731A>C	c.A731C	p.(D244A)
c.731A>G	c.A731G	p.(D244G)
c.731A>T	c.A731T	p.(D244V)
c.732C>G	c.C732G	p.(D244E)
c.733T>G	c.T733G	p.(W245G)
c.735G>C	c.G735C	p.(W245C)
c.736A>G	c.A736G	p.(T246A)
c.737C>A	c.C737A	p.(T246K)
c.737C>G	c.C737G	p.(T246R)
c.737C>T	c.C737T	p.(T246I)
c.739T>A	c.T739A	p.(S247T)
c.739T>G	c.T739G	p.(S247A)
c.740C>A	c.C740A	p.(S247Y)
c.740C>G	c.C740G	p.(S247C)
c.740C>T	c.C740T	p.(S247F)
c.742T>G	c.T742G	p.(F248V)
c.743T>A	c.T743A	p.(F248Y)
c.743T>G	c.T743G	p.(F248C)
c.744T>A	c.T744A	p.(F248L)
c.745A>C	c.A745C	p.(N249H)
c.745A>G	c.A745G	p.(N249D)
c.745A>T	c.A745T	p.(N249Y)
c.746A>C	c.A746C	p.(N249T)
c.746A>G	c.A746G	p.(N249S)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.746A>T	c.A746T	p.(N249I)
c.747C>G or c.747C>A	c.C747G or c.C747A	p.(N249K)
c.748C>A	c.C748A	p.(Q250K)
c.748C>G	c.C748G	p.(Q250E)
c.749A>C	c.A749C	p.(Q250P)
c.749A>G	c.A749G	p.(Q250R)
c.749A>T	c.A749T	p.(Q250L)
c.750G>C	c.G750C	p.(Q250H)
c.751G>A	c.G751A	p.(E251K)
c.751G>C	c.G751C	p.(E251Q)
c.752A>G	c.A752G	p.(E251G)
c.752A>T	c.A752T	p.(E251V)
c.754A>G	c.A754G	p.(R252G)
c.757A>G	c.A757G	p.(I253V)
c.757A>T	c.A757T	p.(I253F)
c.758T>A	c.T758A	p.(I253N)
c.758T>C	c.T758C	p.(I253T)
c.758T>G	c.T758G	p.(I253S)
c.760-762delGTT or c.761-763del	c.760_762delGTT or c.761_763del	p.(V254del)
c.760G>T	c.G760T	p.(V254F)
c.761T>A	c.T761A	p.(V254D)
c.761T>C	c.T761C	p.(V254A)
c.761T>G	c.T761G	p.(V254G)
c.763G>A	c.G763A	p.(D255N)
c.763G>C	c.G763C	p.(D255H)
c.763G>T	c.G763T	p.(D255Y)
c.764A>C	c.A764C	p.(D255A)
c.764A>T	c.A764T	p.(D255V)
c.765T>A	c.T765A	p.(D255E)
c.766G>C	c.G766C	p.(V256L)
c.767T>A	c.T767A	p.(V256D)
c.767T>G	c.T767G	p.(V256G)
c.769G>A	c.G769A	p.(A257T)
c.769G>C	c.G769C	p.(A257P)
c.769G>T	c.G769T	p.(A257S)
c.770C>G	c.C770G	p.(A257G)
c.770C>T	c.C770T	p.(A257V)
c.772G>C or c.772G>A	c.G772C or c.G772A	p.(G258R)
c.773G>A	c.G773A	p.(G258E)
c.773G>T	c.G773T	p.(G258V)
c.775C>A	c.C775A	p.(P259T)
c.775C>G	c.C775G	p.(P259A)
c.775C>T	c.C775T	p.(P259S)
c.776C>A	c.C776A	p.(P259Q)
c.776C>G	c.C776G	p.(P259R)
c.776C>T	c.C776T	p.(P259L)
c.778G>T	c.G778T	p.(G260W)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.779G>A	c.G779A	p.(G260E)
c.779G>C	c.G779C	p.(G260A)
c.781G>A	c.G781A	p.(G261S)
c.781G>C	c.G781C	p.(G261R)
c.781G>T	c.G781T	p.(G261C)
c.782G>C	c.G782C	p.(G261A)
c.787A>C	c.A787C	p.(N263H)
c.788A>C	c.A788C	p.(N263T)
c.788A>G	c.A788G	p.(N263S)
c.790G>A	c.G790A	p.(D264N)
c.790G>C	c.G790C	p.(D264H)
c.790G>T	c.G790T	p.(D264Y)
c.793C>G	c.C793G	p.(P265A)
c.794C>A	c.C794A	p.(P265Q)
c.794C>T	c.C794T	p.(P265L)
c.799A>G	c.A799G	p.(M267V)
c.799A>T	c.A799T	p.(M267L)
c.800T>C	c.T800C	p.(M267T)
c.802T>A	c.T802A	p.(L268I)
c.804A>T	c.A804T	p.(L268F)
c.805G>A	c.G805A	p.(V269M)
c.805G>C	c.G805C	p.(V269L)
c.806T>C	c.T806C	p.(V269A)
c.808A>C	c.A808C	p.(I270L)
c.808A>G	c.A808G	p.(I270V)
c.809T>C	c.T809C	p.(I270T)
c.809T>G	c.T809G	p.(I270S)
c.810T>G	c.T810G	p.(I270M)
c.811G>A	c.G811A	p.(G271S)
c.[811G>A; 937G>T]	c.G811A/G937T	p.(G271S/D313Y†)
c.812G>A	c.G812A	p.(G271D)
c.812G>C	c.G812C	p.(G271A)
c.814A>G	c.A814G	p.(N272D)
c.818T>A	c.T818A	p.(F273Y)
c.823C>A	c.C823A	p.(L275I)
c.823C>G	c.C823G	p.(L275V)
c.827G>A	c.G827A	p.(S276N)
c.827G>C	c.G827C	p.(S276T)
c.829T>G	c.T829G	p.(W277G)
c.830G>T	c.G830T	p.(W277L)
c.831G>T or c.831G>C	c.G831T or c.G831C	p.(W277C)
c.832A>T	c.A832T	p.(N278Y)
c.833A>T	c.A833T	p.(N278I)
c.835C>G	c.C835G	p.(Q279E)
c.838C>A	c.C838A	p.(Q280K)
c.839A>G	c.A839G	p.(Q280R)
c.839A>T	c.A839T	p.(Q280L)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.840A>T or c.840A>C	c.A840T or c.A840C	p.(Q280H)
c.841G>C	c.G841C	p.(V281L)
c.842T>A	c.T842A	p.(V281E)
c.842T>C	c.T842C	p.(V281A)
c.842T>G	c.T842G	p.(V281G)
c.844A>G	c.A844G	p.(T282A)
c.844A>T	c.A844T	p.(T282S)
c.845C>T	c.C845T	p.(T282I)
c.847C>G	c.C847G	p.(Q283E)
c.848A>T	c.A848T	p.(Q283L)
c.849G>C	c.G849C	p.(Q283H)
c.850A>G	c.A850G	p.(M284V)
c.850A>T	c.A850T	p.(M284L)
c.851T>C	c.T851C	p.(M284T)
c.852G>C	c.G852C	p.(M284I)
c.853G>A	c.G853A	p.(A285T)
c.854C>G	c.C854G	p.(A285G)
c.854C>T	c.C854T	p.(A285V)
c.856C>G	c.C856G	p.(L286V)
c.856C>T	c.C856T	p.(L286F)
c.857T>A	c.T857A	p.(L286H)
c.860G>T	c.G860T	p.(W287L)
c.862G>C	c.G862C	p.(A288P)
c.862G>T	c.G862T	p.(A288S)
c.863C>G	c.C863G	p.(A288G)
c.863C>T	c.C863T	p.(A288V)
c.865A>C	c.A865C	p.(I289L)
c.865A>G	c.A865G	p.(I289V)
c.866T>C	c.T866C	p.(I289T)
c.866T>G	c.T866G	p.(I289S)
c.868A>C or c.868A>T	c.A868C or c.A868T	p.(M290L)
c.868A>G	c.A868G	p.(M290V)
c.869T>C	c.T869C	p.(M290T)
c.870G>A or c.870G>C or c.870G>T	c.G870A or c.G870C or c.G870T	p.(M290I)
c.871G>A	c.G871A	p.(A291T)
c.871G>T	c.G871T	p.(A291S)
c.872C>G	c.C872G	p.(A291G)
c.874G>T	c.G874T	p.(A292S)
c.875C>G	c.C875G	p.(A292G)
c.877C>A	c.C877A	p.(P293T)
c.880T>A	c.T880A	p.(L294I)
c.880T>G	c.T880G	p.(L294V)
c.881T>C	c.T881C	p.(L294S)
c.882A>T	c.A882T	p.(L294F)
c.883T>A	c.T883A	p.(F295I)
c.883T>G	c.T883G	p.(F295V)
c.884T>A	c.T884A	p.(F295Y)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.884T>C	c.T884C	p.(F295S)
c.884T>G	c.T884G	p.(F295C)
c.886A>G	c.A886G	p.(M296V)
c.886A>T or c.886A>C	c.A886T or c.A886C	p.(M296L)
c.887T>C	c.T887C	p.(M296T)
c.888G>A or c.888G>T or c.888G>C	c.G888A or c.G888T or c.G888C	p.(M296I)
c.889T>A	c.T889A	p.(S297T)
c.892A>G	c.A892G	p.(N298D)
c.893A>C	c.A893C	p.(N298T)
c.893A>G	c.A893G	p.(N298S)
c.893A>T	c.A893T	p.(N298I)
c.895G>A	c.G895A	p.(D299N)
c.895G>C	c.G895C	p.(D299H)
c.897C>G or c.897C>A	c.C897G or c.C897A	p.(D299E)
c.898C>A	c.C898A	p.(L300I)
c.898C>G	c.C898G	p.(L300V)
c.898C>T	c.C898T	p.(L300F)
c.899T>C	c.T899C	p.(L300P)
c.901C>G	c.C901G	p.(R301G)
c.902G>A	c.G902A	p.(R301Q)
c.902G>C	c.G902C	p.(R301P)
c.902G>T	c.G902T	p.(R301L)
c.904C>A	c.C904A	p.(H302N)
c.904C>G	c.C904G	p.(H302D)
c.904C>T	c.C904T	p.(H302Y)
c.905A>T	c.A905T	p.(H302L)
c.907A>G	c.A907G	p.(I303V)
c.907A>T	c.A907T	p.(I303F)
c.908T>A	c.T908A	p.(I303N)
c.908T>C	c.T908C	p.(I303T)
c.908T>G	c.T908G	p.(I303S)
c.911G>A	c.G911A	p.(S304N)
c.911G>C	c.G911C	p.(S304T)
c.911G>T	c.G911T	p.(S304I)
c.916C>G	c.C916G	p.(Q306E)
c.917A>C	c.A917C	p.(Q306P)
c.917A>T	c.A917T	p.(Q306L)
c.919G>A	c.G919A	p.(A307T)
c.919G>C	c.G919C	p.(A307P)
c.919G>T	c.G919T	p.(A307S)
c.920C>A	c.C920A	p.(A307D)
c.920C>G	c.C920G	p.(A307G)
c.920C>T	c.C920T	p.(A307V)
c.922A>C	c.A922C	p.(K308Q)
c.922A>G	c.A922G	p.(K308E)
c.923A>G	c.A923G	p.(K308R)
c.923A>T	c.A923T	p.(K308I)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.924A>T or c.924A>C	c.A924T or c.A924C	p.(K308N)
c.925G>A	c.G925A	p.(A309T)
c.925G>C	c.G925C	p.(A309P)
c.926C>A	c.C926A	p.(A309D)
c.926C>T	c.C926T	p.(A309V)
c.928C>A	c.C928A	p.(L310I)
c.928C>G	c.C928G	p.(L310V)
c.928C>T	c.C928T	p.(L310F)
c.931C>A	c.C931A	p.(L311I)
c.931C>G	c.C931G	p.(L311V)
c.934C>A	c.C934A	p.(Q312K)
c.934C>G	c.C934G	p.(Q312E)
c.935A>G	c.A935G	p.(Q312R)
c.935A>T	c.A935T	p.(Q312L)
c.936G>T or c.936G>C	c.G936T or c.G936C	p.(Q312H)
c.937G>T†	c.G937T†	p.(D313Y†)
c.[937G>T†; 1232G>A]	c.G937T†/G1232A	p.(D313Y†/G411D)
c.938A>G	c.A938G	p.(D313G)
c.938A>T	c.A938T	p.(D313V)
c.939T>A	c.T939A	p.(D313E)
c.940A>G	c.A940G	p.(K314E)
c.941A>C	c.A941C	p.(K314T)
c.941A>T	c.A941T	p.(K314M)
c.942G>C	c.G942C	p.(K314N)
c.943G>A	c.G943A	p.(D315N)
c.943G>C	c.G943C	p.(D315H)
c.943G>T	c.G943T	p.(D315Y)
c.944A>C	c.A944C	p.(D315A)
c.944A>G	c.A944G	p.(D315G)
c.944A>T	c.A944T	p.(D315V)
c.946G>A	c.G946A	p.(V316I)
c.946G>C	c.G946C	p.(V316L)
c.947T>C	c.T947C	p.(V316A)
c.947T>G	c.T947G	p.(V316G)
c.949A>C	c.A949C	p.(I317L)
c.949A>G	c.A949G	p.(I317V)
c.950T>C	c.T950C	p.(I317T)
c.951T>G	c.T951G	p.(I317M)
c.952G>A	c.G952A	p.(A318T)
c.952G>C	c.G952C	p.(A318P)
c.953C>A	c.C953A	p.(A318D)
c.953C>T	c.C953T	p.(A318V)
c.955A>T	c.A955T	p.(I319F)
c.956T>C	c.T956C	p.(I319T)
c.957C>G	c.C957G	p.(I319M)
c.958A>C	c.A958C	p.(N320H)
c.959A>C	c.A959C	p.(N320T)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.959A>G	c.A959G	p.(N320S)
c.959A>T	c.A959T	p.(N320I)
c.961C>A	c.C961A	p.(Q321K)
c.962A>G	c.A962G	p.(Q321R)
c.962A>T	c.A962T	p.(Q321L)
c.963G>C or c.963G>T	c.G963C or c.G963T	p.(Q321H)
c.964G>A	c.G964A	p.(D322N)
c.964G>C	c.G964C	p.(D322H)
c.965A>C	c.A965C	p.(D322A)
c.965A>T	c.A965T	p.(D322V)
c.966C>A or c.966C>G	c.C966A or c.C966G	p.(D322E)
c.967C>A	c.C967A	p.(P323T)
c.968C>G	c.C968G	p.(P323R)
c.970T>G	c.T970G	p.(L324V)
c.971T>G	c.T971G	p.(L324W)
c.973G>A	c.G973A	p.(G325S)
c.973G>C	c.G973C	p.(G325R)
c.973G>T	c.G973T	p.(G325C)
c.974G>C	c.G974C	p.(G325A)
c.974G>T	c.G974T	p.(G325V)
c.976A>C	c.A976C	p.(K326Q)
c.976A>G	c.A976G	p.(K326E)
c.977A>C	c.A977C	p.(K326T)
c.977A>G	c.A977G	p.(K326R)
c.977A>T	c.A977T	p.(K326M)
c.978G>C or c.978G>T	c.G978C or c.G978T	p.(K326N)
c.979C>G	c.C979G	p.(Q327E)
c.980A>C	c.A980C	p.(Q327P)
c.980A>T	c.A980T	p.(Q327L)
c.981A>T	c.A981T	p.(Q327H)
c.983G>C	c.G983C	p.(G328A)
c.985T>A	c.T985A	p.(Y329N)
c.985T>C	c.T985C	p.(Y329H)
c.985T>G	c.T985G	p.(Y329D)
c.986A>G	c.A986G	p.(Y329C)
c.986A>T	c.A986T	p.(Y329F)
c.988C>A	c.C988A	p.(Q330K)
c.988C>G	c.C988G	p.(Q330E)
c.989A>C	c.A989C	p.(Q330P)
c.989A>G	c.A989G	p.(Q330R)
c.990G>C	c.G990C	p.(Q330H)
c.991C>G	c.C991G	p.(L331V)
c.992T>A	c.T992A	p.(L331H)
c.992T>C	c.T992C	p.(L331P)
c.992T>G	c.T992G	p.(L331R)
c.994A>G	c.A994G	p.(R332G)
c.995G>C	c.G995C	p.(R332T)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.995G>T	c.G995T	p.(R332I)
c.996A>T	c.A996T	p.(R332S)
c.997C>G	c.C997G	p.(Q333E)
c.998A>C	c.A998C	p.(Q333P)
c.998A>T	c.A998T	p.(Q333L)
c.1000G>C	c.G1000C	p.(G334R)
c.1001G>A	c.G1001A	p.(G334E)
c.1001G>T	c.G1001T	p.(G334V)
c.1003G>T	c.G1003T	p.(D335Y)
c.1004A>C	c.A1004C	p.(D335A)
c.1004A>G	c.A1004G	p.(D335G)
c.1004A>T	c.A1004T	p.(D335V)
c.1005C>G	c.C1005G	p.(D335E)
c.1006A>G	c.A1006G	p.(N336D)
c.1006A>T	c.A1006T	p.(N336Y)
c.1007A>C	c.A1007C	p.(N336T)
c.1007A>G	c.A1007G	p.(N336S)
c.1007A>T	c.A1007T	p.(N336I)
c.1009T>G	c.T1009G	p.(F337V)
c.1010T>A	c.T1010A	p.(F337Y)
c.1010T>C	c.T1010C	p.(F337S)
c.1010T>G	c.T1010G	p.(F337C)
c.1011T>A	c.T1011A	p.(F337L)
c.1012G>A	c.G1012A	p.(E338K)
c.1013A>C	c.A1013C	p.(E338A)
c.1013A>G	c.A1013G	p.(E338G)
c.1013A>T	c.A1013T	p.(E338V)
c.1014A>T	c.A1014T	p.(E338D)
c.1015G>A	c.G1015A	p.(V339M)
c.1016T>A	c.T1016A	p.(V339E)
c.1016T>C	c.T1016C	p.(V339A)
c.1021G>C	c.G1021C	p.(E341Q)
c.1022A>C	c.A1022C	p.(E341A)
c.1027C>A	c.C1027A	p.(P343T)
c.1027C>G	c.C1027G	p.(P343A)
c.1027C>T	c.C1027T	p.(P343S)
c.1028C>T	c.C1028T	p.(P343L)
c.1030C>G	c.C1030G	p.(L344V)
c.1030C>T	c.C1030T	p.(L344F)
c.1031T>G	c.T1031G	p.(L344R)
c.1033T>C	c.T1033C	p.(S345P)
c.1036G>T	c.G1036T	p.(G346C)
c.1037G>A	c.G1037A	p.(G346D)
c.1037G>C	c.G1037C	p.(G346A)
c.1037G>T	c.G1037T	p.(G346V)
c.1039T>A	c.T1039A	p.(L347I)
c.1043C>A	c.C1043A	p.(A348D)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.1046G>C	c.G1046C	p.(W349S)
c.1046G>T	c.G1046T	p.(W349L)
c.1047G>C	c.G1047C	p.(W349C)
c.1048G>A	c.G1048A	p.(A350T)
c.1048G>T	c.G1048T	p.(A350S)
c.1049C>G	c.C1049G	p.(A350G)
c.1049C>T	c.C1049T	p.(A350V)
c.1052T>A	c.T1052A	p.(V351E)
c.1052T>C	c.T1052C	p.(V351A)
c.1054G>A	c.G1054A	p.(A352T)
c.1054G>T	c.G1054T	p.(A352S)
c.1055C>G	c.C1055G	p.(A352G)
c.1055C>T	c.C1055T	p.(A352V)
c.1057A>T	c.A1057T	p.(M353L)
c.1058T>A	c.T1058A	p.(M353K)
c.1058T>C	c.T1058C	p.(M353T)
c.1061T>A	c.T1061A	p.(I354K)
c.1061T>G	c.T1061G	p.(I354R)
c.1063A>C	c.A1063C	p.(N355H)
c.1063A>G	c.A1063G	p.(N355D)
c.1063A>T	c.A1063T	p.(N355Y)
c.1064A>G	c.A1064G	p.(N355S)
c.1066C>G	c.C1066G	p.(R356G)
c.1066C>T	c.C1066T	p.(R356W)
c.1067G>A	c.G1067A	p.(R356Q)
c.1067G>C	c.G1067C	p.(R356P)
c.1067G>T	c.G1067T	p.(R356L)
c.1069C>G	c.C1069G	p.(Q357E)
c.1072G>C	c.G1072C	p.(E358Q)
c.1073A>C	c.A1073C	p.(E358A)
c.1073A>G	c.A1073G	p.(E358G)
c.1074G>T or c.1074G>C	c.G1074T or c.G1074C	p.(E358D)
c.1075A>C	c.A1075C	p.(I359L)
c.1075A>G	c.A1075G	p.(I359V)
c.1075A>T	c.A1075T	p.(I359F)
c.1076T>A	c.T1076A	p.(I359N)
c.1076T>C	c.T1076C	p.(I359T)
c.1076T>G	c.T1076G	p.(I359S)
c.1078G>A	c.G1078A	p.(G360S)
c.1078G>C	c.G1078C	p.(G360R)
c.1078G>T	c.G1078T	p.(G360C)
c.1079G>A	c.G1079A	p.(G360D)
c.1079G>C	c.G1079C	p.(G360A)
c.1082G>A	c.G1082A	p.(G361E)
c.1082G>C	c.G1082C	p.(G361A)
c.1084C>A	c.C1084A	p.(P362T)
c.1084C>G	c.C1084G	p.(P362A)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.1084C>T	c.C1084T	p.(P362S)
c.1085C>A	c.C1085A	p.(P362H)
c.1085C>G	c.C1085G	p.(P362R)
c.1085C>T	c.C1085T	p.(P362L)
c.1087C>A	c.C1087A	p.(R363S)
c.1087C>G	c.C1087G	p.(R363G)
c.1087C>T	c.C1087T	p.(R363C)
c.1088G>A	c.G1088A	p.(R363H)
c.1088G>T	c.G1088T	p.(R363L)
c.1090T>C	c.T1090C	p.(S364P)
c.1091C>G	c.C1091G	p.(S364C)
c.1093T>A	c.T1093A	p.(Y365N)
c.1093T>G	c.T1093G	p.(Y365D)
c.1094A>C	c.A1094C	p.(Y365S)
c.1094A>T	c.A1094T	p.(Y365F)
c.1096A>C	c.A1096C	p.(T366P)
c.1096A>T	c.A1096T	p.(T366S)
c.1097C>A	c.C1097A	p.(T366N)
c.1097C>T	c.C1097T	p.(T366I)
c.1099A>C	c.A1099C	p.(I367L)
c.1099A>T	c.A1099T	p.(I367F)
c.1101C>G	c.C1101G	p.(I367M)
c.1102G>A	c.G1102A	p.(A368T)
c.1102G>C	c.G1102C	p.(A368P)
c.1103C>G	c.C1103G	p.(A368G)
c.1105G>A	c.G1105A	p.(V369I)
c.1105G>C	c.G1105C	p.(V369L)
c.1105G>T	c.G1105T	p.(V369F)
c.1106T>C	c.T1106C	p.(V369A)
c.1106T>G	c.T1106G	p.(V369G)
c.1108G>A	c.G1108A	p.(A370T)
c.1108G>C	c.G1108C	p.(A370P)
c.1109C>A	c.C1109A	p.(A370D)
c.1109C>G	c.C1109G	p.(A370G)
c.1109C>T	c.C1109T	p.(A370V)
c.1111T>A	c.T1111A	p.(S371T)
c.1112C>G	c.C1112G	p.(S371C)
c.1117G>A	c.G1117A	p.(G373S)
c.1117G>T	c.G1117T	p.(G373C)
c.1118G>C	c.G1118C	p.(G373A)
c.1120A>G	c.A1120G	p.(K374E)
c.1121A>C	c.A1121C	p.(K374T)
c.1121A>G	c.A1121G	p.(K374R)
c.1121A>T	c.A1121T	p.(K374I)
c.1123G>C	c.G1123C	p.(G375R)
c.1124G>A	c.G1124A	p.(G375E)
c.1124G>C	c.G1124C	p.(G375A)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.1126G>A	c.G1126A	p.(V376M)
c.1126G>C	c.G1126C	p.(V376L)
c.1127T>A	c.T1127A	p.(V376E)
c.1127T>G	c.T1127G	p.(V376G)
c.1129G>A	c.G1129A	p.(A377T)
c.1129G>C	c.G1129C	p.(A377P)
c.1129G>T	c.G1129T	p.(A377S)
c.1130C>G	c.C1130G	p.(A377G)
c.1135A>G	c.A1135G	p.(N379D)
c.1136A>C	c.A1136C	p.(N379T)
c.1136A>T	c.A1136T	p.(N379I)
c.1137T>A	c.T1137A	p.(N379K)
c.1138C>A	c.C1138A	p.(P380T)
c.1138C>G	c.C1138G	p.(P380A)
c.1139C>A	c.C1139A	p.(P380H)
c.1139C>G	c.C1139G	p.(P380R)
c.1139C>T	c.C1139T	p.(P380L)
c.1142C>A	c.C1142A	p.(A381D)
c.1147T>A	c.T1147A	p.(F383I)
c.1148T>A	c.T1148A	p.(F383Y)
c.1148T>G	c.T1148G	p.(F383C)
c.1150A>T	c.A1150T	p.(I384F)
c.1151T>C	c.T1151C	p.(I384T)
c.1152C>G	c.C1152G	p.(I384M)
c.1153A>G	c.A1153G	p.(T385A)
c.1154C>T	c.C1154T	p.(T385I)
c.1156C>A	c.C1156A	p.(Q386K)
c.1157A>T	c.A1157T	p.(Q386L)
c.1158G>C	c.G1158C	p.(Q386H)
c.1159C>A	c.C1159A	p.(L387I)
c.1159C>T	c.C1159T	p.(L387F)
c.1160T>A	c.T1160A	p.(L387H)
c.1160T>G	c.T1160G	p.(L387R)
c.1162C>A	c.C1162A	p.(L388I)
c.1162C>T	c.C1162T	p.(L388F)
c.1162C>G	c.C1162G	p.(L388V)
c.1163T>A	c.T1163A	p.(L388H)
c.1163T>G	c.T1163G	p.(L388R)
c.1168G>A	c.G1168A	p.(V390M)
c.1171A>C	c.A1171C	p.(K391Q)
c.1171A>G	c.A1171G	p.(K391E)
c.1172A>C	c.A1172C	p.(K391T)
c.1172A>G	c.A1172G	p.(K391R)
c.1172A>T	c.A1172T	p.(K391I)
c.1173A>T	c.A1173T	p.(K391N)
c.1174A>G	c.A1174G	p.(R392G)
c.1174A>T	c.A1174T	p.(R392W)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.1175G>A	c.G1175A	p.(R392K)
c.1175G>C	c.G1175C	p.(R392T)
c.1175G>T	c.G1175T	p.(R392M)
c.1177A>C	c.A1177C	p.(K393Q)
c.1177A>G	c.A1177G	p.(K393E)
c.1178A>C	c.A1178C	p.(K393T)
c.1179G>C	c.G1179C	p.(K393N)
c.1180C>A	c.C1180A	p.(L394I)
c.1181T>A	c.T1181A	p.(L394Q)
c.1181T>C	c.T1181C	p.(L394P)
c.1181T>G	c.T1181G	p.(L394R)
c.1183G>C	c.G1183C	p.(G395R)
c.1184G>A	c.G1184A	p.(G395E)
c.1184G>C	c.G1184C	p.(G395A)
c.1186T>A	c.T1186A	p.(F396I)
c.1186T>G	c.T1186G	p.(F396V)
c.1187T>G	c.T1187G	p.(F396C)
c.1188C>G	c.C1188G	p.(F396L)
c.1189T>A	c.T1189A	p.(Y397N)
c.1189T>C	c.T1189C	p.(Y397H)
c.1190A>C	c.A1190C	p.(Y397S)
c.1190A>G	c.A1190G	p.(Y397C)
c.1190A>T	c.A1190T	p.(Y397F)
c.1192G>A	c.G1192A	p.(E398K)
c.1192G>C	c.G1192C	p.(E398Q)
c.1193A>G	c.A1193G	p.(E398G)
c.1195T>A	c.T1195A	p.(W399R)
c.1195T>G	c.T1195G	p.(W399G)
c.1198A>C	c.A1198C	p.(T400P)
c.1198A>G	c.A1198G	p.(T400A)
c.1198A>T	c.A1198T	p.(T400S)
c.1199C>A	c.C1199A	p.(T400N)
c.1199C>T	c.C1199T	p.(T400I)
c.1201T>A	c.T1201A	p.(S401T)
c.1201T>G	c.T1201G	p.(S401A)
c.1202_1203insGACTTC	c.1202_1203insGACTTC	p.(T400_S401dup)
c.1202C>T	c.C1202T	p.(S401L)
c.1204A>G	c.A1204G	p.(R402G)
c.1204A>T	c.A1204T	p.(R402W)
c.1205G>C	c.G1205C	p.(R402T)
c.1205G>T	c.G1205T	p.(R402M)
c.1206G>C	c.G1206C	p.(R402S)
c.1207T>G	c.T1207G	p.(L403V)
c.1208T>C	c.T1208C	p.(L403S)
c.1209A>T	c.A1209T	p.(L403F)
c.1210A>G	c.A1210G	p.(R404G)
c.1211G>A	c.G1211A	p.(R404K)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.1211G>C	c.G1211C	p.(R404T)
c.1211G>T	c.G1211T	p.(R404I)
c.1212A>T	c.A1212T	p.(R404S)
c.1213A>G	c.A1213G	p.(S405G)
c.1216C>G	c.C1216G	p.(H406D)
c.1217A>T	c.A1217T	p.(H406L)
c.1218C>G	c.C1218G	p.(H406Q)
c.1219A>T	c.A1219T	p.(I407L)
c.1220T>C	c.T1220C	p.(I407T)
c.1221A>G	c.A1221G	p.(I407M)
c.1222A>C	c.A1222C	p.(N408H)
c.1222A>G	c.A1222G	p.(N408D)
c.1222A>T	c.A1222T	p.(N408Y)
c.1223A>C	c.A1223C	p.(N408T)
c.1225C>A	c.C1225A	p.(P409T)
c.1225C>G	c.C1225G	p.(P409A)
c.1225C>T	c.C1225T	p.(P409S)
c.1226C>T	c.C1226T	p.(P409L)
c.1228A>G	c.A1228G	p.(T410A)
c.1228A>T	c.A1228T	p.(T410S)
c.1229C>T	c.C1229T	p.(T410I)
c.1231G>A	c.G1231A	p.(G411S)
c.1231G>T	c.G1231T	p.(G411C)
c.1232G>A	c.G1232A	p.(G411D)
c.1232G>C	c.G1232C	p.(G411A)
c.1232G>T	c.G1232T	p.(G411V)
c.1234A>C	c.A1234C	p.(T412P)
c.1234A>G	c.A1234G	p.(T412A)
c.1234A>T	c.A1234T	p.(T412S)
c.1235C>A	c.C1235A	p.(T412N)
c.1235C>T	c.C1235T	p.(T412I)
c.1237G>A	c.G1237A	p.(V413I)
c.1237G>T	c.G1237T	p.(V413F)
c.1238T>G	c.T1238G	p.(V413G)
c.1240T>G	c.T1240G	p.(L414V)
c.1242G>C	c.G1242C	p.(L414F)
c.1243C>A	c.C1243A	p.(L415I)
c.1244T>A	c.T1244A	p.(L415H)
c.1246C>G	c.C1246G	p.(Q416E)
c.1247A>T	c.A1247T	p.(Q416L)
c.1248G>C	c.G1248C	p.(Q416H)
c.1249C>A	c.C1249A	p.(L417I)
c.1252G>A	c.G1252A	p.(E418K)
c.1252G>C	c.G1252C	p.(E418Q)
c.1253A>C	c.A1253C	p.(E418A)
c.1253A>G	c.A1253G	p.(E418G)
c.1254A>T	c.A1254T	p.(E418D)

Nucleotide Change (long)	Nucleotide Change (short)	Protein Sequence Change (one-letter code)
c.1255A>G	c.A1255G	p.(N419D)
c.1255A>T	c.A1255T	p.(N419Y)
c.1256A>C	c.A1256C	p.(N419T)
c.1256A>G	c.A1256G	p.(N419S)
c.1256A>T	c.A1256T	p.(N419I)
c.1258A>C	c.A1258C	p.(T420P)
c.1258A>T	c.A1258T	p.(T420S)
c.1259C>A	c.C1259A	p.(T420K)
c.1259C>G	c.C1259G	p.(T420R)
c.1261A>G	c.A1261G	p.(M421V)
c.1261A>T	c.A1261T	p.(M421L)
c.1262T>A	c.T1262A	p.(M421K)
c.1262T>C	c.T1262C	p.(M421T)
c.1262T>G	c.T1262G	p.(M421R)
c.1263G>C	c.G1263C	p.(M421I)
c.1265A>C	c.A1265C	p.(Q422P)
c.1267A>T	c.A1267T	p.(M423L)
c.1268T>A	c.T1268A	p.(M423K)
c.1268T>C	c.T1268C	p.(M423T)
c.1269G>C	c.G1269C	p.(M423I)
c.1271C>T	c.C1271T	p.(S424L)
c.1275A>C	c.A1275C	p.(L425F)
c.1279G>A	c.G1279A	p.(D427N)
c.1286T>G	c.T1286G	p.(L429R)

† Based on available published data, the *GLA* mutation c.937G>T, (p.(D313Y)) is considered benign (not causing Fabry disease). Consultation with a clinical genetics' professional is strongly recommended in patients with Fabry disease who have this *GLA* variant as additional evaluations may be indicated.

Not all the variants in Table 5 have been tested for amenability in the in vitro HEK-assay (see 10.2 Pharmacodynamics - Variants Amenable to GALAFOLD).

Table 6 *GLA* Variants Not Amenable to GALAFOLD Based on the In Vitro Assay

GLA variants that are not qualified for testing based on the mechanism of action of GALAFOLD (e.g. splicing, nonsense or out-of-frame deletions/insertions) are considered not amenable. The *GLA* variants not amenable to treatment with GALAFOLD, referred to as Table 6, are only accessible by healthcare professionals at www.galafoldamenabilitytable.com (see "Non-amenable *GLA* Mutations" table).

Not all the variants on the website (see "Non-amenable *GLA* Mutations" table) have been tested for amenability in the in vitro HEK-assay (see 10.2 Pharmacodynamics - Variants Amenable to GALAFOLD).

10.2 Pharmacodynamics

Overview: Migalastat is a specific potent reversible competitive inhibitor of human α-Gal A and also a specific structural stabilizer for wild-type and many mutant forms of α-Gal A. Incubation of cells derived from Fabry patients with an amenable mutation or of cells transiently expressing an amenable mutation results in an accumulation of migalastat-inhibited α-Gal A protein in lysosomes. When the concentration

of migalastat drops to a sub-inhibitory level, the accumulated α-Gal A regains enzymatic function, resulting in increased enzymatic activity compared to that without migalastat treatment. For non-amenable mutations, migalastat treatment resulted in a limited or no increase in the cellular α-Gal A activity decreased enzymatic activity.

In Phase 2 pharmacodynamics trials in Fabry patients with amenable mutations, oral treatment with various doses and dosing intervals of migalastat hydrochloride (HCl), including 150 mg every other day, resulted in apparent increases in α-Gal A activity in peripheral blood mononuclear cells (PBMCs), skin, and kidney when assayed in a system where the concentration of migalastat was significantly diluted. Migalastat HCl dosed at 25 mg to 250 mg BID resulted in a dose-dependent and significant increase in urine GL-3 in most of the patients. However, migalastat HCl 150 mg every other day decreased GL-3 in most patients. Increases in PBMC α-Gal A activity and decreases in GL-3 observed with migalastat HCl 150 mg every other day were not further enhanced when patients switched to higher, less frequent doses (250 and 500 mg, 3 days on/4 days off).

In the Phase 2 and Phase 3 clinical trials, in non-amenable patients, GALAFOLD (150 mg migalastat HCl, every other day) resulted in a significant increase from baseline in the levels of plasma lyso-Gb_3 and urine GL-3 in all male patients and 80% of the female patients.

In vitro: Migalastat is a potent specific competitive reversible inhibitor of human α-Gal A with a K_i value in the low nanomolar range, and also specifically increases the physical stability of recombinant human α-Gal A (rhα-Gal A) in vitro at pH 7.4 or at lysosomal pH (about pH 5.2).

In cells derived from Fabry patients with amenable mutations or transiently transfected with a *GLA* construct with an amenable mutation, migalastat incubation increased the cellular α-Gal A activity, which is detected only after the cells had been thoroughly washed to remove migalastat. The increase in α-Gal A activity was associated with increased cellular levels of α-Gal A protein. The sensitivity and the maximum extent of the response to migalastat differed significantly among different mutations.

For non-amenable mutations, migalastat resulted in a limited or no increase in the cellular α-Gal A activity. Normal (wild-type) α-Gal A responded to migalastat similarly to non-amenable α-Gal A mutations. Therefore, α-Gal A response to GALAFOLD in heterozygous female Fabry patients with the same amenable mutation may differ. Moreover, the response in females may be lower than that of male Fabry patients with the same mutation due to suppression of the activity of the wild-type α-Gal A protein in heterozygous females.

Migalastat-induced α-Gal A activity can only be realized after the intracellular migalastat concentration drops below a sub-inhibitory level. For example, fibroblasts derived from male Fabry patients significantly accumulate GL-3. A 7-day incubation with migalastat followed by 3-day incubation without migalastat resulted in a significant reduction in cellular GL-3. However, 10-day incubation with migalastat and no off period did not change the level of cellular GL-3.

Cardiac Electrophysiology: In a randomized, double-blind, double-dummy, positive- and placebo-controlled, four-arm crossover ECG assessment study in healthy subjects (N = 52), single 150 mg and 1250 mg doses of migalastat HCl were not observed to have any clinically relevant effect on the QTc interval, the QRS duration, the PR interval, or heart rate.

Variants Amenable to GALAFOLD: To identify Fabry disease mutations likely to have a clinically relevant response to GALAFOLD, more than 1000 mutations were tested using an in vitro HEK-293 assay. Human Embryonic Kidney (HEK-293) cell lines were transiently transfected with specific *GLA* variants (mutations) which produced mutant α-Gal A proteins. In the transfected cells, amenability of the *GLA*

mutations was assessed after a 5-day incubation with 10 µmol/L migalastat. A *GLA* mutation was classified as amenable to migalastat if the resultant mutant α-Gal A activity (measured in the cell lysates) met two criteria: 1) it showed an absolute increase in α-Gal A activity that is ≥ 3.0% of wild-type α-Gal A activity, and 2) it showed a relative increase in α-Gal A activity that is ≥ 1.20- fold above baseline after the cells are treated with 10 µM migalastat for 5 days. The migalastat concentration of 10 µM used in the assay is close to the mean plasma C_{max} of migalastat following a single oral dose of migalastat 123 mg in healthy individuals (see 10.3 Pharmacokinetics - Table 7). Mutations with an in vitro response to migalastat that do not meet the amenability criteria are classified as non-amenable.

Predictability of the extent of clinical outcome based on the GLP HEK-293 assay is limited. The in vitro HEK-293 assay did not evaluate trafficking of the mutant α-Gal A proteins into the lysosome or the dissociation of migalastat from the mutant α-Gal A proteins within the lysosome. Also, the in vitro assay did not test whether a *GLA* mutation causes Fabry disease or not.

The extent of the in vitro response to 10 µM migalastat differs across amenable mutations. Across amenable mutations listed in Table 5, the absolute increase in α-Gal A activity ranged from 3.0% to 75.9% of wild-type; the relative increase in α-Gal A activity ranged from 1.2-fold to 37.34-fold above baseline; and mean baseline activity ranged from BLD (below the limit of detection) to 124.5% of wild-type.

Phase 3 clinical studies were conducted in patients with Fabry disease having 43 of the amenable mutations listed in Table 5.

Clinical Studies: A Phase 2 study was conducted in Fabry patients with amenable mutations. Migalastat treatment in each patient included dose-escalation from 25, to 100, to 250 mg migalastat HCl BID with each dose level for two weeks, then 25 mg migalastat HCl BID for 6 weeks, and finally 50 mg migalastat HCl QD for 6 weeks. Urine GL-3 was significantly increased from baseline in a dose-dependent manner in most patients dosed at 25, 100, and 250 mg BID. About half of the patients dosed at 50 mg QD had a moderate increase in urine GL-3.

Decreases in GL-3 were observed in most male and female patients with amenable mutations treated with 150 mg migalastat HCl every other day. These decreases were not further enhanced when patients were switched to higher and less frequent doses (250 and 500 mg, 3 days on/4 days off).

There were 9 male patients with 5 different non-amenable mutations and 10 female patients with 7 different non-amenable mutations in clinical trials. GALAFOLD 123 mg every other day resulted in a significant increase from baseline in the levels of plasma lyso-Gb_3 and urine GL-3 in all the male patients and 80% of the female patients.

10.3 Pharmacokinetics

The pharmacokinetic parameters obtained following single and multiple dose studies of GALAFOLD are presented in Table 7.

Table 7 Summary of Migalastat Plasma Pharmacokinetic Parameters in Healthy Subjects

	C_{max}[a]	t_{max}[b] (h)	$t_{½}$[c] (h)	$AUC_{0-\infty}$[a] (ng·hr/mL)	CL/F[c] (L/h)	V_z/F[c] (L)
Single Oral Dose of 150 mg Migalastat HCl	1500 to 1600 ng/mL or about 10 µM	3	4	10000 to 13000	4 to 6	77 to 133

[a]Approximate range of means across Phase 1 studies following single 150 mg migalastat HCl dose
[b]Approximate median across Phase 1 studies
[c]Approximate range of means across Phase 1 studies

Absorption:

The absolute bioavailability (AUC) for a single oral 150 mg migalastat HCl dose was approximately 75%. Following a single oral dose of 150 mg migalastat HCl 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 HCl oral doses from 50 mg to 1,250 mg.

Effect of Food

Migalastat HCl 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. GALAFOLD exposure is decreased by approximately 40% when taken with food, therefore it should not be taken within 2 hours before and after food. GALAFOLD should be taken every other day at the same time of day to ensure optimal benefits to the patient.

Effect of Beverages

Co-administration of a single dose of migalastat with 280 mL of coffee containing 190 mg caffeine resulted in mean reduction of $AUC_{0-\infty}$ by 55% and C_{max} by 60% when compared with administration of migalastat with water. The time to reach the maximum plasma concentration (t_{max}) of migalastat was not affected by administration of caffeine in comparison to water. No clinically significant pharmacokinetic changes were observed for migalastat when co-administered with natural (sucrose) and artificial (aspartame or acesulfame potassium) sweeteners (see 4.4 Administration and 9.5 Drug-Food Interactions).

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 that it is well distributed into tissues. There was no appreciable plasma protein binding in vitro with [^{14}C]-migalastat HCl over the concentration range of 1 to 100 µM (200 to 19,900 ng/mL).

In nonclinical tissue distribution studies in mice and rats, migalastat was shown to penetrate the blood:brain barrier.

Metabolism:

Based upon in vivo data, migalastat is a substrate for UGT, being a minor elimination pathway. A pharmacokinetic trial in healthy male volunteers with 150 mg [^{14}C]-migalastat HCl revealed that 99% of the radio-labeled dose recovered in plasma was comprised of unchanged migalastat (77%) and 3 dehydrogenated O-glucuronide-conjugated metabolites, M1 to M3 (13%). Approximately 9% of the total radioactivity was unassigned.

Elimination:

A pharmacokinetic trial in healthy male volunteers with 150 mg [^{14}C]-migalastat HCl revealed that approximately 77% of the radio-labeled dose was recovered in urine of which 55% 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 radio-labeled dose was excreted in feces, with unchanged migalastat being the only measured component.

Following ascending single oral doses (25-675 mg migalastat HCl), 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 and Conditions:

- **Pediatrics:** The pharmacokinetics of migalastat were characterized in 20 adolescent subjects (12 to < 18 years and weighing ≥ 45 kg) with Fabry disease who received the same dosage regimen as adults (123 mg migalastat capsule every other day) in an open label phase 3b trial (AT1001-020).

  Assessment of exposure was simulated between adolescent subjects (12 to < 18 years and weighing ≥ 45 kg) receiving migalastat 123 mg once every other day compared to adults receiving the same dosing regimen. Model derived AUC_{tau} in adolescent subjects (12 to < 18 years) were similar to adult exposures.

  No dosage adjustment is required for adolescents 12 to < 18 years of age who weigh ≥ 45 kg. See 4 DOSAGE AND ADMINISTRATION.

- **Geriatrics:** Clinical studies of GALAFOLD included a 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.

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

- **Ethnic Origin:** Data generated from a study in subjects of Japanese ethnicity indicated that there are no differences in the pharmacokinetic profile of migalastat due to race.

- **Hepatic Insufficiency:** 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 would affect the pharmacokinetics of migalastat.

- **Renal Insufficiency:** GALAFOLD has not been studied in patients with Fabry disease who have an eGFR 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 (AUC) were increased by 4.3-fold in

subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Mean plasma $T_{1/2}$ in these patients was about 32 hours.

The exposures (AUC) were increased 1.8-fold in subjects with moderate renal impairment (eGFR between 60 mL/min/1.73 m^2 and 30 mL/min/1.73 m^2). Mean plasma $t_{1/2}$ in these patients was about 22 hours.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-30°C) in the original package in order to protect from moisture.

Store in a safe place and out of the reach of children.

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

12 SPECIAL HANDLING INSTRUCTIONS

For disposal instructions, see 11 STORAGE, STABILITY AND DISPOSAL.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

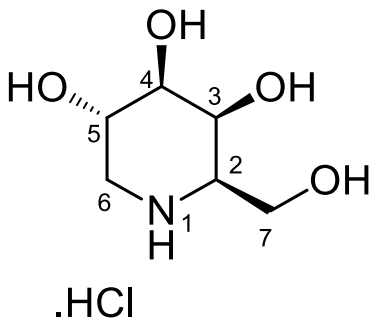
Drug Substance

Proper name: migalastat hydrochloride (USAN); migalastat (INN)

Chemical name: 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-, hydrochloride (1:1), (2R,3S,4R,5S)

Molecular formula and molecular mass: C6H13NO4●HCl, 199.63 g/mol (hydrochloride salt), 163.17 g/mol (free base)

Structural formula:



Physicochemical properties: Migalastat is a white to almost white solid. It is freely soluble between pH 1.2 and 7.5 in aqueous media. It has a pH of 4.7 (1% aqueous solution at room temperature) and pKa of 7.47 ± 0.01.

Solvent	Solution pH	Solubility (mg/mL)	Temperature (°C)
Hydrochloric Acid	1.2	> 500	15 to 25
Phthalate Buffer	4.6	> 500	15 to 25
Phosphate Buffer	6.8	> 500	15 to 25
Phosphate Buffer	7.5	> 500	15 to 25
Methanol	n/a	6	20
Ethanol	n/a	< 1	20
Acetonitrile	n/a	< 1	20

14 CLINICAL TRIALS

The clinical efficacy and safety of GALAFOLD have been evaluated in two completed Phase 3 pivotal trials and two open-label extension (OLE) trials. All patients received the recommended dosage of 123 mg GALAFOLD every other day. Phase 3 clinical studies were conducted in patients with Fabry disease having 43 of the amenable mutations listed in Table 5.

14.1 Trial Design and Study Demographics

Table 8 Summary of Patient Demographics for Clinical Trials in Fabry Disease

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)[1]	Mean age (Range)	Sex
AT1001-012 (enzyme replacement therapy-experienced)	Phase 3 randomized open-label, active-controlled	GALAFOLD 123 mg every other day oral, or enzyme replacement therapy (agalsidase alfa or agalsidase beta) IV infusion every 14 days (as per approved prescribing information) 18 months (Followed by a 12-month open-label period)	57	48.9 years (18 to 72 years)	25/32

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)[1]	Mean age (Range)	Sex
AT1001-011 (enzyme replacement therapy-naïve)	Phase 3 randomized double-blind placebo-controlled trial	GALAFOLD 123 mg or placebo every other day oral 6 months (followed by an 18-month open-label period)	67	42.2 years (16 to 68 years)	24/43

[1] Number of randomized patients with Fabry disease who were predicted to have migalastat-responsive

The first Phase 3 trial (ERT-experienced trial) was an 18-month randomized open-label active comparator trial that evaluated the efficacy and safety of GALAFOLD compared to enzyme replacement therapy (ERT [agalsidase beta or agalsidase alfa]) in male and female patients (84% Caucasian) with Fabry disease who were receiving ERT prior to trial entry and who have amenable mutations (identified based on a GLP-validated in vitro assay, n = 52). At baseline, 53% of patients had neurologic disorders, 72% had cardiac disorders, and 75% of patients had renal disorders. Patients were randomized in a ratio of 1.5:1 to switch to GALAFOLD (150 mg migalastat HCl, every other day) or continue with ERT. After 18 months of treatment, patients in the ERT treatment arm switched to GALAFOLD (150 mg migalastat HCl, every other day) and patients in the GALAFOLD treatment arm continued on the same treatment for a 12-month extension period.

The second Phase 3 trial (ERT-naïve trial) was a 6-month randomized double-blind placebo-controlled trial (through month 6) with an 18-month open-label period that evaluated the efficacy and safety of GALAFOLD in male and female patients (97% Caucasian) with Fabry disease who were naïve to ERT or had previously been on ERT and had stopped for at least 6 months prior to trial entry and who have amenable mutations (identified based on a GLP-validated in vitro assay, n = 50; 32 females, 18 males). Patients were randomized in a ratio of 1:1 to receive either GALAFOLD (150 mg migalastat HCl, every other day) or placebo for 6 months (Stage 1), followed by Stage 2 in which patients in the GALAFOLD arm continued to receive GALAFOLD (150 mg migalastat HCl, every other day) and patients in the placebo arm switched to GALAFOLD (150 mg migalastat HCl, every other day) for 6 months, followed by an open-label extension phase in which all patients from Stage 2 continued to receive GALAFOLD treatment for 12 months.

The first OLE trial (Study AT1001-041) included patients from Phase 2 and Phase 3 studies, and is completed. Study AT1001-041 evaluated the long-term safety (n = 85) and efficacy (n = 68; patients with amenable mutations) of GALAFOLD (150 mg migalastat HCl, every other day) treatment. A total of 62 patients with amenable mutations completed the study. The mean extent of exposure to GALAFOLD for patients with amenable mutations in Study AT1001-041 was 22 months.

The second OLE trial (Study AT1001-042) included patients that either transferred from the OLE Study AT1001-041 or patients who directly continued from the Phase 3 ERT-experienced trial (Study AT1001-012) into the OLE Study AT1001-042. The mean extent of exposure to the marketed dose of GALAFOLD 123 mg every other day in patients in this study was 32.3 (±12.3) months (n=82). The maximum exposure was 51.9 months.

14.2 Study Results

Renal Function

In the ERT-experienced trial, renal function remained stable for up to 18 months of treatment with GALAFOLD. Mean annualized rate of change in $eGFR_{CKD-EPI}$ in patients with amenable mutations 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 annualized rate of change from baseline in $eGFR_{CKD-EPI}$ in patients with amenable mutations treated for 30 months with GALAFOLD was -1.7 mL/min/1.73 m^2 (95% CI: -2.7, -0.8; n = 31).

In the ERT-naïve trial, no clinically significant differences in renal function were observed during the initial 6-month placebo-controlled period. In the open-label period, renal function remained stable over 18-24 months of GALAFOLD treatment (18 months for patients who were administered placebo in Stage 1 and 24 months for patients treated with GALAFOLD in Stage 1). After 18/24 months of GALAFOLD treatment, the mean annualized rate of change in $eGFR_{CKD-EPI}$ in patients with amenable mutations was -0.30 mL/min/1.73 m^2 (95% CI: -1.65, 1.04; n = 41).

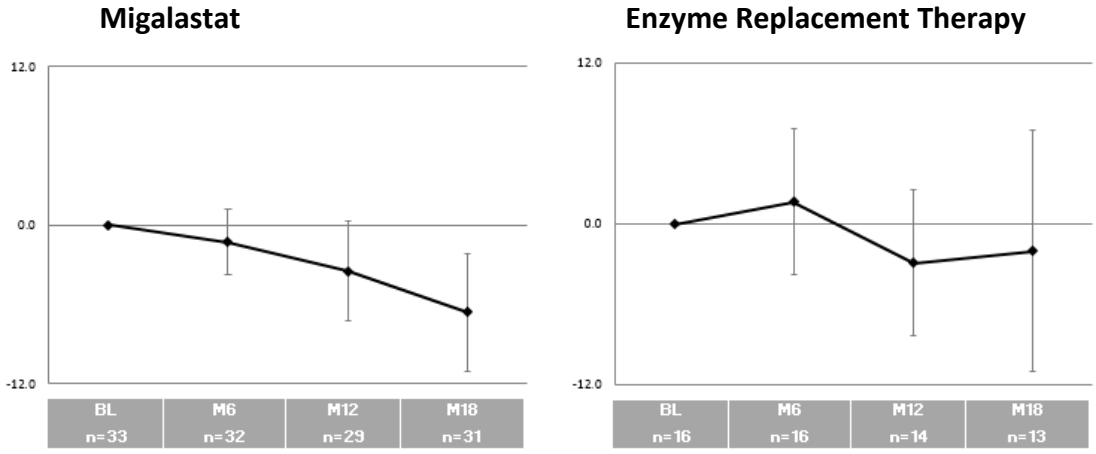
In ERT-naïve patients continuing from Study AT1001-011 into extension Study AT1001-041, the annualized change in $eGFR_{CKD-EPI}$ in patients on migalastat 150 mg every other day remained stable over an average of 3.5 years (minimum: 1.5 years, maximum: 4.9 years). The mean annualized rate of change over this period in patients with amenable mutations was -0.75 mL/min/1.73 m^2/year (95% CI: -1.89, 0.40; n = 41).

In patients continuing treatment in Study AT1001-042, findings showed that after a mean duration of 5.2 years, ERT-naïve patients had a mean annualized rate of change from baseline of -1.71 mL/min/1.73 m^2 (95% CI: -2.83, -0.60; n=47). After a mean duration of 4.3 years, ERT-experienced patients had a mean annualized rate of change from baseline of -1.78 mL/min/1.73 m^2 (95% CI: -3.76, 0.20; n=49).

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 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 g/m^2 (95% CI: -15.7, 2.6; n = 13) for migalastat and 4.5 g/m^2 (95% CI: -10.7, 18.4; n = 5) for ERT. In patients with amenable mutations, after 30 months of 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).

Figure 1 ERT – Experienced Trial: LVMi Change (Mean and 95% CI) Over 18 Months with Migalastat and Enzyme Replacement Therapy (ERT)



The y-axes present change in LVMi and units are g/m^2
BL = baseline; ERT = enzyme replacement therapy; LVMi = left ventricular mass index; M = Month

In the ERT-naïve trial, no clinically significant differences in LVMi were observed during the initial 6-month placebo-controlled period. The mean change from baseline to Month 24 in LVMi in all patients with amenable mutations was -9.1 g/m^2 (95% CI: -16.90, -1.21; n = 29). After follow-up in the OLE Study AT1001-041, the mean change from baseline to Month 36 in LVMi in patients with amenable mutations was -8.3 g/m^2 (95% CI: -17.06, 0.45; n = 25). The mean change from baseline to Month 24 in LVMi in patients with amenable mutations with left ventricular hypertrophy at baseline (females with baseline LVMi > 95 g/m^2 or males with baseline LVMi > 115 g/m^2) was -22.5 g/m^2 (95% CI: -41.64, -3.36; n = 9). After follow-up in the OLE Study AT1001-041, the mean change from baseline in LVMi in patients with amenable mutations with left ventricular hypertrophy at baseline at Month 36 was -30.0 g/m^2 (95% CI: -57.9, -2.2; n = 4) and at Month 48 was -33.1 (95% CI: -60.9, -5.4; n=4).

In the ERT-experienced and ERT-naïve patients, after follow up in OLE clinical study AT1001-042, the mean change in LVMi from AT1001-042 baseline was 1.2 g/m^2 (95% CI: -5.3, 7.7; n=15) and -5.6 g/m^2 (95% CI: -28.5, 17.2; n=4) respectively, for patients treated with GALAFOLD for an average of 2.4 and 2.9 years (up to 4.0 and 4.3 years, respectively).

Disease Substrate

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 with amenable mutations randomized to GALAFOLD in Stage 1 demonstrated a statistically significant greater reduction (± SEM) in mean interstitial capillary GL-3 inclusions (-0.25 ± 0.10; -39%, n = 25) at Month 6 compared to placebo (+0.07 ± 0.13; +14%, n = 20) (p = 0.008). Patients with amenable mutations randomized 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%, n = 17) (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.

In the ERT-naïve trial, the median change from baseline to Month 6 (Stage 1) in plasma lyso-Gb_3 (nmol/L) was -2.37 (range -69.7, 1.8) in patients with amenable mutations on GALAFOLD (n = 18) and 0.53 (range -21.5, 16.3) in patients with amenable mutations on placebo (n = 13) at Month 6. The 13 patients with amenable mutations who were initially on placebo for 6 months and who switched to GALAFOLD for another 6 months (Stage 2) had a median change in plasma lyso-Gb_3 (nmol/L) of -2.72 (range -61.1, -0.3). The 18 patients with amenable mutations who were treated with GALAFOLD for 6 months and then continued on GALAFOLD for another 6 months had no further changes in plasma lyso-Gb_3 at Month 12.

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 months' duration of the study. Plasma lyso-Gb_3 levels also remained low in patients on ERT for up to 18 months. The median change from baseline to Month 18 in plasma lyso-Gb_3 (nmol/L) was 0.54 (range -2.27, 28.3) in patients with amenable mutations on GALAFOLD (n = 30) and -0.03 (range -11.9, 2.57) in patients with amenable mutations on ERT (n = 14). The median change from baseline to Month 30 in plasma lyso-Gb_3 (nmol/L) was 0.81 (range -2.33, 71.60) in patients with amenable mutations treated with GALAFOLD for 30 months (n = 29) and 1.46 (range -0.40, 25.07) in patients with amenable mutations who switched from ERT to GALAFOLD at Month 18 (n = 9).

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.

Table 9 Number (%) of Patients in the Modified Intent to Treat Population Who Experienced the Composite Clinical Outcome

Component	GALAFOLD (n = 34)	Enzyme Replacement Therapy (n = 18)
Renal	8 (24%)	6 (33%)
Cardiac	2 (6%)	3 (17%)
Cerebrovascular	0 (0%)	1 (6%)
Death	0 (0%)	0 (0%)
Any	10 (29%)	8* (44%)

* Two ERT-experienced patients each had 1 cardiac and 1 renal event.

Renal events included increased proteinuria and decreased GFR (GALAFOLD and ERT treatment groups); cardiac events included arrhythmia (GALAFOLD and ERT treatment groups) and cardiac failure (ERT treatment group only); cerebrovascular event was transient ischemic attack.

The frequency of events reported for the composite clinical outcome in patients with amenable mutations treated with GALAFOLD over 30 months (32%; n = 10) was higher than that demonstrated over the 18-month treatment period (23%; n = 7).

Pediatric Population

In Study AT1001-020, a 1-year, Phase 3b, open-label, uncontrolled, multicenter study, the safety, PK, pharmacodynamic (PD), and efficacy of migalastat treatment (123 mg taken once every other day) was

evaluated in 21 adolescent subjects (12 to < 18 years of age and weighing ≥45 kg) with Fabry disease and who have amenable mutations of the gene encoding α-galactosidase A (GLA). Subjects were either naïve to enzyme replacement therapy (ERT) or had stopped ERT at least 14 days before screening. The mean number of years since diagnosis of Fabry disease was 9.6 (± 4.25) years.

At 1 year, consistent renal, cardiac, and pharmacodynamic results as well as responses to patient-reported outcomes were observed, compared to baseline values. The overall mean (SD) change from baseline in eGFR was -1.6 (15.4) mL/min/1.73 m^2 (n=19). The overall mean (SD) change from baseline for LVMi was -3.9 (13.5) g/m^2 (n=18). LVMi decreased in 10 subjects and increased in 8 subjects, but all subjects remained within normal limits at 12 months. Baseline plasma lyso-Gb_3 was 12.00 ng/mL and the overall mean (SD) change from baseline in plasma lyso-Gb3 was -0.06 (32.9) (n=19). A reduction in plasma lyso-Gb3 from baseline was observed in ERT-naïve subjects (median -2.23 ng/ml, n=9) and levels remained generally stable in ERT-experienced subjects (median 0.54 ng/ml, n=10). There were no notable changes in patient reported outcomes.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Repeat-Dose Toxicology

Repeat-dose toxicity studies were conducted for up to 6 months' duration in rats, for up to 14 days' duration in dogs, and for up to 9 months' duration in monkeys. In rats, dogs, and monkeys, migalastat was generally well tolerated with no evidence of systemic toxicity.

In chronic studies in rats and monkeys, the highest doses on study were established as the no-observed-adverse-effect-level (NOAEL). End-of-study systemic exposure to migalastat at the NOAEL dose greatly exceeded the exposure in humans at a clinically relevant dose of 150 mg migalastat HCl once every other day (≥ 55-fold based on AUC in the chronic toxicity studies).

Carcinogenicity:

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.

Genotoxicity:

Migalastat was non-mutagenic in vitro in a 5-strain bacterial mutagenicity study and in the mouse lymphoma L5178Y cell Tk gene mutation assay in the presence and absence of metabolic activation. In vivo, migalastat did not induce micronuclei in bone marrow erythrocytes upon migalastat dosing at 2,000 mg/kg/day for 2 days.

Reproductive and Developmental Toxicology:

In male rats, migalastat treatment impaired fertility at systemic exposures that were less than that in humans at a clinically relevant dose (< 0.2-fold, based on AUC). Effects on male fertility were reversible following a 4-week non-dosing recovery period. At doses which impaired male fertility, there were no macroscopic changes or histological changes in the male reproductive system or changes in sperm parameters that could account for the reduction in fertility.

In the rabbit embryo-fetal toxicity study, findings including embryo-fetal death, a reduction in mean fetal weight, retarded ossification, and slightly increased incidences of minor skeletal abnormalities were observed at doses associated with maternal toxicity (≥ 300 mg/kg/day; ≥ 240-fold, based on AUC).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Galafold®

Migalastat capsules

Read this carefully before you start taking **Galafold** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Galafold**.

What is Galafold used for?

Galafold is used for the long-term treatment of Fabry disease in adults and adolescents aged 12 years and older who have certain genetic mutations (changes) in an enzyme called alpha-galactosidase A (α-Gal A). Galafold is not to be used in patients with Fabry disease who have other genetic mutations. Your doctor will perform a genetic test to determine if you can take Galafold.

Galafold is NOT for use in children younger than 12 years of age or in adolescents weighing less than 45 kg.

How does Galafold work?

Fabry disease is caused by a defect in the α–Gal A enzyme. This 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.

Galafold works by fixing a defect in the α–Gal A enzyme so that it can work better to reduce the amount of GL-3 that has built up in your cells and tissues. This helps the organs affected by Fabry disease work better.

What are the ingredients in Galafold?

Medicinal ingredients: migalastat hydrochloride

Non-medicinal ingredients: black printing ink, gelatin, indigo carmine (FD&C Blue 2), magnesium stearate, pregelatinized starch (maize), and titanium dioxide.

Galafold comes in the following dosage forms:

Capsule: 123 mg migalastat (as migalastat hydrochloride)

Do not use Galafold if:

- you are allergic to migalastat or any of the other ingredients in Galafold
- you are allergic to any component of the Galafold container
- you are also receiving another medicine used to treat Fabry disease called Enzyme Replacement Therapy (ERT)
- you have severe kidney problems

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Galafold. Talk about any health conditions or problems you may have, including if you:

- have problems with your kidneys
- have problems with your liver
- or your partner are planning a pregnancy

Other warnings you should know about:

- **Pregnancy:**
  Do not take Galafold if you are pregnant. Galafold may harm an unborn baby. You must tell your healthcare professional if you are or think you may be pregnant before taking Galafold. You must use an effective birth control method while taking Galafold. Talk to your healthcare professional for advice on effective methods of birth control.
- **Breast-feeding:**
  You should not breastfeed if you are taking Galafold since it may get into your breast milk and harm your baby. Talk to your healthcare professional if you are planning on breastfeeding in the future.
- **Fertility:**
  It is not known if Galafold affects fertility in men and women. Talk to your healthcare professional if you and your partner are planning to have a baby in the future.
- **Testing:**
  Before you start taking Galafold your healthcare professional will do tests to check how well your kidneys work. You will also have tests done during your treatment with Galafold to check how Galafold is affecting your blood, kidneys and heart. These tests will be done at least every 6 months, possibly more often.
- **Driving and using machines:**
  Before doing tasks which require special attention, wait until you know how you respond to Galafold.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Galafold:

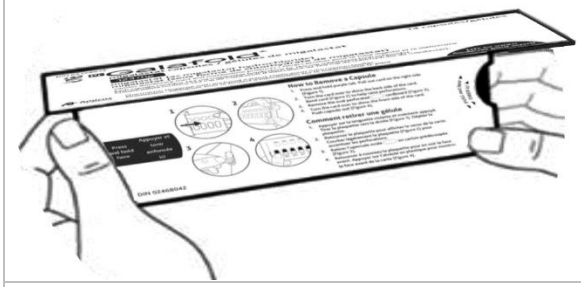
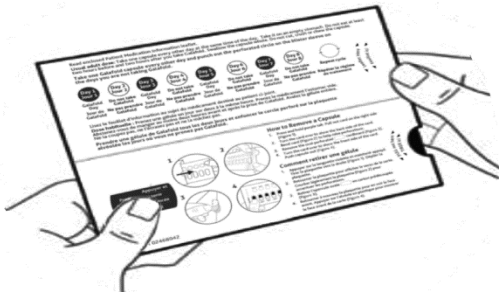
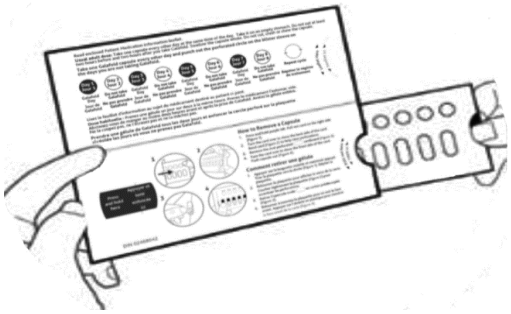
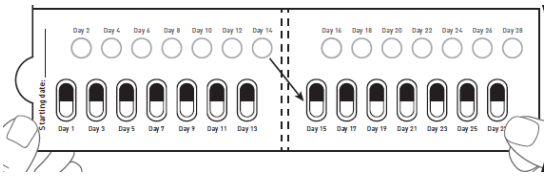
- Other medicines used to treat Fabry disease called enzyme replacement therapy (ERT) like agalsidase.
- Caffeine. This includes medicines, supplements or any other products containing caffeine.

How to take Galafold:

- Take one capsule every other day at the same time of the day.
- Do not take Galafold two days in a row.
- Take Galafold on an empty stomach. Your body may not absorb the medicine completely if it is taken with food. Do not consume food or caffeine for at least 2 hours before and for 2 hours after you take Galafold. This will give you a period of at least 4 hours of fasting.
- You can drink water (plain, flavored, or sweetened), fruit juices without pulp, and caffeine-free carbonated beverages during this 4-hour fasting period.
- Swallow the capsule whole. Do not cut, crush or chew the capsule.
- Do not stop taking this medicine without talking to your doctor.

- Galafold will be given to you by a healthcare professional who has experience in the diagnosis and treatment of Fabry disease.
- Always take Galafold exactly as your healthcare professional has told you.
- If you are not sure how to take Galafold, talk to your healthcare professional.

How to remove a capsule:

Figure A 	**Step 1.** Remove the adhesive seal holding the cover. Lift the cover of your Galafold carton (See Figure A).
Figure B – Opened carton 	**Step 2.** Using your thumb, press and hold down the purple tab. The tab is at the **left** side of the carton (See Figure B). Continue to Step 3.
Figure C 	**Step 3.** Now Grasp the tab on the **right** side where it says “Pull Out here” and pull out the folded blister card (See Figure C).
Figure D – Front of the blister card 	**Step 4.** Unfold the blister card (See Figure D).

Your Galafold is packaged in a blister card. Each Galafold blister card has 14 capsules and 14 white cardboard circles. Each blister card is for 28 days. The white cardboard circles are to remind you to take Galafold every **other** day.

Capsules and white cardboard circles for days 1 to 14 of the cycle are on the left side of the blister card. After day 14, follow the arrow to the capsules and cardboard circles for days 15 to 28 of the cycle. These are on the right side of the blister card (See Figure E).

Figure E – Front of the blister card

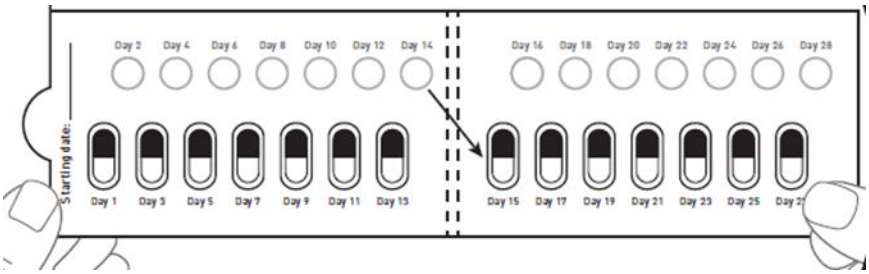
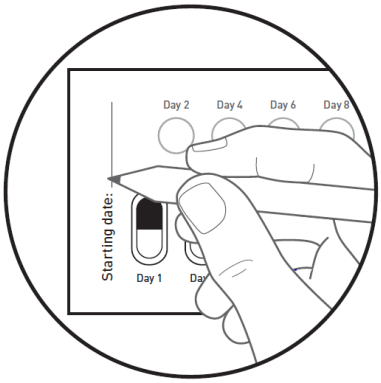
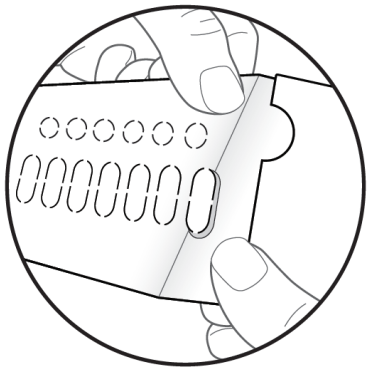


Figure F – Front of the blister card



Step 5. On your first day of taking Galafold from a new blister card, write the date on the blister card (See Figure F). There is a spot for the date labelled “Starting date:”.

Figure G – Back of the blister card



Step 6. Turn the blister card over to show the back side of the card.

Find the capsule to remove.
Bend the blister card as shown (See Figure G). This will help to raise the oval perforations.

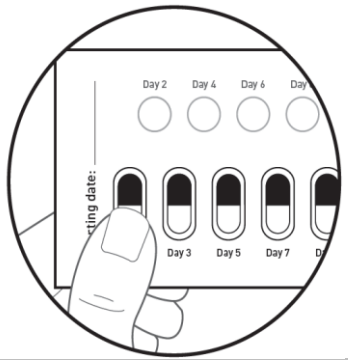
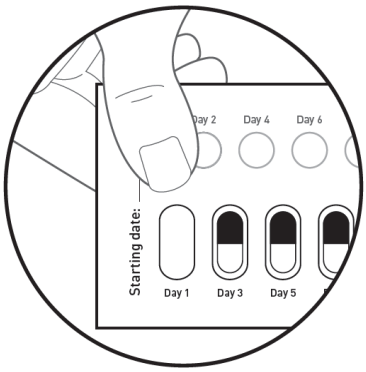
Figure H – Back of the blister card 	**Step 7**. Remove the oval perforated  cardboard (See Figure H). Note: After removing the cardboard, the white backing of the foil may be present. This is ok.
Figure I – Front of the blister card 	**Step 8.** Turn the blister card over to show the front side of the blister card. Push the capsule out (See Figure I).

Figure J – Front of the blister card



Step 9. On the next day, move to the perforated white cardboard circle on the top row labelled Day 2.

Press down on the white cardboard circle to remove it (See Figure J).

Note: Removing this circle will help you remember which day you do not take Galafold.

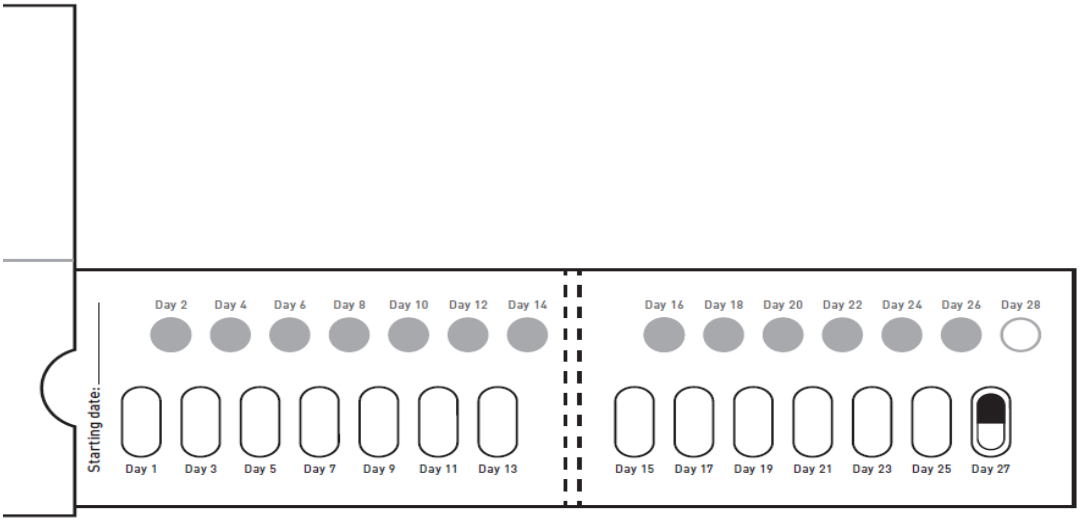
Take 1 Galafold capsule every **other** day.

Close package and store after each use.

After Day 2, move to Day 3 and so on through all 28 days on the blister card.

Alternate between taking the capsule and pushing out the perforated white cardboard circles for each day of the cycle, up to and including day 28. See Figure K.

Figure K – Front of the unfolded blister card.



Usual dose:

Adults and adolescents (12 years or older **and** weigh 45 kg or more):

One 123 mg capsule every other day

Overdose:

If you think you, or a person you are caring for, have taken too much Galafold, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take your capsule, and it is less than 12 hours from when you should have taken it:
  - Take the capsule as soon as you remember.
- If you forget to take your capsule, and it is more than 12 hours from when you should have taken it:
  - Do not take the missed capsule.
  - Wait and take a capsule on the day when you would usually take this medicine.
- Never take Galafold two days in a row.
- Never take two capsules to make up for a missed dose.

What are possible side effects from using Galafold?

These are not all the possible side effects you may feel when taking Galafold. If you experience any side effects not listed here, contact your healthcare professional.

- headache, migraine (intense headaches, usually on one side of the head)
- abdominal pain or discomfort, including upper abdominal pain
- back pain
- flank pain (pain in the side)
- joint pain
- muscle pain in the chest
- muscle pain, twitching, spasms or weakness
- painful and twisted neck
- pain in arms or legs
- itching of the eye
- change in vision
- dizziness or a sensation of spinning
- sleep disorder, including somnolence (sleepiness or drowsiness) and insomnia (difficulty falling asleep or staying asleep)
- tremor (unintentional trembling or shaking movements)
- memory problems
- feeling aggressive or impatient
- increased or decreased sense of touch or sensation
- increase or decrease in appetite
- change in typical or normal bowel movements
- constipation
- sudden urge to pass stools or inability to control bowel movements
- indigestion
- nausea and vomiting
- increase or decrease in weight
- dry mouth
- excessive sweating
- night sweats (excessive sweating during the night)
- feeling hot
- feeling tired
- fever
- flu-like feeling (body aches, feeling tired, fever)

- frequent urination
- local swelling
- inflammation (pain, redness and swelling)
- swelling at the front of the neck from an enlarged thyroid gland (goitre)
- dryness in areas that are usually moist such as the mouth, throat or vagina
- itching
- skin rash, redness or changes in the pigmentation of the skin
- hair loss
- nosebleed
- runny nose
- sneezing
- cough
- inflammation of nose and back of the throat (nasopharyngitis)

Galafold may cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Ataxia (lack of muscle coordination): difficulty walking or difficulty with fine motor tasks, lack of coordination	✓		
Atrial fibrillation (abnormal heart rhythm which is rapid and irregular): occasional chest pain, heart palpitations, fainting, lightheadedness, rapid heartbeat, shortness of breath		✓	
Bile duct stone, biliary dilation (presence of a gallstone in the bile duct, widening of the bile duct): sudden severe pain on the upper right side of the abdomen, fever or chills, jaundice (yellowing of the eyes or skin), dark urine, itching, light-colored stools, nausea and vomiting		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Blood in stools		✓	
Chest discomfort	✓		
Depression		✓	
Diarrhea: loose or watery stools	✓		
Difficult or labored breathing		✓	
Hypertension (high blood pressure): headaches, vision changes, nausea and vomiting	✓		
Hypoglycemia (low blood sugar): change in mood or vision, feeling faint or fainting, headache, hunger, rapid heartbeat, shaking, sweating	✓		
Irritable bowel syndrome (bouts of pain or cramping of stomach, bloating, diarrhea and/or constipation): swelling, excessive gas		✓	
Movement disorders: involuntary muscle movements, lack of coordination, tremor	✓		
Myocardial ischemia (lack of blood flow to the heart which can lead to heart attack): sudden chest pain, pressure or discomfort, feeling faint, feeling anxious, shortness of breath, irregular heartbeat, nausea, sudden heavy sweating			✓
Palpitations: awareness of heartbeat, fluttering of heart, rapid or strong heartbeats		✓	
Paresthesia (tingling in extremities): feeling of tingling or pins and needles in hands or feet	✓		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Neuralgia (pain that follows the path of the nerve): sudden attacks of severe sharp shooting pain		✓	
Peripheral edema (buildup of fluid in the arms / legs which causes the affected tissue to become swollen and stiff, and may cause weight gain)		✓	
Proteinuria (protein in the urine): cloudiness of the urine, foaming of the urine, and in severe cases swelling of the feet and legs and weight gain		✓	
Psoriasis (chronic skin disease): red, itchy, scaly patches of the skin	✓		
Urinary tract infection: difficulty or increased need to urinate, pain or burning sensation when passing urine, pain in the pelvis or mid-back, urine that appears cloudy		✓	
UNCOMMON			
Balance problems	✓		
Liver injury (damage to the liver): abdominal pain, dark urine, fatigue, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice)		✓	
UNKNOWN FREQUENCY			
Angioedema (sudden swelling of skin or mucous membrane [e.g. lip, tongue, eye, etc.]) difficulty breathing; swollen face, hands and feet, genitals, tongue, or throat; swelling of the digestive tract causing diarrhea, nausea or vomiting			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store between 15°C and 30°C in the original package to protect from moisture.
- Keep out of reach and sight 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.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away unused capsules.

If you want more information about Galafold:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.almacgroup.com, or by calling + 44 (0) 28 3833 2200

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