Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for migalastat

Proprietary Product Name: Galafold

Sponsor: Amicus Therapeutics Pty Ltd

August 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
α-Gal A	alpha-galactosidase A
ACM	Advisory Committee on Medicines
ADME	absorption, distribution, metabolism, and excretion
AT1001	migalastat HCl
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ARB	angiotensin-receptor blocker
AUC	area under the concentration-time curve
AUC 0-24	area under the concentration-time curve from time zero to 24 hours
AUC 0-48	area under the concentration-time curve from time zero to 48 hours
AUC 0-t	area under the concentration-time curve from time zero to time t
AUC 0-∞	area under the concentration-time curve from time zero (pre-dose)
BID	twice daily
BPI	Brief Pain Inventory
CKD	chronic kidney disease
CI	confidence interval
CLcr	creatinine clearance
C_{max}	maximum observed concentration
CMI	Consumer Medicines Information
Cmin	minimal observed concentration
CYP450	cytochrome P450
ECG	electrocardiogram
ECHO	echocardiography

Abbreviation	Meaning
eGFR	estimated glomerular filtration rate
eGFR CKD-EPI	estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation
eGFR MDRD	estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation
EMA	European Medicines Agency
ERT	enzyme replacement therapy
FDA	Food and Drug Administration (US)
GAA	Acid α-glucosidase
GFR	glomerular filtration rate
GL-3	globotriaosylceramide
GLA	gene encoding α-Gal A
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSRS	Gastrointestinal Symptoms Rating Scale
HCl	hydrochloride
HEK	human embryonic kidney
hR301Q α-Gal A Tg/KO	mouse model of Fabry disease that expresses a human mutant α-Gal A transgene (R301Q, found in Fabry disease) on a mouse Gla knockout background
hERG	human ether-a-go-go related gene
IAR	infusion-associated reaction
IC	interstitial capillary
IC 50	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ITT	intent to treat
IV	Intravenous
Ki	dissociation constant for binding of inhibitor to enzyme

Abbreviation	Meaning
LC-MS/MS	liquid chromatography with tandem mass spectrometry method
LLOQ	lower limit of quantitation
LV	left ventricular
LVH	left ventricular hypertrophy
LVMi	left ventricular mass index
lyso-Gb3	globotriaosylsphingosine
mGFR	measured glomerular filtration rate
$mGFR_{iohexol}$	glomerular filtration rate measured by the plasma clearance of unlabelled iohexol
mITT	modified intent-to-treat
mITT-amenable	patients with amenable mutations in the mITT population
NAGA	α-N-Acetylgalactosaminidase
OLE	open-label extension
P-gp	P-glycoprotein
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PI	Product Information
PK	pharmacokinetic
PXR	pregnane X receptor
QC	quality control
QD	once daily
QOD	once every other day
RBC	red blood cell
rhα-Gal A	recombinant human α-Gal A
RI	renin inhibitor
SAE	serious adverse event

Abbreviation	Meaning
SD	standard deviation
SEM	standard error of the mean
SF-36v2	Short Form Health Survey with 36 questions, version 2
SGLT1	sodium glucose co-transporter 1
t1/2	terminal phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of occurrence of C_{max}
UGT	uridine 5'-diphospho-glucuronosyltransferase
WT	wild type

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	9 August 2017
Date of entry onto ARTG	11 August 2017
ARTG number:	276051
Active ingredient:	Migalastat
Product name:	Galafold
Sponsor's name and address:[1]	Amicus Therapeutics Pty Ltd 21 Dorset Road Northbridge NSW 2063
Dose form:	Capsules
Strength:	123 mg migalastat (equivalent to 150 mg migalastat hydrochloride)
Container:	PVC/PCTFE/PVC/Al blister packs
Pack size:	14 capsules
Approved therapeutic use:	Galafold is indicated for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in the section on *Mechanism of Action*).
Route of administration:	Oral
Dosage:	The recommended dosage regimen in adults and adolescents 16 years and older is 123 mg migalastat (1 capsule) orally once every other day at the same time of day. Capsules must be swallowed whole. The capsules must not be cut, crushed, or chewed.

Product background

This AusPAR describes the application by ERA Consulting to register a new chemical entity, migalastat (Galafold), for the long-term treatment of adult and adolescent patients

[1] ERA Consulting Pty Ltd was the sponsor of this submission but after the inclusion of the product on the ARTG, the sponsor was changed to Amicus Therapeutics Pty Ltd.

16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.

Fabry disease is a rare, X-linked lysosomal storage disorder that affects males and females. The disease is caused by mutations in the GLA gene encoding the lysosomal enzyme α-galactosidase A (α-Gal A) resulting in a deficiency of the enzyme. This enzyme is required for glycosphingolipid substrate (e.g., GL-3, lyso-Gb3) metabolism. Therefore, reduced α-Gal A activity is associated with the progressive accumulation of glycosphingolipid substrates in tissues (particularly the kidneys, heart and brain) resulting in disruption of normal cellular activity and leading to the development of serious complications and reduced life expectancy.

The natural course of Fabry disease is variable, with the first symptoms of acroparaesthesia (burning pain in the extremities associated with numbness and tingling in the hands and feet) usually commencing in childhood. Premature death usually occurs in the fourth or fifth decade of life and results from renal, cardiac or cerebrovascular complications. Heterozygous females have an intermediate level of enzyme activity and are usually asymptomatic or exhibit mild manifestations. Rarely females may be as severely affected as hemizygous males due to skewed X-chromosome inactivation.

There are two enzyme replacement therapy (ERT) products approved in Australia for the treatment of Fabry disease: agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme). Both Replagal and Fabrazyme are produced by genetic engineering technology and provide an exogenous source of α-galactosidase A enzyme. Each product is administered by intravenous infusion fortnightly.

Migalastat, a low molecular weight iminosugar, is an analogue of the terminal galactose of globotriaosylceramide (GL-3). It acts as a pharmacological chaperone, selectively and reversibly binding to the active site of specific mutant forms of α-Gal A, the genotypes of which are referred to as amenable mutations. This binding stabilises these mutant forms of α-Gal A in the endoplasmic reticulum, facilitating their proper trafficking to lysosomes where dissociation of migalastat allows α-Gal A to reduce the level of GL-3 and lyso-Gb3.

Galafold is formulated as a single strength, hard capsule containing migalastat hydrochloride 150 mg for oral administration every other day.

Migalastat had not been previously considered by the Advisory Committee on Medicines (ACM). Migalastat was designated as an orphan drug in Australia on 2 February 2016 for the long-term treatment of adult and adolescent patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) who have an amenable mutation.

Regulatory status

This section reflects the regulatory status at the time of publication of this AusPAR by the TGA.

Migalastat was approved by the European Medicines Agency (EMA) in May 2016. The approved indication in Europe is the same as the proposed Australian indication. Migalastat is also currently approved in Switzerland Canada, Israel, Japan, and South Korea.[2]

[2] US FDA have accepted the Galafold submission for expedited review with a PDUFA (Prescription Drug User Fee Act) date of 13 August 2018.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Description	Date
Submission dossier accepted and first round evaluation commenced	30 June 2016
First round evaluation completed	16 December 2016
Sponsor provides responses on questions raised in first round evaluation	3 February 2017
Second round evaluation completed	18 April 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	28 April 2017
Sponsor's pre-Advisory Committee response	15 May 2017
Advisory Committee meeting	2 June 2017
Registration decision (Outcome)	9 August 2017
Completion of administrative activities and registration on ARTG	11 August 2017
Number of working days from submission dossier acceptance to registration decision*	221

* Legislative timeframe is 255 working

III. Quality findings

Introduction

The sponsor is proposing to register the product in polyvinylchloride (PVC) / polychlorotrifluoroethylene (PCTFE) / PVC /Al blister packs containing 14 capsules.

The recommended dosage regimen in adults and adolescents 16 years and older is 123 mg migalastat (1 capsule) orally once every other day at the same time of day. Capsules must be swallowed whole. The capsules must not be cut, crushed, or chewed.

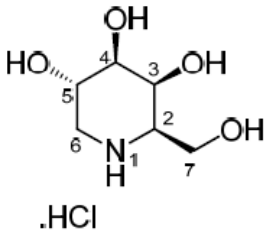
Migalastat hydrochloride is not subject to a USP or BP/Ph Eur. monographs.

Drug substance

Migalastat hydrochloride is a white to almost white crystalline solid. It is freely soluble between pH 1.2 and pH 7.5 in aqueous media.

Migalastat hydrochloride is made by chemical synthesis. The API contains 4 stereogenic centres and is the isomer with the 2R,3S,4R,5S configuration as proven by single crystal X-ray crystallography. A single solid state form, Form 1, has been identified for migalastat hydrochloride, no other polymorphs have been identified.

Figure 1: Migalastat hydrochloride.



Related substances, residual solvents and heavy metal impurities have been controlled according to the ICH guidelines.

Drug product

Migalastat 123 mg capsules are size 2 hard capsules with an opaque blue cap and opaque white body printed with the identifying code 'A1001' printed in black containing white to pale brown powder. The formulation for each capsule is conventional and the capsule powder is composed of pregelatinised maize starch and magnesium stearate.

The container/closure system proposed is polyvinylchloride PVC/PCTFE/PVC blister packs with aluminium foil lidding of 14 tablets.

The manufacturing process for migalastat capsules consists of milling, dry mixing, encapsulating and packaging.

The finished product is appropriately controlled using the finished product specifications. The specifications include acceptable tests and limits for appearance, identity (IR and HPLC), uniformity of dosage units, assay, related substances, dissolution and microbial limits. No degradation impurities have been identified in the finished product and all individual degradation products are controlled according to the ICH identification threshold.

The dissolution method employs a paddle apparatus at 50 rpm in 900 mL with 0.1 N HCl. A dissolution limit of NLT 80% (Q) in 15 minutes was set and this is considered appropriate.

A shelf-life of 48 months 'Store below 30°C' is recommended in PVC/PCTFE/PVC/Al blister packs.

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

Absolute bioavailability [Study AT1001-018]

Exposures following IV infusion of single ascending doses of 0.3, 1.0, and 10 mg/kg migalastat HCl were dose proportional.

After a single oral dose of 150 mg migalastat HCl, the median t_{max} of migalastat was 2.75 h post-dose. After a single IV infusion of 150 mg migalastat HCl, the median t_{max} of migalastat was at the end of infusion (approximately 2 h post start of the infusion). The absolute bioavailability arm of the study demonstrated that exposures after IV infusion of 150 mg migalastat HCl were approximately 1.3-fold higher than the exposures observed after oral administration of the same dose. The absolute bioavailability was approximately 75% for the 150 mg oral dose of migalastat HCl.

Effect of food

Study FAB-CL-103

This study investigated a migalastat HCl solution and migalastat HCl capsule formulations and to assess the effect of food on the 100 mg single oral dose of migalastat HCl capsules.

t_{max} was delayed by approximately 28% (from 3.067 to 3.929 hrs) when migalastat HCl capsules were administered with food in healthy male volunteers. In addition, the rate and extent of migalastat biovailability (C_{max}) and total systemic biovailability of migalastat (AUC) significantly decreased by approximately 40 and 38%, respectively, as compared to the fasting state.

Study AT1001-016

This study investigated a single 150 mg oral dose of migalastat HCl administered either in the fasting state, with a glucose drink, 1 hour before a high-fat meal, 1 hour before a light meal, or 1 hour after a light meal.

After coadministration of 50 g of glucose and migalastat, minor reductions of 14% in mean total exposure ($AUC_{[0\text{-}inf]}$) and 10% in mean peak exposure (C_{max}) were observed compared with the fasting state, and were considered clinically inconsequential. No difference in median t_{max} was observed after the administration of a glucose drink compared with the fasting state.

When migalastat was administered 1 hour before consumption of a high-fat meal or 1 hour before consumption of a light meal, significant reductions of 37% and 42% were observed in mean total exposure and reductions of 15% and 18% were observed in mean peak exposure of migalastat, respectively. The administration of migalastat 1 hour before either a high-fat or a light meal resulted in a statistically significant reduction in median t_{max}.

The timing of the meal was an important consideration, as a reduction of 39% was observed in mean peak exposure when migalastat was administered 1 hour after the consumption of a light meal. No effect was observed on median t_{max} when migalastat was administered 1 hour after the consumption of a light meal when compared with the fasting state.

Quality summary and conclusions

Registration of the product with respect to chemistry and quality control is recommended.

IV. Nonclinical findings

Introduction

The quality of the nonclinical dossier was generally good. The range of studies was consistent with ICH guidelines. Pivotal studies examining safety pharmacology, repeat-

dose toxicity and reproduction/development were conducted under GLP conditions. The exposure ratios are adequate to assess the potential toxicological profile of the drug.

Pharmacology

Primary pharmacology

The effects of migalastat on the binding, inhibition and stabilisation of α-Galactosidase A (α-Gal A) were investigated in vitro. Migalastat binds to recombinant human α-Gal A (rhα-GAL A) and α-Gal A from tissues from mouse, rat, monkey and human with high affinity (K_i around 10 nM).

Migalastat was shown to stabilise degradation of rhα-GAL A enzymes preparations (agalsidase alpha and beta) at different pH and temperatures. Increased levels of α-Gal A were measured in studies using cell lines from human volunteers and Fabry patients, demonstrating that migalastat can reach intracellular α-Gal A and bind to both wild-type and mutant forms of the enzyme. Migalastat increased α-Gal A protein levels in fibroblasts from Fabry patients; half of the missense mutant forms associated with classic (early-onset) Fabry disease, and 90% of those associated with later-onset Fabry disease, were responsive (EC_{50} values of 820 nM to >1 mM). In a separate study, migalastat bound to 23 of 29 mutants with similar affinity as wild-type α-Gal A.

Migalastat inhibits α-Gal A activity with IC_{50} values of ~20-90 nM for wild-type α-Gal A from mouse, rat, monkey and human. The activity of some mutant forms of α-Gal A were also inhibited by migalastat (24 of 29 tested mutant forms had an IC_{50} < 180 nM, with the remaining 5 having an IC_{50} of 289-441 nM). Inhibitory effects were also demonstrated in fibroblasts from Fabry patients. Fibroblasts with two specific mutations showed a decrease in GL-3 levels when treated for 7 days with a 3 day wash-out period. However, GL-3 was not decreased after 10 days of continuous treatment. When GL-3 turnover was measured in normal human fibroblasts, rapid removal of migalastat from the enzyme was observed when treatment was stopped (half-life of α-Gal A inhibition by migalastat was 2 to 5 hours). In contrast, half-lives of sustained increased enzyme activity (after removal of migalastat from the medium) varied depending on the specific mutation (11 to > 120h).

In vivo pharmacodynamic studies used a Fabry mouse model that expresses a human mutant α-Gal A transgene on a mouse Gla knockout background (hR301Q α-GAL A Tg/KO). These animals display age-dependent accumulation of GL-3 in disease-relevant tissues (skin, heart, kidney, brain). α-Gal A tissue levels were increased, with a concomitant decrease in GL-3, in skin, heart and kidney, dose-dependently up to 300 mg/kg/day following 4 weeks continuous treatment (Study RR1001-06). Evaluation of different dosing regimens demonstrated that dosing for 4 days followed by 3 days wash-out resulted in a greater reduction in tissue GL-3 than daily dosing at 300 mg/kg/day (Study RR1001-13). Administration of migalastat for 6 months (4 days on/3 days off) produced even greater GL-3 reductions in heart and skin, in both young (4-week-old) and older (24 week old) hR301Q α-Gal A Tg/KO mice, demonstrating both prophylactic and therapeutic effects. In contrast, migalastat did not affect α-Gal A activity or GL-3 levels in Gla Knock-out Mice (RR1001-12). This indicates that the α-Gal A protein (even if defective) needs to be present in order for migalastat to exert its pharmacological properties.

Together, the in vitro and in vivo data indicate that migalastat binds to, stabilises and inhibits α-Gal A. As the half-life for inhibition is markedly shorter than the half-life for the effect on enzyme stability, there is a net increase in α-Gal A activity following treatment with migalastat. The balance between stabilisation and inhibition appears to be optimised by non-continuous dosing.

Secondary pharmacodynamics and safety pharmacology

A standard assay showed no significant binding by migalastat to 83 receptors and enzymes, demonstrating selective binding to α-Gal A (Study MDS1080607).

In evaluations using other lysosomal enzymes and lysates from human blood (Study RR1001-01) significant binding by migalastat was only shown for the lysosomal enzyme α-N-acetylgalactosaminidase (NAGA) with an IC_{50} of 6.94 μM (1.4 μg/mL). Similarly, migalastat inhibited NAGA from human and rat liver with IC_{50} values of 7.7 and 8.5 μM, respectively. While this inhibition is 120 x lower than the affinity for α-Gal A (IC_{50} of 57.7 nM), it is similar to the predicted clinical C_{max} (1.2 μg/mL). NAGA is a lysosomal enzyme that cleaves α-N-acetylgalactosaminyl moieties from glycoproteins and glycolipids, and patients with Schindler disease display extreme NAGA deficiency (98% persistent loss of activity).

Since there is high homology between human and rat NAGA, the rat is a suitable species to investigate inhibitory effects on NAGA by migalastat. Signs of Schindler disease (such as hepatomegaly, muscular weakness or motor problems) were not present in rats, suggesting a lack of significant inhibition of NAGA. Furthermore, the dosing regimen is unlikely to lead to persistent inhibition of NAGA clinically.

Migalastat is a low affinity substrate and inhibitor of SGLT1 (a sodium-glucose linked transporter found predominantly in the intestinal mucosa), with EC_{50} and IC_{50} values markedly higher than the expected clinical C_{max} and predicted intestinal concentration (> 60 mM (around 12 mg/mL) compared with 1.2 μg/mL and around 300 μM, respectively). The Sponsor has stated that a clinical study investigating the effects of a high-glucose drink on the pharmacokinetics of migalastat showed minor reductions in absorption (C_{max} and AUC) which were considered clinically inconsequential.

Migalastat did not affect levels of mutant acid α-glucosidase (GAA) or acid β-glucosidase (GCase) in Pompe or Gaucher patient fibroblast lines. Similarly, GCase and GAA were not affected in an *in vivo* study where administration of migalastat HCl to wild-type C57BL/6 mice resulted in selective, dose-dependent increases in tissue α-Gal A activity (Study RR1001-05). Migalastat HCl did not modify the activity of galactokinase, galactose-1-phosphate uridyltransferase, or UDP-galactose-4-epimerase (Study 2012N137381_00), demonstrating that the pathways involved in galactose metabolism are not affected by ≤ 1 mM migalastat. Migalastat was not cytotoxic to normal human fibroblasts or human liver HepG2 cells (≤ 1 mM; Study RR1001-09).

Dedicated safety pharmacology studies examined effects of migalastat on the cardiovascular system in vitro and in dogs, and on the CNS and pulmonary function in rats. Migalastat had no effect on the hERG currents when tested up to 47.5 μM (9.5 μg/mL; around 8 x the clinical C_{max} of 1.2 μg/mL). When administered to dogs at up to 100 mg/kg/day, migalastat caused no cardiovascular effects (including in mean, diastolic, or systolic arterial blood pressure, heart rate, or ECGs, including the QT and corrected QT intervals). Exposure extrapolation from other dog studies indicate that C_{max} and AUC at 100 mg/kg/day is > 60 and > 40 times higher than those in the clinical studies with MRHD of migalastat.[3]

In rats, no effect on the central nervous system was observed at doses tested up to 100 mg/kg, with an achieved exposure of around 8 (C_{max})[4] and 4 (AUC) times higher than those in the clinical studies with the MRHD of migalastat. In rats, no respiratory effects were

[3] The C_{max} in dogs that received 50 mg/kg dose was ~39 μg/mL on day 1 in Study ITR2978 (C_{max} was multiplied by 2 then divided by the predicted human C_{max} of 1.2 μg/mL). The $AUC_{0–24h}$ on day 1 was 106,615 ng.h/mL in dogs that received 50 mg/kg in Study ITR2978, *cf.* a predicted $AUC_{0–48h}$ of 9033 ng.h/mL in humans (dog AUC was multiplied by 4 to account for dose and time differences then divided by the human AUC value).
[4] C_{max} and AUC extrapolated from day 1 data from Study ITR5850 in which rats received a 100 mg/kg dose which resulted in a C_{max} of 9.5 μg/mL and an AUC of 19,369 ng.h/mL.

observed after treatment with up to 100 mg/kg. In addition, no adverse CNS effects were observed in rat repeat-dose toxicity studies with doses up to 1500 mg/kg/day (relative exposures of 18 and 27 based on C_{max} and AUC, respectively).

Pharmacodynamic drug interactions

The effects of combination therapy of migalastat with enzyme replacement therapy were investigated in Fabry patient-derived fibroblast cell lines. Migalastat enhanced the effects of agalsidase alfa and agalsidase beta on increasing cellular α-Gal A levels and activity, and reducing GL-3 levels (Studies RR1001-17 and RR1001-37).

In a murine Fabry disease model (Gla KO) and in SD rats, co-administration of oral migalastat with intravenous agalsidase alfa or beta increased the plasma half-life and protein levels of both enzymes (Study RR1001-16). In the GLA KO mice, co-administration of migalastat with either enzyme increased the extent of the enzymes effects, i.e. increased α-Gal A activity and reduced GL-3 levels in disease-relevant tissues (plasma, skin, heart, kidney) (Studies RR1001-20, RR1001-18, RR1001-31). Migalastat HCl also increased the potency of a 10-fold lower dose of agalsidase beta when administered 30 minutes prior to and 2 hours after agalsidase beta (Study RR1001-18).

In summary, concurrent treatment with enzyme replacement therapies (agalsidase alfa and agalsidase beta) and migalastat has an additive therapeutic effect.

Pharmacokinetics

The pharmacokinetics of migalastat in species that are involved in toxicity assessment have been adequately evaluated in the current dossier. All of the plasma kinetics were determined using validated assays.

Oral bioavailability was high (66 to > 100%) in mice (bioavailability was not assessed in any other species). Absorption was rapid in the nonclinical species and humans, with t_{max} values of 0.25 to 1 h in mice, rats and rabbits, 1 to 2 h in dogs and monkeys, and 2 to 4.5 h in humans after oral administration.

The increase of AUC was generally less than dose-proportional, with no gender differences in rats, dogs or monkeys. Exposure was higher in female mice, but only at doses ≥ 1000 mg/kg/day. Plasma migalastat concentrations declined rapidly ($t_{½}$ < 9 h), and accordingly, it did not accumulate in plasma after repeat dosing. Saturated oral absorption of migalastat was only observed over the dose ranges studied in monkeys, where exposure was only 1.1 to 1.4 times after receiving 500 mg/kg/day for 14 days cf. 200 mg/kg/day.

Volume of distribution was less than or equal to body water in mice, whereas in humans it exceeded the volume of body water (> 77 L compared with 44 L), suggesting extensive distribution into tissues. The short elimination half-life observed in male mice after IV administration was considered due to the relatively low distribution volume. There was no significant plasma protein binding in the nonclinical species (mouse, rat, monkey) and humans, therefore distribution into tissues can be readily achieved. Migalastat did not distribute readily into blood cells, indicated by the blood to plasma ratio of ^{14}C-Migalastat related radioactivity in male rats.

In mice and rats, distribution to the major excretory organs was observed, as well as to organs/tissues which are relevant to the clinical indication, such as heart, kidney, skin, spleen, liver, and brain. In rats, brain to plasma ratio was 0.1 and the t_{max} was slower than for other tissues, indicating slower penetration of the brain compared to the other tissues. However, migalastat crossed the blood-brain barrier and caused pharmacological effects in the brain. The uptake or retention of migalastat in melanin, or in organs of the reproductive or GI tract was not investigated.

Significant distribution of migalastat to rat milk was observed in the pre-postnatal rat toxicity study. There was placental transfer of migalastat into the fetus of pregnant SD rats, with fetal plasma levels generally ≤ 30% of maternal plasma levels.

Comparing a single oral dose of ^{14}C-migalastat/kg to the same dose of non-labelled migalastat in rats, it was found that at t_{max} most of the circulating material consists of unchanged migalastat. In in vitro;[5] and in vivo metabolic profiling studies using ^{14}C-migalastat, unchanged migalastat was the predominant radioactive component, including in rat plasma, urine, and faeces. In both rats and humans, around 20% of an oral dose was excreted as metabolites. Rats excreted most of the dose in faeces (followed by urine), whereas humans excreted most of an oral radioactive dose in urine. Since excretion in bile was not studied, it is not known if the material excreted in faeces had been absorbed.

According to ICH Guideline M3 (R2);[6] nonclinical characterisation of a human metabolites is only warranted when that metabolite(s) is observed at exposures greater than 10% of total drug-related exposure. Since no metabolite accounted to more than 6% of the dose, the lack of metabolite characterisation is acceptable. Also, since no major metabolites were identified in human plasma, it is acceptable that in vivo metabolism was only studied in rats.

The toxicokinetic data demonstrated that all doses evaluated in the various toxicology studies elicited significant plasma exposure to the drug. No consistent gender differences in the pharmacokinetics of, or systemic exposure to, migalastat were observed. Overall, based on the available pharmacokinetic data, sufficient similarities between the pharmacokinetic profiles of animal species (rats, mice and monkeys) in toxicity testing and of patients allow these species to serve as adequate models of drug toxicity in humans.

Pharmacokinetic drug interactions

No significant migalastat-related in vitro inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 was observed in human liver microsomes. No induction of CYP1A2 or CYP3A4 was caused by migalastat in human hepatocytes.

Migalastat did not inhibit BCRP, MDR1, or BSEP human efflux transporters, or OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K human uptake transporters in vitro. Migalastat was not a substrate for P-glycoprotein in vitro.

Co-administration of migalastat with agalsidase beta and agalsidase alfa increased the potency of both enzyme replacement therapy (ERT) drugs, increasing α-Gal A activity and reducing GL-3 levels in disease-relevant tissues of Gla knockout mice, beyond those effects observed with the individual drugs (see *Pharmacodynamic drug interactions*).

Toxicology

Acute toxicity

Acute toxicity of migalastat was examined in rats and dogs using the PO route. No mortalities occurred in either species, with a maximum non-lethal dose of 1500 mg/kg in rats and 316 mg/kg in dogs. No clinical signs were observed within 3 days of dosing. Although higher doses and a longer observation phase could have been used, the extent of

[5] Hepatocytes from SD rats, cynomolgus monkeys, and humans.
[6] Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.

acute oral toxicity is readily discerned from repeat-dose toxicity study findings, as discussed below. Migalastat displays a low order of acute toxicity by the clinical route.

Repeat-dose toxicity

The sponsor submitted 9 repeat dose toxicity studies that were up to 2 weeks in dogs, 4 weeks in mice, 6 months in rats and 9 months in monkeys. Studies used the clinical (PO) route and all pivotal studies were GLP-compliant. Consistent with ICH M3(R2);[7] duration of pivotal studies (that is ≥ 6 months) were sufficient to support a product intended for long-term use. For the 6-month study in rats and both studies in monkeys (of 2 and 39 weeks duration), daily dosing was divided in 2 occasions (BID, 6 hours apart) in order to increase exposure due to the relatively short plasma half-life (< 9 hours) of migalastat in nonclinical species. In a 4-week combination study in Gla null mice, migalastat was administered orally 3 times a week, together with agalsidase beta intravenously once per week. The choice of species used is acceptable, due to good bioavailability via the oral route, similar metabolic profile, and 98% α-Gal A protein homology between humans and monkeys. In all nonclinical studies, the hydrochloride salt of migalastat was used, which is the form of the drug used in the manufacture of the final drug product. Recovery periods were appropriately employed in the rat and monkey pivotal studies.

Relative exposure

Adjustments to AUC values have been made to calculate relative exposures to account for differences in dosing regimens between the proposed human use (every other day) and daily administration in toxicity studies. Relative exposures were calculated by multiplying the animal AUC_{0-24h} by 2 and comparing the resulting value with human AUC_{0-48h}. Human reference AUC values were from population PK values from Study MGM 116016. Total AUC values were used as the plasma protein binding was negligible in human and nonclinical species. All doses evaluated in the various toxicology studies elicited sufficiently high plasma exposure to migalastat.

Table 1: Relative exposure in oral repeat-dose toxicity and carcinogenicity studies

Species	Study duration [Study no.]	Dose (mg/kg/day PO)		AUC_{0-t}^ (ng·h/mL)	Exposure ratio#
CByB6F 1 mice	1 month [Study No. ITR70575]	500		47,200	10.5
		1,000		101,000	22.4
		2,000		373,000	82.6
	6 months; carcinogenicity [Study No. ITR70576]	F	50	13,500	3.0
			150	31,800	7.0
			500	94,400	20.9
		M	100	25,800	5.7
			300	38,900	8.6

[7] Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.

Species	Study duration [Study no.]	Dose (mg/kg/day PO)	AUC_{0-t}^ (ng·h/mL)	Exposure ratio#
		1,000	121,000	26.8
SD rats	6 months [Study No. AA17017]	100 (A)	30,147	6.7
		500 (A)	96,659	21.4
		1,500 (A)	248,355	55.0
	24 months; carcinogenicity [Study No. G4970]	50 (A)	13,800 (B)	3.1
		200 (A)	33,300 (B)	7.4
		800 (A)	103,000 (B)	22.8
		1,200 (A)	176,000 (C)	39.0
Beagle dogs	2 weeks [Study No. ITR2978]	50	100,920	22.3
		200	347,363	76.9
		500	513,332	114
Cynomolgus monkeys	9 months [Study No. AA17227]	50 (A)	71,849	15.9
		200 (A)	184,705	40.9
		500 (A)	305,823	67.7
Human	Predicted PK from AT1001-011 (MGM 116016)	150 mg every other day	9,033	–

= animal 2xAUC_{0-24h}:1xhuman AUC_{0-48h} (since the animals were treated daily (AUC0-24) whereas the clinical dosing regimen is once every other day); ^ = data are for the sexes combined at the last sampling occasion; A = daily dose given BID 6 hours apart; B = sampling on week 29; C = sampling on week 37.

Major toxicities

No consistent changes were noted in toxicity studies irrespective of animal species and duration of treatment. Mortalities were only observed when oral migalastat was administered in combination with intravenous agalsidase beta in Gla (-/-) knockout mice. Repeated administration of migalastat at up to 500 mg/kg/day for 9 months in monkeys did not cause toxicity (at a relative exposure (RE) of 68). Target organs in rodents and dogs included the male reproductive system, gastrointestinal tract, spleen and kidneys, as discussed below.

Male reproductive system

Administration of migalastat at doses of ≥ 2.5 mg/kg/day (subclinical exposure) was associated with reversible infertility in male rats. Infertility may be observed in male patients receiving migalastat. See 'Reproductive toxicity'.

Gastrointestinal tract (GIT)

Minimal to mild, diffuse mucosal inflammation of the large intestine (caecum, colon, and rectum) was observed in female mice receiving ≥ 1000 mg/kg/day migalastat for 4 weeks and in males at 2000 mg/kg/day (RE of 22 and 86, respectively). Increased apoptosis of the mesenteric lymph node was also noted in 2/10 males at 2000 mg/kg/day and was considered to be a secondary response to the gastrointestinal tract changes. Due to the highly concentrated solutions used in the mouse study, this local irritation is likely to be direct contact-mediated and unlikely to be clinically relevant.

In rats receiving 1500 mg/kg/day for 14 days, eosinophil infiltrates in the glandular stomach and oedema at the junction of the glandular and non-glandular stomachs (changes consistent with irritation were also observed in the stomach) were observed. However, these findings were not observed in rats receiving similar doses (and with RE ≤ 55) for 6 to 24 months. Gastrointestinal irritation was not observed in monkeys (at RE < 68).

Considering the lack of consistency of the GIT effects within and among species, and its association with daily or twice-daily administration of high concentration formulations, this GIT toxicity is not expected to be clinically relevant. In addition, given that Fabry disease itself causes GIT symptoms (such as diarrhoea, abdominal pain), improved disease management with migalastat may improve GI symptoms.

Spleen

Minimal to slight increases in the number of lymphoid follicles were observed microscopically in the spleens of rats treated with ≥ 100 mg/kg/day for 26 weeks (RE ≥ 7), and this finding was associated with an increase in the spleen weight (relative to body weight) at 1500 mg/kg/day (RE 55). Although both of the findings were non-reversible, there were no secondary immunotoxic effects, and no evidence of drug-related histopathology findings in the spleen in the 2-year rat carcinogenicity study at doses up to 800/1200 mg/kg/day (REs ≥ 23). No drug-related effects were observed in the spleen of monkeys receiving migalastat at 500 mg/kg/day for 39 weeks (68-fold the clinical exposure). No toxicity to the spleen is expected due to clinical use.

Kidneys

Urinary chloride and potassium were elevated in rats and dogs but only in short-duration studies. These findings are unlikely to be of clinical relevance due to fact that the effects were not consistently observed, and were not accompanied by any histopathological changes to the kidneys.

Genotoxicity

The genotoxicity of migalastat was investigated in a bacterial mutation assay (up to 5000 µg/plate), an in vitro forward mutation test (in mouse lymphocytes, up to 5000 µg/mL) and in rat micronucleus test (up to 2000 mg/kg/day). The studies were compliant with the recommended guidelines and the tested concentrations were appropriate. Migalastat was not genotoxic when tested up to the limit doses in the above studies.

Carcinogenicity

The carcinogenic potential of migalastat was assessed in a 6 month transgenic Tg.rasH2 mouse study and in a 2 year rat study. Administration was by the clinical route (oral) in both studies. The design of the studies was consistent with relevant ICH/EU guidelines

(CPMP/ICH/140/95 [ICH S1A];[8] CPMP/SWP/2877/00):[9] the group sizes used (25/sex and 50/sex in the mouse and rat studies, respectively) and duration of dosing (26 weeks and 2 years in the mouse and rat studies, respectively) were appropriate. A concurrent positive control group (urethane-treated) was included in the transgenic mouse study and the expected increased incidence in neoplastic findings was observed, confirming the validity of the study.

The exposure ratios achieved in the mouse study (27 and 21 for HD males and females, respectively) were adequate (human AUC values were from population PK values from Study MGM 116016). In the 2-year rat study, the high dose was increased from 800 to 1200 mg/kg/day from week 36 to achieve a higher exposure ratio (the 50 and 200 mg/kg/day low- and mid-doses remained unchained). The dose adjustment increased the relative exposure from 22 to 39 x, thereby achieving a relative exposure > 25 x expected clinical AUC values. The high dose is therefore considered adequate as it is consistent with the recommended exposure margins as described in ICH guidance S1C(R2).[10]

While the two year rat study ultimately showed no migalastat-related carcinogenicity, a higher incidence of pancreatic islet-cell adenomas was noted in the 800/1200 mg/kg/day male treatment group compared with vehicle control males (20% compared with 6%). The increased incidence of islet-cell adenomas was also statistically significant and above the historical rate for spontaneous occurrences, and was therefore considered test article-related by the initial contract research organisation. However, in the absence of a statistically significant correlation in the trend test for a linear dose-relatedness, the absence of increased islet cell hyperplasia, the absence of increased islet cell carcinomas, or islet cell adenomas and carcinomas combined, and in the absence of accelerated onset of adenomas, the sponsor concluded the increase in islet-cell adenomas to be incidental. This conclusion is plausible given the absence of increased islet-cell adenomas in female treatment groups, the absence of histological differences in adenomas across all the male treatment groups, and the absence of macro- or microscopic findings.

The 26-week mouse carcinogenicity study used 100, 300 and 1000 mg/kg/day doses of migalastat in males, and 50, 150 and 500 mg/kg/day in females (RE of ≤ 27 in males and ≤ 21 in females). Some microscopic pre-neoplastic changes were observed. However, the incidence was low, not dose-related and did not reach statistical significance. In addition, the observed changes were generally consistent with background lesions commonly reported in this transgenic mouse strain.[11] No increases in islet cell adenomas were observed in the mouse study.

Taken together, the two carcinogenicity studies indicate that migalastat is unlikely to be carcinogenic at up to 21 and 39 times the clinical exposures, in mouse and rat respectively.

Reproductive toxicity

Seven reproductive toxicity studies encompassing three fertility (rat), three embryofetal development (rat and rabbit) and one postnatal development study (rat) were submitted. All pivotal studies were GLP compliant, conducted in accordance with the relevant ICH guidelines, included appropriate test group sizes, and initiated test article administration at appropriate time points and for appropriate duration.

Relative exposure

See Table 2.

[8] The Need for Carcinogenicity Studies of Pharmaceuticals
[9] Note for Guidance on Carcinogenic Potential
[10] Dose Selection for Carcinogenicity Studies of Pharmaceuticals.
[11] Paranjpe MG, et al. Historical Control Data of Spontaneous Tumors in Transgenic CByB6F1-Tg(HRAS)2Jic (Tg.rasH2) Mice. *Int J Toxicology*. 32: 48-57 (2013).

Table 2: Relative exposure in reproductive toxicity studies

Species	Study [Study no.]	Dose (mg/kg/day)	AUC_{0-24h} (ng·h/mL)	Exposure ratio#
Rat (SD)	Male fertility [Study AA31159]	2.5	736	0.2
		10	2030	0.4
		25	6663	1.5
Rabbit (NZW)	Embryofetal development [Study AA26552]	120	334988	74
		300	1101185	244
		750	1962625	435
Human (capsule)	Predicted PK from AT1001- 011 (MGM 116016)	150 mg every other day	9,033	–

= animal 2× AUC_{0-24h}:1× human AUC_{0-48h} (since the animals were treated daily (AUC_{0-24}) whereas the clinical dosing regimen is once every other day)

The pre- and postnatal study indicated placental transfer and secretion into milk in rats, with fetal:maternal plasma ratios between 0.1 to 0.8 and milk:plasma ratios between 2.5 and 8.1.

The rat fertility and early development studies demonstrated a significant reduction in fertility of treated males at all doses leading to a presumptive NOAEL below 2.5 mg/kg/day for male fertility. The decrease in male fertility however did not correlate to changes in sperm counts, morphology, or motility, suggesting a possible effect on mature sperm. The macro- and microscopic findings of male and female reproductive tissue was also unremarkable. The loss of fertility was restored following a 4-week recovery period. The fertility index appeared lower when treated male rats were mated with treated female rats compared to mating of treated males with untreated females. While this observation is suggestive of a possible additive effect when both sexes were under treatment, the female fertility study revealed no migalastat-related fertility effects at up to 100 mg/kg/day.

Decreased male fertility has been associated with miglustat (another imino sugar). Although in the case of migalastat spermatogenesis did not seem to be affected, imino sugars may impair spermatogenesis due to their potential to attenuate the biosynthesis of glucosylceramide-based sphingolipids.[12] Impairment of fertility, which may be reversible, is likely in male patients receiving migalastat given that it was observed at subclinical exposures in rats.

No migalastat-related embryofetal development issues were reported up to 1500 mg/kg/day in rats or 120 mg/kg/day in rabbits (74 times clinical exposure). Upon administration of higher doses of 300 and 750 mg/kg/day in rabbits, embryofetal toxicity was observed in association with maternal toxicity which manifested as anorexia. There was a dose-related increase in spontaneous abortions, post-implantation loss, mainly as early resorptions, which led to a reduction in the number of live foetuses and also fetal

[12] Van der Spoel AC, et al. Reversible infertility in male mice after oral administration of alkylated imino sugars: A nonhormonal approach to male contraception. *Proc Natl Acad Sci U S A.* 99: 17173–17178 (2002).

weight. These effects were generally significant in the high dose group (RE 435). There were no treatment-related external or skeletal malformation, but there were increased skeletal variations in the mid and high dose groups which exceeded the historical control range. These variations were mainly incomplete or no ossification in the paws, pelvis and/or sternum which is consistent with the observed maternal toxicity. Visceral malformations were observed at low incidence in the mid dose (malformed eye) and high dose (hydrocephaly and absent kidney), with malpositioned kidneys also observed at the high dose.

A rat postnatal study was conducted with migalastat doses of 50, 200 and 1000 mg/kg/day. No pre- or post-natal toxicity was noted in any of the treatment groups.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3;[13] which is appropriate given the findings in the rabbit embryofetal development study. Furthermore, the sponsor recommends that Galafold not be used during pregnancy.

Phototoxicity

Phototoxicity studies were not conducted using migalastat. This is acceptable since the drug had a molar extinction coefficient of <1000 $L \cdot mol^{-1}cm^{-1}$, which indicate that it is unlikely to be photoreactive.

Impurities

The proposed specifications for impurities/degradants in the drug substance/product are below the ICH qualification thresholds.

Paediatric use

Galafold is indicated for long-term treatment of adult and adolescent patients 16 years and older, as such, no juvenile studies were submitted, which is acceptable.

Nonclinical summary and conclusions

Summary

- The data provided were adequate for evaluation and were in general accordance with the ICH guidelines (M3(R2)).[14] The pivotal studies were GLP compliant and conducted with the proposed clinical formulation and achieved adequate relative exposures.
- Migalastat is an iminosugar. Migalastat selectively and reversibly binds with high affinity (Ki and IC_{50} around 10 to 20 nM) to wild-type and mutant forms of α-Gal A (known as amenable mutations). Migalastat binding stabilises these mutant forms, allowing normal function. Migalastat also inhibits α-Gal A, but the inhibitory effect has a markedly shorter half-life compared to effects on activity.
- In vitro, migalastat bound to, and increased levels of, α-Gal A in 49/75 mutant forms (from Fabry patients), with similar affinity to wild-type α-Gal A. In vivo, migalastat

[13] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
[14] Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.

increased α-Gal A activity and reduced GL-3 levels in mice which express a human mutant α-Gal A transgene on a mouse Gla knockout background. After 4 weeks, there was a dose-dependent increase in α-Gal A tissue levels in skin, heart and kidney. A dosing regimen of 4 days on/3 days off resulted in a greater reduction in tissue GL-3 than daily dosing. Migalastat also decreased GL-3 in both young and old transgenic mice, suggesting both prophylactic and therapeutic effects.

- Concurrent treatment with enzyme (α -Gal A) replacement therapies (agalsidase alfa and agalsidase beta) and migalastat had additive therapeutic effects in a number of nonclinical models.
- Migalastat was shown to be selective for α-Gal A in Fabry, Pompe and Gaucher disease patient-derived fibroblast cell lines, and in mice. In addition, migalastat did not affect galactose metabolism and was not cytotoxic to normal human fibroblasts or human liver HepG2 cells.
- Secondary pharmacology studies identified significant binding by migalastat only for the lysosomal enzyme α-N-Acetylgalactosaminidase (NAGA), with an IC_{50} in the range of migalastat's clinical C_{max}. Migalastat's affinity for NAGA was 120 times less than that for α-Gal A, and given the short half-life and every other day dosing regimen it is unlikely that persistent NAGA inhibition would be observed clinically. Signs of NAGA inhibition (for example, hepatomegaly, muscular weakness or motor problems) were not observed in rats, despite homology between rat and human NAGA.
- Migalastat is a low affinity substrate for, and inhibitor of, SGLT1. EC_{50} and IC_{50} values were markedly higher than the clinical C_{max}. Adverse glycaemic effects were not observed in repeated dose toxicity studies.
- In vitro, migalastat did not show any significant interaction (inhibition, induction, or a substrate for) any of the relevant drug transporters or drug metabolising enzymes.
- Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Oral bioavailability was high (80-100%) in mice, with rapid and extensive absorption in the nonclinical species and humans. The increase in AUC was generally less than dose-proportional, with no gender differences. Migalastat displayed extensive distribution into tissues, including those relevant to the clinical indication (heart, kidney, skin, spleen, liver, and brain). Penetration into the brain was relatively slow. Plasma protein binding was negligible and distribution to red cells was limited. Elimination after oral administration was similar between nonclinical species and humans ($t_{½}$ of around 1.5 to 7 h compared to around 3 to 5 h).
- Migalastat did not undergo extensive metabolism (around 80% excreted unchanged in rats and humans). Faecal excretion was predominant in rats, compared to renal excretion in humans. Nonclinical characterisation of metabolites was not performed or warranted.
- Safety pharmacology studies found no respiratory or CNS effects in rats at relative exposures of around 8 and 4 based on C_{max} and AUC, respectively. No adverse effects were observed in these systems in repeat dose toxicity studies with higher exposures. Migalastat had no effect on the hERG currents at concentrations around 8 times the clinical C_{max}. There was no cardiovascular effects in dogs at exposures > 40 times those in the clinical studies with MRHD of migalastat.
- Single dose studies demonstrated that migalastat has low acute toxicity via the oral route.
- Repeat dose toxicity studies were conducted in dogs (2 weeks), mice (≤ 4 weeks), rats (≤ 6 months) and monkeys (≤ 9 months). Maximum exposures were high based on AUC (≥ 39 times).

- Signs of gastrointestinal irritation were observed in mice receiving large oral doses of migalastat but were considered likely to be direct contact-mediated. Microscopic splenic abnormalities (increased lymphoid follicles) occurred in the 26 week rat study. These effects are not considered clinically relevant since GIT irritation and splenic changes were not observed in the 2 year rat study or 9 month monkey study, both of which achieved exposure ratios of > 50.
- Migalastat was not genotoxic based on a bacterial mutation assay, forward mutation test and a rat micronucleus test.
- There were no migalastat-related neoplastic findings in a 6 month carcinogenicity study in transgenic Tg.rasH2 mice. There was an increased incidence of pancreatic islet cell adenoma in HD males in the 2 year rat study (relative exposure around 23). However, islet cell hyperplasia or morphologic islet changes were not observed in chronic toxicity studies, the finding was not present in females, and proliferative endocrine lesions are a common background finding in rats. Therefore, this finding is not expected to be clinically relevant.
- Migalastat was excreted into milk and crossed the placenta in rats. The rat fertility and early development studies demonstrated a significant, but reversible, impairment of male fertility at subclinical relative exposures. Female fertility was not impaired.
- While no embryofetal toxicity was noted in rats, embryofetal toxicity subsequent to maternal toxicity was reported in rabbits at > 75 times the clinical exposure. The observed embryofetal toxicities included spontaneous abortion, post-implantation loss, decreased mean foetal body weights, and increased incidences of skeletal variation such as delayed ossification. There was also an apparent increase in visceral malformations and variations (eye, brain and kidney).

Conclusions and recommendation

- There were no major deficiencies in the nonclinical dossier.
- Results from pharmacological studies on migalastat support its use for the proposed indication and did not identify any clinically relevant off-target binding sites.
- The safety pharmacology and repeat dose toxicity studies did not reveal any treatment-related adverse effects of concern.
- Migalastat is not considered to have any genotoxic or carcinogenic potential.
- Migalastat is expected to impair fertility in male patients. The effect was reversible in rats.
- The proposed pregnancy category of B3 is considered appropriate based on the observed embryofetal toxicity in rabbits.
- There are no nonclinical objections to the registration of migalastat as proposed.
- The draft PI should be amended as directed.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

The Clinical Overview outlined the clinical spectrum of Fabry disease, and noted that enzyme replacement therapy with Replagal and Fabrazyme administered by IV infusion every 2 weeks is the only authorised treatment available for patients with the condition. The sponsor stated that in clinical trials, migalastat increased α-Gal A activity, reduced disease substrates, stabilised renal function and was comparable to ERT, significantly reduced left ventricular mass, improved gastrointestinal symptoms, and showed frequencies of Fabry-associated renal, cardiac, and cerebrovascular events that compared favourably to ERT. Migalastat was generally safe and well tolerated following short and long-term treatment. With its unique mechanism of action and convenient oral route of administration, migalastat addresses unmet needs that remain for patients receiving ERT.

The sponsor notes the following features of migalastat, which offer potential benefits compared with currently available ERT: (1) avoids the burden of chronic lifelong ERT infusion therapy for the patient and the patients' families; (2) avoids the risks of ERT infusion-associated reactions and infections, and removes the need for pre-infusion medications; (3) avoids the immune response associated with ERT; (4) has broader tissue distribution than ERT; and (5) chaperones endogenous α-Gal A, which more closely mimics natural enzyme trafficking than the every-other-week infusions of exogenous ERT.

Guidance

A pre-submission meeting was held between the TGA and the sponsor in February 2016. The dossier included a tabulated summary of the main issues discussed at the meeting, and the relevant outcomes relating to these issues. These are summarised immediately below:

- *TGA requested the information be provided on the source of the comparator enzyme replacement therapy (ERT) product included in the Phase III Study AT1001-12. The sponsor indicated that the available information has been provided in the dossier and identified the location of the data.*

The sponsor provided listings of the ERT lot numbers for each of the individual subjects in the safety population of Study AT1001-012. However, it is unclear whether the different lots represent the same formulation of the comparator ERT products used in the study and whether formulations of the comparator ERT products used in the study are the same as the relevant Australian formulations. The sponsor also stated that the available information was to be discussed.

- *TGA requested discussion on the amenable mutations studied in the clinical trials and on the responder analyses. The sponsor indicated that the available information has been provided in the dossier and identified the location of the data.*

The information has been reviewed and relevant comment has been provided.

- *TGA requested clinical data for the Phase III Study AT1001-012 30 month extension. The sponsor indicated that the available information has been provided in the dossier and identified the location of the data.*

The information has been reviewed and relevant comment has been provided.

The sponsor declared that the submission was consistent with the pre-submission planning form submitted to the TGA in March 2016, with the exception of identified Sections that have been updated or revised in accordance with agreements during the pre-submission meeting, or as a result of the compilation of the final dossier. The sponsor

stated that the TGA's Planning Letter of May 2016 did not include any requests for additional information or revision to the proposed dossier content.

Contents of the clinical dossier

The dossier documented a full clinical development program for migalastat comprising 20 studies relating to pharmacology, clinical efficacy and safety.

- 10 Phase I studies evaluating the clinical pharmacology and initial safety and tolerability of migalastat.
- 5 Phase II studies evaluating the safety and tolerability of various migalastat doses and dosage regimens in subjects with Fabry disease.
- 1 Phase II study in subjects with Fabry disease evaluating the pharmacokinetic drug-drug interaction between co-administered migalastat and agalsidase.
- 2 Phase III studies which were identified by the sponsor as being the pivotal efficacy and safety studies (Study AT1001-011 migalastat versuss placebo; Study AT1001-012 migalastat versus ERT).
- 2 Phase III studies which were open-label long-term extension trials and enrolled subjects who had successfully completed selected Phase II and III studies.
- Other data included tables, figures and listings relating to the Summary of Safety and the Summary of Efficacy provided.
- Literature references

Paediatric data

The dossier included data supporting use of migalastat in adolescent subjects aged 16 and 17 years. The sponsor stated that it had submitted data to the EU supporting approval of migalastat in subjects aged 16 and 17 years. The sponsor stated that it had an agreed Paediatric Investigation Plan in Europe. No data have been submitted to the US FDA for paediatric or adolescent subjects and the sponsor does not have an agreed paediatric plan under the relevant US legislation. The sponsor does not have a US waiver from submitting paediatric data. Information provided by the sponsor in the EU Risk Management Plan (RMP) indicated that the clinical development programme for migalastat focused on adults and adolescents at least 16 years of age. The sponsor stated that a planned open-label, non-comparative, multicentre trial will evaluate the pharmacokinetics, pharmacodynamics, safety, and activity of migalastat in children from 2 years to less than 18 years of age with Fabry disease and amenable GLA mutations as part of an agreed Paediatric Investigation Plan. The sponsor stated that an EU waiver has been granted for all subsets of the paediatric population from birth to 2 years of age based on the grounds that clinical studies cannot be expected to be of significant therapeutic benefit or to fulfil a therapeutic need in this subset. The sponsor should indicate whether it intends submitting data to the TGA supporting approval in children and adolescents younger than 16 years of age.

Good clinical practice

The clinical studies are stated by the sponsor to have been conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Pharmacokinetics

Studies providing pharmacokinetic data

The PK of migalastat have been evaluated in ten Phase 1 studies conducted in 242 subjects (218 healthy volunteers and 24 subjects with renal impairment), of whom 218 received migalastat and 24 received placebo (across Studies FAB-CL-103, AT1001-016, FAB-CL-101, FAB-CL-102, FAB-CL-104, AT1001-014, MGM115806, AT1001-015, AT1001-010, and AT1001-018).

In addition, the PK of migalastat have been evaluated in 126 patients with Fabry disease. These studies included two Phase II studies in 18 patients following dense PK sampling (Studies FAB-CL-201 and FAB-CL-204), one Phase II study in 23 patients following sparse PK sampling (StudyFAB-CL-205), one Phase II study in 23 patients exploring PK interactions between migalastat and agalsidase (Study AT1001-103), and 62 patients in one Phase III study with sparse PK sampling (Study AT1001-011).

The PK of migalastat have also been investigated in a population pharmacokinetic analysis (PPK) using pooled data from Phase I, II, and III studies at doses of 25 to 675 mg in 260 subjects (179 healthy subjects from 8 studies; 81 subjects with Fabry disease from 4 studies). No studies with PK data were excluded from consideration.

The studies with PK data are summarised below.

Table 3: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	N *
PK in healthy adults	General PK - Single dose	FAB-CL-101 FAB-CL-104	32 24
	- Multi-dose	FAB-CL-102	16
	Absolute Bioavailability	AT1001-018	10
	Bioequivalence † - Single dose	FAB-CL-103	15
	- Multi-dose	No studies	-
	Food effect – Single-dose	FAB-CL-103 AT-1001-016	14 20
	Mass balance / ADME – Single-dose	AT 1001-014	6
PK in special populations	Target population - Fabry Disease	FAB-CL-201 FAB-CL-204 FABCL-205 AT1001-103 AT1001-011	9 9 23 23 62
	Hepatic impairment	No studies	-
	Renal impairment	AT1001-015	32

PK topic	Subtopic	Study ID	N *
	Neonates/infants/children/adolescents	No studies	-
	Elderly	No studies	-
	Healthy Japanese volunteers	MGM115806	14
	QT/QTc study – healthy volunteers	QT1001-010	52
Genetic/gender related PK	Males versus females	No studies	-
	Other genetic variable	No studies	-
PK interactions	Migalastat – agalsidase (Fabry disease)	AT1001-013	23
Population PK analyses	Non Fabry Disease	MGM116016	179 (HV=155; RI=24)
	Target population	MGM11606	81

* Indicates the primary PK aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

PK parameters

In the individual Phase I studies with PK information, PK parameters were calculated using standard non-compartmental methods and appropriate computer software. The range of PK parameters calculated in the individual Phase I studies was comprehensive and allowed adequate characterisation of the PK of migalastat in plasma, urine and faeces.

Analytical methods for migalastat in plasma and urine

The plasma and urine concentrations of migalastat were quantified using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. The LC-MS/MS assay to quantify migalastat in plasma was linear over the calibration range 5.88 to 2940 ng/mL. The assay was validated to a lower limit of quantitation (LLOQ) of 5.88 ng/mL. The LLOQ was reported to be sufficient to characterise the PK of migalastat in the clinical studies. The initial LC-MS/MS assay to quantify migalastat in urine was validated to a LLOQ of 10.0 mcg/mL. However, a more sensitive LC-MS/MS method was subsequently developed to quantify migalastat in urine validated to a LLOQ of 100 ng/mL.

Evaluator's conclusions on pharmacokinetics

Overview

The PK of migalastat have been satisfactorily characterised in ten Phase I studies conducted in 242 subjects (218 healthy volunteers and 24 subjects with renal impairment), of whom 218 received migalastat and 24 received placebo. In addition, the PK of migalastat have been investigated in four Phase II and III studies conducted in 126 patients with Fabry disease. The PK of migalastat in healthy subjects and in patients with Fabry disease were similar, allowing the PK data from healthy subjects to be satisfactorily extrapolated to patients with Fabry disease.

Absorption

The sponsor reports that migalastat HCl is categorised as a BCS Class III compound (that is, high solubility, low permeability). Despite low in vitro permeability, migalastat HCl 150 mg capsules are rapidly absorbed following oral single-dose administration in healthy subjects, with median t_{max} values being approximately 3 hours in the fasted state (Studies AT1000-016 and AT1001-018). Geometric mean AUC_{inf} values were approximately 9800 to 9900 ng·h/mL and geometric mean C_{max} values were approximately 1550 to 1880 ng/mL following oral administration of single-dose migalastat HCl capsules to healthy subjects in the fasted state (Studies AT1000-016 and AT1001-018). Inter-subject variability in the exposure parameters of AUC_{inf} and C_{max} was moderate, with CV% values ranging from 25% to 34% for the parameters in Studies AT1000-016 and AT1001-018. There were no data on intra-subject variability for the PK parameters of migalastat.

In healthy subjects, the absolute oral bioavailability of migalastat based on AUCinf values was 74.6% (90% CI: 67.2, 82.7) following single-dose oral and IV administration of migalastat HCl 150 mg (Study AT1001-018). In healthy subjects, the relative oral bioavailability of migalastat HCl capsule (100 mg = 4 x 25 mg) and solution (100 mg) formulations was 98% (90% CI: 89%, 108%) based on AUC_{inf} values and 97% (90% CI: 87%, 109%) based on C_{max} values. The relative bioavailability data indicate that the capsules have been optimally formulated.

There were no clinical studies comparing the relative oral bioavailability of the migalastat HCl formulation proposed for marketing to the migalastat HCl formulation used in the pivotal Phase III Study AT1001-011. However, in vitro dissolution data suggest that the two formulations are likely to be clinically bioequivalent. Nevertheless, the sponsor is requested to provide a formal justification for not submitting a relative bioavailability study comparing the proposed marketing and the Phase III migalastat HCl formulations.[15]

The administration of migalastat in association with food significantly decreased the bioavailability of migalastat by approximately 40%. In healthy subjects, a high-fat meal administered with an oral single-dose of migalastat HCl 100 mg (4 x 25 mg capsules) significantly decreased the plasma AUC_{inf} and C_{max} values by 37% and 40%, respectively, and delayed the median t_{max} from 3.1 to 3.9 hours (Study FAB-CL-103). In this study, subjects received migalastat HCl within 30 minutes of the administration of a standard high-fat breakfast during the fed period. The effect of meal type and timing of the meal on the PK of single oral doses of migalastat HCl 150 mg capsules in healthy volunteers was investigated in Study AT-1001-016. In this study, reductions in bioavailability of approximately 40% based on AUC_{inf} values were observed when migalastat HCl 150 mg was administered 1 hour before or 1 after a light meal.

The sponsor proposes that migalastat HCl should not be taken within the 2 hours before or the 2 hours after a meal. In the pivotal Phase III Study AT1001-011, subjects were required to fast for 2 hours before and 2 hours after taking each dose of migalastat HCl. In the sponsor's response to the Day 150 clinical questions raised by the EMA relating to the proposed dosing recommendation, the sponsor commented that a 40% reduction in exposure from concomitant intake of food is generally regarded as clinically meaningful. In the PK food studies, the food effect was seen with meals given 1 hour before or 1 after dosing. Therefore, the sponsor states that dosing with migalastat ± 2 hours around meals is considered necessary to address the food effect. Furthermore, the sponsor noted that the 2-hour fasting window (before and after food) appeared to be adequate, based on predicted exposures from the PPK analysis performed on sparse blood sampling for plasma migalastat concentrations in the pivotal Phase III Study AT1001-011. Predicted exposures based on the 2-hour fasting window (before and after food) were reported to be approximately similar to those observed in healthy volunteers in the fasted condition.

[15] This issue was resolved by the justification provided by the sponsor.

The alternative to the 2-hour fasting window around food would be to recommend standard fasting dosing. However, based on the PK data and the efficacy data from the pivotal Phase III study, the proposed dosing regimen is considered to be acceptable.

The bioavailability of migalastat following multiple BD dosing was consistent with bioavailability following single dosing. In Study FAB-CL-102, the geometric mean AUC values following single and multiple (BD x 7 days) dosing with migalastat HCl capsules 150 mg were 9,482 µg.h/mL (AUC_{inf}) and 10,680 µg.h/mL (AUC_{0-t}), respectively, and the corresponding geometric mean C_{max} values were 1,723 µg/L and 1,659 µg/L, respectively. The AUC results showed that no significant accumulation of migalastat occurred following multiple migalastat 150 mg BD dosing for 7 days. However, statistical analysis of C_{min} values indicated that steady state had not been reached on Day 7, which was an unexpected finding given that the mean terminal half-life of migalastat following single dose administration was 2.4 hours. The sponsor is requested to comment on this unexpected finding.[16]

Exposure to migalastat was dose proportional over the dose range 75 to 1250 mg following single-dose oral administration of migalastat HCl to healthy subjects (Studies FAB-CL-101, FAB-CL-104, and MGM115806). However, less than dose proportionality in exposure was demonstrated between doses of 1250 and 2000 mg (Study FAB-CL-104).

Distribution

In a crossover design in healthy subjects, the mean (CV%) volume of distribution (Vz) was 59.4 L (33.7%) following IV migalastat 150 mg and the mean (CV%) apparent volume of distribution (CL/Vz) was 123 L (46.0%) following oral migalastat HCl 150 mg (Study AT1001-018). The values for volume of distribution were greater than the volume of total body water (approximately 42 L for a 70 kg subject), indicating that migalastat is distributed into the extravascular tissues.

Geometric mean [^{14}C] blood/plasma ratios were relatively constant between 2 and 6 hours post-dose (ranging between 0.76 and 0.82), with the ratio increasing to 1.12 at 24 hours post-dose and being unable to be calculated at 48 hours post-dose (Study AT1001-014). Overall, the data suggest that [^{14}C]-radioactivity equilibrated slowly between plasma and red blood cells and may have reached equilibrium by 24 hours post-dose with some preferential association of [^{14}C]-radioactivity with red blood cells.

In vitro protein binding evaluation using equilibrium dialysis over a concentration range of 1 to 100 µM (that is, 163 to 16300 ng/mL free base) showed that migalastat did not bind to plasma proteins (Study 0332-145-02).

Uptake of migalastat into clinically relevant tissues such as skin, leucocytes, and kidney was demonstrated in Fabry patients from observed increases in α-Gal A activity and/or substrate (GL-3) reduction (Study AT1001-103).

Metabolism

Metabolism is a minor route of clearance for migalastat. In vitro studies in human hepatocytes demonstrated that migalastat was not metabolised by CYP450 isoenzymes (Study 0322-145-01). In vivo, three dehydrogenated O-glucuronide metabolites of migalastat (M1, M2, M3) have been identified (Study AT1001-014). This results indicates that migalastat is a substrate for UGT (uridine 5'-diphospho-gluuronyl transferase), and undergoes glucuronidation which is most likely to occur primarily in the liver.

In the mass balance Study AT1001-014, the major circulating component of the plasma radioactivity following administration of [^{14}C]-labelled migalastat HCl to healthy subjects was unchanged migalastat, which accounted for 77% of the plasma radioactivity. The

[16] This issue was resolved by the justification provided by the sponsor.

three dehydrogenated O-glucuronide metabolites of migalastat (M1, M2, and M3) accounted for 13% of the total radioactivity in the plasma with approximately 9% of the total radioactivity in the plasma being unassigned. Total recovered radioactivity in the plasma (unchanged migalastat, metabolites, unassigned) accounted for 99% of the total radiolabelled dose recovered in the plasma.

Excretion

In the human mass-balance Study AT1001-014, 77% of the administered dose of migalastat HCl was excreted in urine (parent plus metabolites) and 20% was excreted unchanged in faeces. Of the administered dose excreted in the urine, 55% was excreted as unchanged migalastat and 4% was excreted as the combined metabolites (M1, M2, and M3). No radioactivity was detected in expired air.

In Study AT-1001-018, mean (CV%) CL following IV administration of migalastat HCl 150 mg was 9.34 L/h (14.6%) and mean (CV%) CL/F following oral administration of migalastat HCl 150 mg was 12.8 L/h (26.1%). The mean (CV%) terminal half-life was 4.54 h (44.8%) following IV administration and 7.28 h (59.2%) following oral administration.

In Study FAB-CL-101, total clearance ranged from 13.0 to 19.0 L/h across the dose range 25 mg to 625 mg in healthy subjects, while the mean renal clearance ranged from 5.90 L/h to 7.66 L/h (comparable to the normal filtration rate).

Renal impairment

In Study AT1001-015, after a single oral dose of migalastat HCl 150 mg to subjects with mild, moderate and severe renal impairment the $AUC_{0\text{-}t}$ values were 1.2-, 1.8- and 4.3-fold greater, respectively, compared to subjects with normal renal function. In addition, plasma migalastat concentrations at 48 hours after dosing (C_{48h}) were notably greater in subjects with severe and moderate renal impairment compared to subjects with normal renal function. Terminal elimination half-live values were 6.4, 7.7, 22.1 and 32 .3 hours for subjects with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment, respectively.

In the PPK analysis MGM116016, renal function was the most important determinant of variability in the exposure of migalastat, with an average 3-fold range in exposure occurring for baseline eGFR values between 30 and 120 mL/min/1.73 m^2 (that is, subjects with low eGFR values have higher exposures than patients with high eGFR values).

The sponsor considers that treatment with migalastat is not recommended in patients with severe renal impairment, but proposes no dosage adjustment for patients with mild or moderate renal impairment. However, the sponsor is requested to justify its proposal not to adjust the dosage in patients with moderate renal impairment, given the exposure data for this patient group in Study AT1001-015.[17]

Hepatic impairment

No dedicated PK studies have been undertaken in subjects with hepatic impairment. However, based on the in vitro metabolic studies and the mass-balance study in humans, clinically significant increased exposure to migalastat in patients with hepatic impairment is unlikely. Nevertheless, the sponsor is requested to formally justify its decision not to submit a dedicated PK study in subjects with hepatic impairment.[18]

Elderly subjects

The submission included no dedicated PK studies in elderly subjects. In the PPK analysis MGM116016, no clinically relevant effect of age on exposure was observed.

[17] This issue was resolved by the justification provided by the sponsor.
[18] This issue was resolved by the justification provided by the sponsor.

Children and adolescents

The submission included no dedicated PK studies in children and adolescents. Treatment with migalastat HCl is not being proposed for treatment of patients younger than 16 years.

Gender

The submission included no dedicated PK studies specifically comparing male and female patients. The PPK analysis indicated that gender had no effect on the PK of migalastat (PPK analysis MGM116016).

Race

The PK in healthy Japanese subjects (Study MGM115806) were similar to the PK of healthy Caucasian subjects.

Weight

The PPK analysis indicated that, after baseline creatinine clearance, baseline weight was the second largest determinant of variability in exposure to migalastat, with subjects with lower weight having higher exposures. There was a less than 2-fold average difference in exposure for baseline body weights between 50 and 170 kg (PPK analysis MGM116016), which suggests that dosage adjustments based on weight are not required.

Pharmacodynamics

Studies providing pharmacodynamic data

The primary pharmacodynamics (PD) of migalastat were investigated in 5 Phase II studies in 28 subjects with Fabry disease (Studies FAB-CL-201, FAB-CL-202, FAB-CL-203, FAB-CL-204, FAB-CL-205). The primary PD outcome variables for the Phase II studies are summarised below.

Table 4: Primary PD outcomes in the Phase II studies in patients with Fabry disease.

Study ID	N	Primary PD Outcome Variables
FAB-CL-201	9 M	• α-Gal A activity (leukocytes and skin). • GL-3 (plasma, urine, and skin). • Cardiac function measures (ECHO, cardiac MRI). • Renal function measures (serum creatinine, serum total protein, 24-hour creatinine clearance, 24-hour urine protein excretion, urine protein electrophoresis, microalbumin, urine β2-microglobulin titres). • Nerve conduction (Quantitative Sudomotor Axon Reflex Test [QSART] and Computer-Assisted Sensory Evaluation [CASE, also referred to as quantitative sensory testing]; both QSART and CASE were performed at the NIH site only).
FAB-CL-202	4 M	• α-Gal A activity (PBMCs, kidney, skin). • GL-3 (urine, kidney, plasma, skin). • Cardiac function (cardiac MRI, ECHO, BNP level). • Renal assessments (serum creatinine, 24-hour creatinine clearance, 24-hour protein excretion, microalbumin, β-2

Study ID	N	Primary PD Outcome Variables
		microglobulin, eGFR). • Neurological assessments (brain MRI and, at the Porto Alegre site, transcranial Doppler ultrasound and a sympathetic skin response test).
FAB-CL-203	5 M	• α-Gal A activity (PBMCs, kidney, skin). • GL-3 (urine, kidney, plasma, skin). • Cardiac function (24-hour Holter Monitor, cardiac MRI, BNP level). • Renal assessments (serum creatinine, 24-hour creatinine clearance). • CNS function (transcranial Doppler ultrasound).
FAB-CL-204	9 F	• α-Gal A activity (leucocytes, kidney, skin). • GL-3 (urine, kidney, plasma, skin). • Cardiac function (e.g., cardiac MRI, Holter ECG). • Renal assessments (e.g., creatinine clearance, eGFR). • Neurological assessments (e.g., cognitive testing).
FAB-CL-205	14 M 4 F	• α-Gal A activity (leucocytes). • GL-3 (urine, plasma, kidney). • Renal assessments (e.g., serum creatinine, creatinine clearance, eGFR).

Note: In the sponsor's response to the CHMP's Day 120 list of questions, comment was provided that the "word 'Leukocytes' and 'PMBC' have the same meaning" and were "used interchangeably between studies, but they both refer to the same validated method for measuring α-Gal A activity in white blood cell lysate

Study FAB-CL-205 was a long-term extension study for male and female patients with Fabry disease who had completed the treatment period of one of the four Phase II clinical studies. Subjects could enter this extension trial immediately upon completion of participation in their previous migalastat HCl study, or at a later time point. Therefore, some subjects did not have continuous treatment with migalastat HCl between the original Phase II feeder study and the extension study. Of the 28 subjects in the four Phase II feeder studies, 23 subjects entered the long-term extension Phase II study.

Evaluator's conclusions on pharmacodynamics

Primary pharmacodynamics

The PD effects of migalastat were investigated in 5 Phase II studies in subjects with Fabry disease. The most notable PD effect of migalastat HCL observed in the 3 Phase II studies in male subjects (n = 18) with Fabry disease was an increase in leucocyte α-Gal A activity from baseline to last assessment (Studies FAB-CL-201, FAB-CL-202, FAB-CL-203). In each of the studies, changes in other biochemical parameters in the total male population were inconsistent both between patients and within the same patient over time. However, there was a trend in male subjects with migalastat amenable *GLA* mutations for urine GL-3 and renal interstitial cell GL-3 inclusions to respond favourably to treatment. This trend was not observed in male subjects with migalastat non-amenable *GLA* mutations.

In the one Phase II study in females (n = 9) with Fabry disease (FAB-CL-204), baseline leucocyte α-Gal A activity was lower than the upper value for the normal reference range for males (presumably also applicable for females) in all 9 subjects. Of the 9 female subjects, 7 subjects had an increase in leucocyte α-Gal A activity following treatment with migalastat, with activity at Week 48 being greater than at baseline. In female subjects, increased leucocyte α-Gal A activity occurred irrespective of whether or not subjects had migalastat amenable *GLA* mutations. Of the 5 subjects with migalastat amenable *GLA* mutations, 4 subjects had an increase level of α-Gal A enzyme activity at Week 48 compared to baseline. Of the 4 subjects with migalastat non-amenable *GLA* mutations, 3 subjects had an increased level of α-Gal A enzyme activity at Week 48 compared to baseline.

As Fabry disease is X-linked, females with the disease are mosaic harbouring cells that express either the wild type or the mutant α-Gal A. It has been reported that in samples derived from female patients, the measured α-Gal A enzyme activity is dominated by the wild type α-Gal A. Therefore, in females with Fabry disease neither baseline leucocyte α-Gal A activity nor the effect of migalastat on the mutant form can be accurately determined. In contrast to female patient cell lines or samples, α-Gal A activity determined in the HEK cell-based assay is purely due to the heterologously-expressed mutant form of the enzyme.

In contrast to baseline leucocyte α-Gal A activity, 8 of the 9 females in the Phase II study had baseline urine GL-3 concentrations greater than the upper value for the normal reference range for this parameter in healthy women. Furthermore, of the 9 female subjects in the study, 7 had urine GL-3 concentrations that were lower at Week 48 compared to Baseline. All 5 subjects with a migalastat amenable *GLA* mutation had lower urine GL-3 concentrations at Week 48 compared to baseline. Of the 4 subjects with migalastat non-amenable *GLA* mutations, 2 subjects had lower urine GL-3 concentrations at Week 48 compared to baseline.

Most male and female subjects in the Phase II PD studies had at least minimal functional impairment due to Fabry disease at baseline, and no clinically meaningful changes in baseline abnormalities were observed following treatment with migalastat. Therefore, the limited data suggest that stabilisation of impaired function is possible with migalastat treatment.

The data from the Phase II PD studies point to the importance of patients with Fabry disease for whom treatment with migalastat might be treatment option having their genotype assessed for responsiveness to migalastat. In general, the biochemical parameters associated with the disease improved to a greater extent in patients with migalastat amenable *GLA* mutations compared to patients with migalastat non-amenable *GLA* mutations.

The long-term extension study in male and female patients with Fabry disease (Study FAB-CL-205) showed that the benefit/risk ratio, based on the safety and PD data, was more favourable for the 50 mg QOD regimen than for the 250 mg escalating to 500 mg dose regimen of 3 days on followed by 4 days off.

Secondary pharmacodynamics

The 'thorough QT/QTc' study in healthy subjects (Study AT1001-010) showed no association between single-dose migalastat at therapeutic (150 mg) or supra-therapeutic (1250 mg) doses and QTc prolongation. The exploratory analysis showed no statistically or clinically significant differences in QTc changes following migalastat between male and female subjects. In addition, the study showed no relationship between increasing migalastat plasma concentration and QTc prolongation. No significant morphological ECG changes were observed with migalastat. The limited safety data in male and female patients with Fabry disease from the Phase II Studies FAB-CL-203 (males) and FAB-CL-

204 (females) showed no clinically significant adverse events relating to QTc prolongation following treatment with migalastat at dose of 50 mg, 150 mg and 250 mg QOD.

Dosage selection for the pivotal studies

Rationale

The sponsor indicates that the proposed dosage regimen (migalastat HCl 150 mg QOD) was selected to maximise in situ α-Gal A activity and GL-3 substrate reduction by balancing migalastat target organ concentration against clearance. Dose selection was stated to have been based on the findings from both the nonclinical and clinical studies. The rationale for the proposed dose and regimen selected for assessment in the Phase III studies is outlined below. The rationale was provided. In addition, information relating to dose selection has also been included in the outline below based on the evaluation of the relevant Phase I and Phase II studies.

In nonclinical studies, using a knock-out mouse model of Fabry disease (hR301Q α-Gal A Tg/KO) in mice lacking the endogenous murine α-Gal A gene (*GLA*), but expressing a human R301Q GLA transgene, the sponsor reports that a 30 mg/kg dose of migalastat was found to be optimal. Significant increases in α-Gal A activity and GL-3 substrate reduction were reported at this dose across all tissues, while at higher doses no further improvements in activity were reported.

Investigation of mouse and human exposures following oral administration were reported to demonstrate that migalastat exposure after a 30 mg/kg dose in mice (AUC = 18,400 ng·hr/mL (Study RR1001-08)) was similar to migalastat exposure observed after a single oral dose of 150 mg in humans (AUC = 13,521 ng·hr/mL (Study AT1001-013)). Nonclinical studies were also reported to show that greater GL-3 reductions were observed using less-frequent dosing regimens, including a QOD regimen, compared to daily administration.

In the first-in-human Phase I dose-escalation Study AT1001-101, single-dose administration of migalastat (aqueous solution) was shown to be safe and well tolerated at doses of 25, 75, 225, and 675 mg in healthy male subjects (n = 6). The starting dose of 25 mg was selected based on the nonclinical safety data and allometric scaling suggesting that this dose was expected to be a safe starting dose in humans.

In the first repeat-dose Phase I study in humans (StudyAR1001-102), two doses of migalastat were administered for 7 days to 16 healthy male subjects (50 mg BD and 150 mg BD). The 50 mg BD dose was selected as, based on the nonclinical data, it was expected to be the therapeutic dose. The 150 mg BD dose was selected based on the demonstrated safety and tolerability of single-doses of 25, 75, 225 and 675 mg in Study AT1001-102. The sponsor reported that, in Study AT1001-102, greater increases in wild type α-Gal A activity levels were observed in white blood cells (WBC) after 7 day oral administration of 150 mg migalastat BD than after migalastat 50 mg BD, indicating an increased effect of the higher dose compared to the lower dose.

In the five Phase II studies, a range of migalastat doses and regimens were explored in 27 subjects with Fabry disease (18 M/9 F). These regimens and doses were BD (25, 100, 250 mg), once daily (QD) (50 mg), QOD (50, 150, 250 mg) and 3 days on/4 days off (250, 500 mg). In these studies, the sponsor considered that the migalastat 150 mg QOD regimen resulted in the best balance of substrate reduction (urine GL-3) and safety in subjects with amenable *GLA* mutations, compared to the other doses and regimens studied. Treatment with 150 mg QOD also resulted in decreases in kidney interstitial capillary GL-3 and was associated with long-term stability of renal function.

In Study FAB-CL-205, when subjects were switched from 150 mg QOD to higher, less-frequent doses (that is, 250/500 mg 3 days on/4 days off), no further increases in leucocyte α-Gal A activity or reductions in urine GL-3 were observed. The sponsor commented that migalastat 150 mg QOD maintained migalastat plasma concentrations in a more consistent exposure range compared to higher peaks and longer valleys with the migalastat 250/500 mg 3 days on/4 days off regimens. Additionally, a higher rate of treatment-related AEs was observed at the 250 mg and 500 mg doses compared to the 150 mg dose. Consequently, the sponsor considered that the migalastat 150 mg QOD regimen provided more regular and consistent chaperoning of enzyme to lysosome more closely mimicking natural protein trafficking than the higher dose, less frequently administered regimens.

The sponsor concluded that, based on the collective nonclinical, Phase I and Phase II data, migalastat 150 mg QOD was the optimal dose and regimen for the Phase III studies for the treatment of Fabry disease in patients with amenable GLA mutations.

Evaluator's conclusions on dose finding for the pivotal studies

The rationale for the dose selection in the pivotal Phase III studies is acceptable.

Efficacy

Studies providing efficacy data

The submission included two Phase III studies, which the sponsor identified as the pivotal efficacy and safety studies:

- Study AT1001-011 is a Phase III, randomised, double-blind, placebo-controlled clinical trial designed to evaluate the efficacy and safety of migalastat HCl in ERT-naïve male and female patients with amenable GLA mutations. The total duration of the study was 24 months, consisting of a 6 months placebo-controlled period followed by an 18 months open-label, single-group treatment period.
- Study AT1001-012 is a Phase III, randomised, open-label active-controlled trial to evaluate the efficacy and safety of migalastat HCl compared to ERT in ERT-experienced male and female patients with amenable GLA mutations. The total duration of the study was 30 months, consisting of an 18 month open-label, active-controlled treatment period followed by a 12-month open-label, single-group treatment period.

In addition to the two main Phase 3 efficacy and safety studies, the submission also included the protocols from two, Phase III, open-label, long-term extension Studies AT1001-041, andAT1001-042 stated by the sponsor to have been 'provided for reference'. The Clinical Study Reports (CSRs) for the two, open-label extension studies were not included in the submission. Patients completing either of the two pivotal Phase III studies were eligible to enrol in the two open-label extension studies. A total of 115 patients received migalastat in the two, pivotal Phase III studies, and 82 on-going patients continue to receive migalastat as their only treatment for Fabry disease in the Phase III long-term extension studies. Long-term efficacy data from Study AT1001-041 relating to changes in renal and cardiac function in patients from Study AT1001-011 continuing treatment with migalastat were provided in the submission. In addition, long-term safety data were provided on 85 patients in Study AT1001-041 continuing treatment with migalastat from the three feeder studies (Studies FAB-CL-205, AT-1001-011, and AT-1001-012). The long-term efficacy and safety data from Study AT1001-041 have been discussed. The sponsor stated that Study AT1001-041 has now been discontinued for administrative reasons, and patients from this study can continue treatment in the on-going long-term extension Study AT1001-042.

Evaluator's conclusions on efficacy

The two studies supporting the efficacy of migalastat were undertaken in 107 subjects with Fabry disease and amenable GLA mutations identified by the GLP HEK assay (Study AT1001-011 and AT-1001-012). The sponsor states that the two Phase III studies complement one another. Study AT1001-012 was designed to determine the comparability of the effects of migalastat and ERT over 18 months on renal function, cardiac function assessed by ECHO parameters, composite clinical events, and plasma lyso-Gb3 levels. Study AT1001-011 focused on the effect of migalastat on disease substrate burden (kidney interstitial capillary GL-3 and plasma lyso-Gb3 levels) during a 6-month placebo controlled period, and also assessed renal function, cardiac function assessed by ECHO parameters, and gastrointestinal symptoms over the entire 24 months. The sponsor states that the two Phase 3 studies, including the inclusion of male and female Fabry patients, were designed based on multiple interactions with the EMA.

Medical history and baseline characteristics of subjects in the two studies indicated that a majority of subjects with amenable GLA mutations had Fabry disease involvement in two or more organ systems, consistent with significant disease burden (91%, 97/107). The baseline assessment of disease severity based on organ system involvement in the two studies is summarised below. It is considered that the efficacy data from the two studies can be extrapolated to the general Australian population of patients aged ≥ 16 years with Fabry disease and amenable GLA mutations, based on the GLP HEK assay, who might be offered treatment with migalastat if the medication is approved.

Table 5: Baseline assessment of disease severity in the patients with amenable mutations in the two Phase III studies, percentage of patients with symptoms by organ class

Gender	≥ 2 organ systems	Angio-keratoma or corneal whorling [a]	Cardiac involvement [b]	CNS involvement [c]
Study AT1001-012 (n=57)				
Males	21/24 (88%)	13/24 (54%)	16/24 (67%)	18/24 (75%)
Females	29/33 (88%)	16/33 (48%)	25/33 (75%)	12/33 (36%)
Study AT1001-012 (n=50)				
Males	18/18 (100%)	12/18 (67%)	15/18 (83%)	11/18 (61%)
Females	29/32 (91%)	13/32 (41%)	11/32 (35%)	16/32 (50%)

Gender	Neuropathic pain [a]	Renal involvement [d]	Gastro-intestinal [a]
Study AT1001-012 (n=57)			
Males	14/24 (58%)	18/22 (75%)	14/22 (64%)
Females	22/33 (67%)	25/33 (76%)	22/31 (71%)
Study AT1001-012 (n=50)			

Gender	Neuropathic pain [a]	Renal involvement [d]	Gastro-intestinal [a]
Males	13/18 (72%)	18/18 (100%)	10/18 (56%)
Females	25/32 (78%)	27/32 (84%)	18/32 (56%)

Source: Rapporteurs 195 Joint CHMP and PRAC Response Assessment Report, Q12, Table 1. a = Based on medical history. b = Includes previous cardiac event (based on medical history), LVH, or conduction abnormality based on medical history or baseline assessment of LVMi. c = Based on medical history (stroke/TIA, tinnitus/hearing loss). d = Based on medical history or baseline eGFR < 60 mL/min/1.73 m^2, 24-hr Protein ≥ 300 mg.

The sponsor stated that approximately 30% to 50% of subjects with Fabry disease have amenable GLA mutations, and that the majority of amenable GLA mutations are associated with the classic phenotype of the disease. The sponsor referred to the published literature which attributes the classic phenotype primarily to males with undetectable to low α-Gal A activity, elevated plasma lyso-Gb3 levels, and early onset of multiple organ involvement, and the late onset phenotype primarily to males with some residual α-Gal A activity and later onset of disease manifestations. However, as is now recognised female patients may also exhibit the classic phenotype or the late-onset phenotype. The different manifestations of the disease reflect the heterogeneity of the Fabry population.

The sponsor indicated that at the time of the submission to the EMA, 841 GLA mutations had been reported in Fabry patients identified from the Human Gene Mutation Database, the Shire Human Genetic Therapies Fabry Outcome Survey registry, clinical trials for migalastat, and other public sources. The sponsor stated that 642 mutations had been identified that qualified for testing in the GLP HEK assay, of which 600 had been tested (268 identified as amenable; 332 identified as non-amenable) and 42 were awaiting testing. Mutations that qualified for testing include missense mutations, nonsense mutations near the carboxyl terminus, small insertions and deletions that maintain reading frame, and complex mutations comprised of two or more of these types of mutations on a single GLA allele. There were 241 mutations that did not qualify for testing in the GLP HEK assay and were categorised as non-amenable. Mutations that did not qualify for testing include large deletions, insertions, truncations, frameshift mutations, and splice site mutations. The sponsor reported that these types of mutations often lead to the loss of entire protein domains that grossly alter the structure and function of the enzyme, and may even result in the complete loss of expression. The sponsor commented that splice site mutations, in general, can lead to incorrect processing of mRNA precursors, including exon skipping or splicing at cryptic splice points, resulting in gross structural and functional alterations. Furthermore, the sponsor stated that splice site mutations are not testable in the GLP HEK assay because the assay uses recombinant GLA cDNA; thus, the mutant α-Gal A is expressed independent of pre-mRNA splicing. Mutations that do not qualify for testing in the GLP HEK assay are categorised as non-amenable.

The sponsor provided tabulated lists of the amenable mutations for 53 subjects from the mITT population from Study AT1001-012 and for 49 subjects from the ITT population from Study AT1001-011, and their associated phenotype based on published reports. The amenable GLA mutations in subjects in Studies AT1001-012 and AT1001-011 are summarised below. In Study AT100-012, approximately equal proportions of enrolled subjects had GLA mutations associated with the classic Fabry and late-onset Fabry phenotypes (36% versus 38% respectively), while 23% of subjects had mutations not characterised in the literature. In Study AT1001-011, a majority (approximately 60%) of patients had mutations associated with the classic phenotype, while 2% had the late onset phenotype, 6% had both, and 32% were unclassified. Overall, among the mutations

characterised in the medical literature, a majority of patients in the Phase III studies had mutations associated with the classic Fabry phenotype.

Table 6: Study AT1001-012 Amenable mutations of enrolled subjects and the corresponding clinical phenotype based on the medical literature, mITT population

Amino Acid Change	Literature Phenotype	Amino Acid Change	Literature Phenotype
M96I	Unknown	G260A	Classic (Okumiya, Ishii et al. 1995)
L32P (n=3)	Unknown	Q279E	Non-classic (Ishii 1992)
G35R	Non-classic (Davies, Christomanou et al. 1994)	M284T	Classic (Blanch, Meaney et al. 1996)
D55V/Q57L	Unknown	M296I	Non-classic (Nakao 1995)
G85D (n=4)	Unknown	R301P (n=3)	Classic (Ashley, Shabbeer et al. 2001)
A97V	Non-classic (Eng 1997)	R301Q	Both (Sakuraba, Oshima et al. 1990; Ishii 1992; Germain and Poenaru 1999; Germain, Shabbeer et al. 2002)
R112G	Unknown	G328A	Classic (Eng 1993)
R112H	Non-classic (Eng, Niehaus et al. 1994)	Q312R	Non-classic (Shimotori, Maruyama et al. 2008)
A143T (n=3)	Non-classic (Spada, Pagliardini et al. 2006)	D322E (n=4)	Classic (Lee, Heo et al. 2010)
A156T (n=6)	Classic (Eng 1994)	R356Q	Non-classic (Chien, Olivova et al. 2011)
P205T	Classic (Blanch, Weber et al. 1997)	R363H	Both (Blaydon, Hill et al. 2001; Shabbeer, Yasuda et al. 2002)
N215S (n=10)	Non-classic (Dobrovolny, Dvoraková et al. 2005)	L403S	Classic (Shimotori, Maruyama et al. 2008)
Y216C	Classic (Filoni, Caciotti et al. 2010)	P409T	Unknown
I253S	Unknown		

Table 7: Study AT1001-011 Amenable mutations of enrolled subjects and the corresponding clinical phenotype based on the medical literature, ITT-amenable population.

Amino Acid Change	Literature Phenotype	Amino Acid Change	Literature Phenotype
D33G	Unknown	P259R (n=3)	Classic (Ashley, Shabbeer et al. 2001)
L36W (n=2)	Unknown	G260A	Classic (Okumiya, Ishii et al. 1995)
D55V/Q57L	Unknown	D264Y	Classic (Shabbeer, Yasuda et al. 2006)
G85D	Unknown	I270T	Classic (Ries, Gupta et al. 2005)
R112H	Non-classic (Eng 1994)	G271S D313Y	Classic (Shabbeer, Yasuda et al. 2006)*
G144V	Classic (Eng 1994)		Both (Eng 1993; Froissart, Giffon et al. 2003)
A156T (n=3)	Classic (Eng 1994)	M284T (n=2)	Classic (Blanch, Meaney et al. 1996)
C174R	Classic (Meng, Zhang et al. 2010)	P293T (n=2)	Classic (Shabbeer, Yasuda et al. 2006)
G183D (n=2)	Classic (Topaloglu, Ashley et al. 1999)	F295C	Unknown
M187I	Unknown	L300P	Unknown
P205T (n=2)	Classic (Blanch, Meaney et al. 1996)	R301Q (n=3)	Both (Sakuraba, Oshima et al. 1990; Ishii 1992; Germain and Poenaru 1999; Germain, Shabbeer et al. 2002)
Y216C (n=3)	Classic (Filoni, Caciotti et al. 2010)	I317T	Classic (Shabbeer, Yasuda et al. 2002)
L243F	Classic (Germain, Shabbeer et al. 2002)	D322E (n=2)	Classic (Lee, Heo et al. 2010)
D244N	Classic (Eng 1994)	G325R (n=2)	Unknown
G258R (n=2)	Unknown	R356W	Classic (Bernstein 1989)
I253T (n=4)	Unknown	G373S	Classic (Okumiya, Ishii et al. 1995)

The amenable GLA mutations identified in Studies AT1001-011 and AT1001-012 are a subset of the 268 mutations so far identified as being amenable. This raises the question of whether the efficacy data relating to subjects with the amenable GLA mutations included in the two studies can be extrapolated to subjects with amenable GLA mutations that were not included in the two studies. It is considered that it is biologically plausible that the efficacy data can be reasonable extrapolated to all subjects with Fabry disease with amenable GLA mutations. The subjects in Studies AT1001-011 and AT1001-012 had a variety of amenable GLA mutations and it is not possible from the provided data to apportion contributions to the efficacy outcomes to individual mutations. It is considered reasonable to infer that if a subject has an amenable GLA mutation based on the GLP HEK assay then treatment with migalastat will be effective.

Patients completing either Phase III study were eligible to enrol in the OLE Studies AT1001-041 and AT1001-042. The OLE study assessments included eGFR and ECHO parameters. A total of 115 patients received migalastat in the two Phase III studies, and 82

patients continue to receive migalastat as their only treatment for Fabry disease in the OLE studies.

Study AT1001-011

Study AT1001-001 failed to meet its pre-specified primary efficacy endpoint. This might have been the result of approximately 25% (17/67) of subjects included in the primary efficacy analysis not having an amenable GLA mutation, based on the GLP HEK assay. However, post-hoc analysis of the Stage 1 data and pre-specified analyses of the Stage 2 and open-label extension data in subjects with amenable GLA mutations, based on the GLP HEK assay, are considered to support migalastat for the treatment Fabry disease. Limited data from the study has been recently published in the New England Journal of Medicine.6 The published results refer to the pre-specified Stage 1 primary and secondary efficacy endpoint analyses comparing changes between baseline and month 6 in the migalastat and placebo treatment groups.

In Study AT1001-011, male and female subjects with Fabry disease with a confirmed GLA mutation, based on the clinical trial HEK assay, and naive to ERT or not having received ERT for at least 6 months before screening were randomised to treatment with migalastat 150 mg QOD or matching placebo for 6 months (double-blind treatment period). This 6 month, randomised, double-blind treatment period was followed by a further 18 months of treatment with open-label migalastat 150 mg QOD. Therefore, the total duration of treatment with migalastat for an enrolled patient could be up to 18 months for subjects randomised to placebo (placebo-migalastat group) and up to 24 months for subjects randomised to migalastat (migalastat-migalastat group).

A total of 67 subjects entered Stage 1 (0 to 6 months), including 34 in the migalastat group and 33 in the placebo group. A total of 63 subjects entered Stage 2 (6 to 12 months), including 33 in the migalastat-migalastat group and 30 in the placebo-migalastat group. A total of 57 subjects entered the open-label extension period (12-24 months), including 29 in the migalastat-migalastat group and 28 in the placebo-migalastat group. Overall, 54 (95%) subjects completed 24 months of treatment, including 27 (93%) in the migalastat-migalastat group completing 24 months of treatment with migalastat and 27 (96%) in the placebo-migalastat group completing 18 months of treatment with migalastat. The number of subjects included in the study is considered to be adequate to assess the efficacy of a rare disease such as Fabry disease.

The Stage 1 pre-specified efficacy endpoints were described in the Stage 1 Statistical Analysis Plan, dated 17 February 2012. In the Stage 1 pre-specified efficacy endpoint analyses (ITT population), all subjects were required to have amenable GLA mutations based on the clinical trial HEK assay. The pre-specified primary efficacy endpoint was a responder analysis in which success was defined as a ≥ 50% reduction from baseline to month 6 in the average number of renal IC GL-3 inclusions. The results showed that, although a numerically greater percentage of subjects in the migalastat group (n = 34) were responders compared to subjects in the placebo group (n = 33), the difference between the two groups was not statistically significant: 40.6% (13/34) versus 28.1% (9/33), respectively; difference (migalastat minus placebo) = 12.5% (95% CI: -13.4, 37.3), p = 0.2996, CMH test stratified by sex. Similar results were observed in separate analyses in female and male subjects. The study is considered to have failed to meet its pre-specified primary efficacy endpoint.

The Stage 1 pre-specified secondary efficacy endpoints were change from baseline to month 6 in urine GL-3 (percent change), GFRiohexol, eGFRMDRD, 24-hour urine protein, albumin and creatinine, and IC GL-3 inclusions (percent change in average number). No statistical adjustments were made for the multiple pairwise comparisons of the pre-specified secondary efficacy endpoints. However, none of the pairwise comparisons were statistically significant. The only notable difference between the two treatment groups in

the pre-specified secondary efficacy endpoint pairwise comparisons related to IC GL-3 inclusion. The median percent reduction from baseline to month 6 in the average number of IC GL-3 inclusions was numerically greater in the migalastat group compared to the placebo group (-40.8% versus -5.5%, respectively), but the difference between the two groups was not statistically significant (p = 0.0974).

Stage 1 also included a number of pre-specified tertiary efficacy endpoints analyses. The only differences of note between the two treatment groups in these endpoints related to the percent of renal ICs with zero GL-3 inclusions, and the diarrhoea subscale of the GSRS. For both of these endpoints, the changes between month 6 and baseline numerically favoured the migalastat group compared to the placebo group, and the difference between the two treatment groups was statistically significant for the percent of renal ICs with zero GL-3 inclusions. However, no statistical adjustment was made for multiplicity of pairwise testing. No notable differences between the two treatment groups were observed for the other tertiary efficacy endpoints including ECHO parameters, the BPI short form assessment, the SF-36 V2 assessment, GSRS assessments (other than diarrhoea), or WBC α-Gal A activity in males.

During the conduct of study AT1001-011, a third-party validated GLP HEK assay became available and all subjects had their GLA status reassessed with the GLP HEK assay. This resulted in the α-GAL activity in 17 (25%) of the 67 subjects in the study being reclassified from responsive (clinical trial HEK assay) to non-amenable (GLP HEK assay). The 17 re-classified subjects included 6 subjects who had been randomised to migalastat and 11 subjects who had been randomised to placebo. Following unblinding of the Stage 1 efficacy data, additional post-hoc analyses of the Stage 1 data were undertaken in subjects with amenable GLA mutations based on the GLP HEK assay. The Stage 1 (post-hoc) analysis, together with pre-specified analyses for the Stage 2 period and the OLE phase, were described in a SAP dated 26 February 2014 (that is, Stage 1 (post-hoc), Stage 2, and Open-Label Extension Statistical Analysis Plan).

The ITT population for the Stage 1 (post-hoc) analysis included 28 subjects (82%) who had initially been randomised to migalastat and 22 subjects (64%) who had been initially randomised to placebo. The major difference between the Stage 1 pre-specified and post-hoc analyses related to additional assessments of the renal IC GL-3 inclusion data. In the Stage 1 (post-hoc) analysis, the average number of renal IC GL-3 inclusions was treated as a continuous variable rather than a categorical variable. This switch in focus from categorical to continuous analysis was justified by the sponsor on the grounds that quantitative differences in renal IC GL-3 inclusions from baseline 'more accurately assessed the biological effect of migalastat on renal IC GL-3 inclusions than the responder analysis'. There were also methodological issues relating to the responder analysis of renal IC GL-3 inclusions, including a notable imbalance in the baseline mean number of renal IC GL-3 inclusions between the migalastat and placebo groups, resulting in a lower threshold required for subjects in the placebo group to meet the 50% reduction from baseline to month 6 in the average number of renal IC GL-3 inclusions compared with subjects in the migalastat group. No 50% responder analysis relating to renal IC GL-3 inclusions was undertaken in the Stage 1 (post-hoc) analysis.

In the Stage 1 (post-hoc) analysis (ITT population), the reduction in the average number of renal IC GL-3 inclusions from baseline to month 6 in subjects with amenable mutations was statistically significantly greater in the migalastat group compared to the placebo group: difference in LSMs (migalastat minus placebo) = -0.3 (95% CI: -0.6, -0.1); p = 0.0078. In the Stage 2 (pre-specified) analysis (mITT population), the reduction in the average number of renal IC GL-3 inclusions from month 6 to month 12 in the placebo-migalastat group was statistically significant, indicating that switching from placebo to migalastat had a beneficial effect on this parameter: difference in LSMs (month 12 minus month 6) = -0.320 (95% CI: -0.5719, -0.0677); p = 0.014. Subjects with amenable GLA

mutations in the migalastat-migalastat group maintained reduced levels of IC GL-3 inclusions observed at 6 months through to month 12 (mean values of 0.250 and 0.239, respectively).

When data from Stages 1 and 2 were combined for the mITT population with amenable GLA mutations, there was a statistically significantly greater decrease in renal IC GL-3 inclusions after 6 months of treatment with migalastat (n = 30), compared with 6 months of treatment with placebo (n = 30): difference in LSMs (migalastat minus placebo) = -0.312 (95% CI: -0.5316, -0.0930); p = 0.006. Overall, the results provide support for the efficacy of migalastat in reducing and maintaining renal IC GL-3 burden in subjects with amenable mutations. In general, these outcomes were supported by the analyses relating to changes in the percentage of subjects with IC with zero GL-3 inclusions. Exploratory qualitative analysis of GL-3 inclusions in other renal cells (podocytes, mesangial, and endothelial) provided limited support for the efficacy of migalastat compared with placebo.

In subjects with amenable GLA mutations, mean annualised changes from baseline in eGFRCKD-EPI (n = 31), eGFRMDRD (n = 41), and mGFRiohexol (n = 37), remained stable over 18 to 24 months of treatment with migalastat. These results are considered to be clinically meaningful in subjects with Fabry disease, in whom progressive deterioration in renal function can be predicted to occur in the absence of treatment. The results compared favourably with published data relating to annualised changes in eGFRCKD-EPI and mGFRiohexol in untreated patients with Fabry disease. The annualised changes in the eGFR parameters in Study AT1001-011 were less favourable in male subjects than in female subject, and in subjects with higher urine 24-hour protein levels than with lower levels.

Most subjects in the study had baseline proteinuria. There were no significant differences in urine 24-hour protein, albumin, or creatinine levels between the migalastat and placebo group for changes from baseline to month 6 in the Stage 1 (post-hoc) analysis. In the OLE population, urine 24-hour protein and albumin levels increased from baseline to month 24 in subjects who had been treated with migalastat for 18 or 24 months, while the urine 24 hour creatinine level remained stable. Post-hoc analysis of the data indicated that the increased proteinuria observed from baseline to month 24 in subjects treated with migalastat was primarily driven by subjects with baseline proteinuria > 300 mg/24h. In subjects with baseline proteinuria ≤ 300 mg/24h, urine 24-hour protein levels remained relatively stable over the course of the study. Urine GL-3 levels were highly variable throughout the study and no definite conclusions can be made about the effect on migalastat treatment on this biomarker.

The effect of migalastat on cardiac function was primarily assessed by changes in LVMi based on ECHO, with changes in other ECHO parameters being predominantly exploratory. In the Stage 1 (post-hoc) analysis, no notable changes from baseline to month-6 were observed in either the migalastat group or the placebo group in the LVMi (or in any other ECHO parameter). In the Stage 2 (pre-specified) analysis, no notable changes from baseline to month 12 were observed in the LVMi (or in any other ECHO parameter). At month 12, all subjects with amenable GLA mutations had normal fractional shortening, and 97% had a normal ejection fraction.

Gastrointestinal symptoms (diarrhoea, constipation, reflux, abdominal pain, indigestion) were assessed using GSRS subscales. In the Stage 1 (post-hoc) analysis, significant improvements in diarrhoea symptoms from baseline to month 6 were observed in GLA amenable subjects treated with migalastat compared to placebo, and significant improvements were observed in reflux symptoms in amenable subjects with baseline reflux symptoms. In the OLE population (pre-specified) analysis, significant improvements in symptoms of diarrhoea and indigestion were observed in subjects treated with migalastat for 18 to 24 months.

For subjects with GLA amenable mutations and abnormal SF-36 v2 baseline values treated with migalastat for 18 to 24 months, improvements in SF-36 v2 scores were observed for the vitality subscale (mean increase, 4.0) and the general health domain (mean increase, 4.5). No other notable changes were observed during the study for any other patient reported outcomes based on SF-36 v2 assessments. There were no notable changes in pain in subjects with GLA amenable mutations assessed using the BPI.

In a pre-specified exploratory analysis of plasma lyso-Gb3, levels were similar at baseline for subjects with GLA amenable mutations in both the migalastat and placebo groups, but at month 6 levels had significantly decreased in the migalastat group compared to the placebo group. In the placebo-migalastat group, plasma lyso-Gb3 levels decreased significantly from month 6 to month 12 following the switch from placebo to migalastat, while levels remained constant between the two time-points for the migalastat-migalastat group.

Study AT1001-012

The results of Study AT1001-012 support the efficacy of migalastat in patients with Fabry disease previously treated with ERT. The results established that migalastat (n = 34) was comparable to ERT (n = 18), based on the pre-specified descriptive comparability criteria for the annualised rates of change from baseline to month 18 being met for the two co-primary efficacy endpoints of $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$. The primary analysis of the two co-primary efficacy endpoints was based on the mITT population. Subjects with amenable GLA mutations based on the GLP HEK assay were identified after enrolment in the study, but before the data were unblinded. Therefore, the efficacy analyses in the study are based on GLA amenable subjects based on the GLP HEK assay,

The difference between the two groups (migalastat minus ERT) in the LS mean annualised change from baseline to month 18 for $eGFR_{CKD\text{-}EPI}$ was +0.63 mL/min/1.73 m^2 (in favour of migalastat) and the corresponding result for $mGFR_{iohexol}$ was -1.1 mL/min/1.73m^2 (in favour of ERT). For both parameters, the migalastat LS mean annualised change in GFR was no greater than 2.2 mL/min/1.73 m^2 below the corresponding ERT change (i.e. pre-specified comparability criteria). The 95% CIs for the migalastat annualised rates of change from baseline to month 18 for $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ were > 50% above the lower bound of the 95% CI for the corresponding ERT change (that is, pre-specified comparability criteria).

The limitation of the primary efficacy analysis of the co-primary endpoints was that comparison of the two treatments was based on descriptive rather than inferential statistics. The sponsor commented that the rarity of Fabry disease precluded recruitment of a sample size large enough to undertake an inferential statistical analysis aimed at establishing non-inferiority of migalastat to ERT. The randomised, open-label, active-controlled (0 to 18 month), single-group extension (18 to 30 month), non-inferential design of Study AT1001-012 has been accepted by the EMA as being sufficient to support the efficacy of migalastat for the treatment of Fabry disease.

The analysis of the secondary efficacy endpoints in subjects with amenable GLA mutations were summarised descriptively in the mITT population. The results for all secondary efficacy parameters relating to the GFR (that is, the annualised rate of change in $eGFR_{MDRD}$ and the change from baseline in $eGFR_{CKD\text{-}EPI}$, $eGFR_{MDRD}$, and $mGFR_{iohexol}$) were consistent with the results for the co-primary primary efficacy analysis. The results for all other secondary efficacy endpoints (0 to 18 months) were similar for the two treatment groups, based on comparisons using descriptive statistics. The increases from baseline to month 18 in 24-hour urine protein and 24-hour urine albumin:creatinine ratio were comparable between the two treatment groups. The LVMi as assessed by ECHO decreased from baseline to 18 months in subjects in both treatment groups, but to a greater extent in the migalastat group compared to the ERT group. Levels of plasma lyso-Gb_3 remained low

and stable in subjects with in both treatment groups during the 18-month treatment period. Males in the migalastat group had an increase in WBC α-Gal A activity from baseline to month 18. The BPI short form and SF-36 v2 remained stable throughout the 18-month treatment period in both treatment groups. During the 18-month randomised treatment period, the composite clinical outcome in subjects with amenable GLA mutations was 23% in subjects receiving migalastat and 40% in subjects receiving ERT.

The long-terms results for Study AT1001-012 showed that renal and cardiac response to migalastat (migalastat-migalastat group) in the OLE population was durable throughout the duration of the study (0 through 30 months). Over the 30 months of treatment, the annualised rate of change GFR parameters remained stable in the migalastat-migalastat group in the OLE population (that is, $eGFR_{CKD\text{-}EPI}$, $eGFR_{MDRD}$ and $mGFR_{iohexol}$). In addition, the results for the GFR parameters were consistent across subjects in each of the migalastat-migalastat subgroups based on sex, age, and baseline GFR severity. The LVMi based on ECHO decreased from baseline to month 30 in all subjects and in subjects with LVH at baseline.

In subjects in the migalastat-migalastat group with amenable GLA mutations, the composite clinical outcome was 32% during the 30-months treatment period with migalastat. The percentage of subjects in the migalastat-migalastat group who had a renal, cardiac, or cerebrovascular event during the study (0 to 30 months) was 29%, 3%, and 0%, respectively. In subjects in the ERT-migalastat group with GLA amenable mutations, the percentage of subjects who had a composite clinical outcome was comparable during the 18-month randomised treatment period when subjects were receiving ERT (40%) and in the OLE period (40%) when subjects were receiving migalastat (18 to 30 months).

Plasma lyso-Gb_3 levels remained low throughout the study, with a slight increase from baseline to month 30 in subjects in the migalastat-migalastat group with GLA amenable mutations. In subjects in the ERT-migalastat group with amenable mutations, plasma lyso-Gb_3 remained low throughout the 30 month study. The BPI short form and SF-36 v2 remained stable throughout the 30 month study in the migalastat-migalastat group.

Safety

Studies providing safety data

The submission did not include an integrated safety summary for migalastat due to differences in subject characteristics (that is, healthy volunteers/patients with Fabry disease), study designs and dosing regimens. Therefore, the Summary of Clinical Safety (SCS) presented safety data from the individual studies included in the clinical development program.

The key safety data in the submission are considered to be from the two Phase III Studies AT1001-011 and AT1001-012. The evaluation of the safety of migalastat in this CER focuses on the safety data from these two studies primarily identified in the individual study reports. The safety data from these two studies are considered to be pivotal because the migalastat dosage regimen and the Fabry patient population reflect the proposed usage of the drug. Furthermore, because Study AT1001-011 included a placebo comparator group (initial 6 months of treatment) and Study AT1001-012 included an ERT comparator group (initial 18 months of treatment) clinically meaningful comparative assessments of the safety of migalastat with placebo and ERT can be made.

Patient exposure

In the clinical development program, 386 subjects have been exposed to migalastat including 168 subjects with Fabry disease in the Phase II (n = 53) and Phase III (n = 115)

studies. One-hundred and nineteen (119) patients with Fabry disease have been treated for at least 1 year. The longest patient exposure at the time of the submission was 9.8 years.

In the 10 Phase I studies, 218 subjects were exposed to migalastat and 24 to placebo. These studies were performed in healthy volunteers, apart from Study AT1001-015 which included patients with renal impairment.

In the 6 Phase II and 4 Phase III studies, 180 subjects with Fabry disease were assessed, including 168 subjects exposed to migalastat. The migalastat Phase III studies also included 21 subjects exposed to ERT and 33 subjects exposed to placebo, and of these, 15 of the ERT exposed subjects and 30 of the placebo exposed subjects were later exposed to migalastat. The exposure data for oral migalastat in patients with Fabry disease in the Phase II and IIII studies are summarised.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Study AT1001-011

- In Stages 1 and 2, there were no hepatobiliary disorders (System Organ Class (SOC)) reported in either the migalastat-migalastat group or the placebo-migalastat group. In the OLE, hepatobiliary disorders (SOC) were reported in 3% (n = 1) of subjects in the migalastat-migalastat group (1 x hepatocellular injury) and no subjects in the placebo-migalastat group. No serious treatment-emergent hepatobiliary disorders were reported during the study.
- There were no clinically meaningful changes from baseline in clinical chemistry parameters relating to hepatic function. There were no potentially clinically significant results for alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase or bilirubin in any of the treatment groups during the study. The criteria for potentially clinically significant laboratory abnormalities are summarised.

Study AT1001-012

- In the 18-month treatment-period, hepatobiliary disorders (SOC) were reported in 11% (n = 4) of subjects in the migalastat group and no subjects in the ERT group. The TEAEs in the 4 subjects in the migalastat group were 1 each for bile duct stone, cholelithiasis, gall bladder disorder, gall bladder polyp, and hepatic steatosis. There was 1 hepatic disorder (SOC) treatment-emergent SAE (bile duct stone). In the safety population (0 to 30 months), hepatobiliary disorders (SOC) were reported in 8% (n = 4) of subjects. The TEAEs in the 4 subjects were 1 each for cholelithiasis, gall bladder disorder, gall bladder polyp, hepatic function abnormality, and hepatic steatosis. There was 1 hepatobiliary (SOC) treatment-emergent SAE (bile duct stone).
- The clinical chemistry data relating to liver function testing demonstrated no clinically meaningful changes in mean values from baseline during the study, or in shifts from normal baseline values. In the 18-month treatment period there were no potentially clinically significant abnormalities relating to liver function tests in either the migalastat or the placebo group (that is, ALT, AST, alkaline phosphatase, bilirubin). In the OLE the only potentially clinical significant abnormality relating to liver function tests was high bilirubin in 1 (3%) subject in the migalastat-migalastat group. There were no potentially clinical significant results relating to other liver function tests in the OLE (that is, ALT, AST, alkaline phosphatase). The criteria for potentially clinically significant laboratory abnormalities are summarised.

Renal function and renal toxicity

Study AT1001-011

- In Stage 1, renal and urinary disorders (SOC) were reported in 12% (n = 4) of subjects in both the migalastat group and the placebo group. In the migalastat group, the TEAEs were haematuria (x 3) and 1 each for hydronephrosis, leucocyturia and renal impairment. In the placebo group, the TEAEs were 1 each for hypertonic bladder, nephrolithiasis, nephropathy, pyuria, and urine abnormality. Serious treatment-emergent renal and urinary disorders (SOC) were reported in 1 (3%) subject in the migalastat group (hydronephrosis) and no subjects in the placebo group.
- In Stage 2, renal and urinary disorders (SOC) were reported in 6% (n = 2) of subjects in the migalastat-migalastat group and 10% (n = 3) of subjects in the placebo-migalastat group. In the migalastat-migalastat group, the TEAEs were 1 each for haematuria and proteinuria. In the placebo-migalastat group, the TEAEs were 1 each for haematuria, pollakiuria, and urine abnormality. No serious treatment-emergent renal and urinary disorders (SOC) were reported in Stage 2.
- In the OLE, renal and urinary disorders (SOC) were reported in 28% (n = 8) of subjects in the migalastat-migalastat group and 21% (n = 6) of subjects in the placebo-migalastat group. In the migalastat-migalastat group, the TEAEs were proteinuria (x 4), dysuria (x 2), and 1 each for costovertebral tenderness, nephrolithiasis, and urinary retention. In the placebo-migalastat group, the TEAEs were proteinuria (x 5) and micoalbuminuria (x 3). No serious treatment-emergent renal and urinary disorders (SOC) were reported in the OLE.
- There were no clinically meaningful changes from baseline in renal function clinical chemistry parameters during the study in any of the treatment groups. In Stage 1, potentially clinically significant results for clinical chemistry parameters (migalastat versus placebo) were observed for high blood urea nitrogen (0% versus 6%, 2/33), and high creatinine (3%, 1/34 versus 0%). In Stage 2, the only potentially clinically significant result for clinical chemistry parameters (migalastat-migalastat versus placebo-migalastat) was high blood urea nitrogen (0% versus 7%, 2/30). In Stage 3, the only potentially clinically significant result for clinical chemistry parameters (migalastat-migalastat versus placebo-migalastat) was high blood urea nitrogen (0% versus 4%, 1/28). The criteria for potentially clinically significant laboratory abnormalities are summarised.

Study AT1001-012

- In the 18-month treatment period, renal and urinary disorders (SOC) were reported in 6% (n = 3) of subjects in the migalastat group and 10% (n = 2) of subjects in the ERT group. The TEAEs were proteinuria (x 1) and renal impairment (x 1) in the migalastat group and hypertonic bladder (x 1) and microalbuminuria (x 1) in the ERT group. There were no serious TEAEs in either of the two treatment groups during the 18 month treatment-period.
- In the safety population (0 to 30 months), renal and urinary disorders (SOC) were reported in 6% (n = 12) subjects in the all migalastat group. The TEAEs were proteinuria (x 2), renal impairment (x 2), nephrolithiasis (x 1), and strangury (x 1). Serious TEAEs were reported in 1 subject (proteinuria x 1).
- There were no clinically meaningful changes in mean values from baseline or shifts from normal baseline values in renal function chemistry parameters during the study. In the 18-month treatment period, the only potentially clinically significant result was a high blood urea nitrogen in 1 (3%) subject in the migalastat group. In the OLE period, high blood urea nitrogen was reported in 1 (7%) subject in the ERT-migalastat group and high serum creatinine was reported in 1 (3%) subject in the migalastat-

migalastat group. The criteria for potentially clinically significant laboratory abnormalities are summarised.

Other clinical chemistry

Study AT1001-011

- There were no clinically meaningful changes in mean values from baseline for clinical chemistry parameters during the study. No important treatment group differences were noted in the mean change from baseline for any clinical chemistry parameter. Shifts from normal baseline values were rare in all treatment groups for clinical chemistry parameters during the study. The potentially clinically significant results in the renal function tests have been described above. There were no clinically significant changes from baseline during the course of the study in urinalysis parameters in any of the treatment groups.

Study AT1001-012

- In the 18-month treatment period, there were no clinically meaningful changes in mean values from baseline for clinical chemistry parameters in the migalastat group or the ERT group. Shifts from a normal baseline value were infrequent and not clinically meaningful for all clinical chemistry parameters in the migalastat group and the ERT group. No potentially clinical significant abnormalities were reported in the clinical chemistry parameters in the migalastat group or the ERT group, apart from 1 report of high blood urea nitrogen in the migalastat group referred to above. There were no clinically meaningful changes in mean values in urinalysis parameters from baseline to month 18 in either the migalastat group or the ERT group.
- In the OLE, in the OLE population there were no clinically meaningful changes in mean values from baseline for clinical chemistry parameters during the study. No important treatment group differences were noted in the mean change from baseline for any clinical chemistry parameter. Shifts from normal baseline values were rare in all treatment groups for clinical chemistry parameters during the study. No potentially clinically significant clinical chemistry abnormalities were reported in the OLE, apart the results in hepatic and renal function described above. The criteria for potentially clinically significant laboratory abnormalities are summarised. There were no clinically meaningful changes from baseline during the course of the study in urinalysis parameters in the OLE population.

Haematology and haematological toxicity

Study AT1001-011

- In Stage 1, blood and lymphatic system disorders (SOC) were reported in 3% (n = 1) of subjects in the migalastat group (1x increased tendency to bruise) and no subjects in the placebo group. In Stage 2, blood and lymphatic system disorders (SOC) were reported in 3% (n = 1) of subjects in the migalastat-migalastat group (1x anaemia) and no subjects in the placebo-migalastat group. In the OLE, blood and lymphatic system disorders (SOC) were reported in 3% (n = 1) of subjects in the migalastat-migalastat group (1x anaemia) and no subjects in the placebo-migalastat group. No serious treatment-emergent blood and lymphatic system disorders were reported during the study.
- There were no clinically meaningful changes in mean values from baseline for haematology parameters during the study. No important treatment group differences were noted in the mean change from baseline for any haematology parameter. Shifts from normal baseline values were rare in all treatment groups for haematology parameters during the study.

- In Stage 1, potentially clinically significant results in haematology parameters were uncommon in both the placebo and migalastat groups. Potentially clinically significant results for haematology parameters (migalastat versus placebo) were low haematocrit (6%, 2/34 versus 18%, 6/33), low haemoglobin (3%, 1/34 versus 6%, 2/33), high leucocytes (3%, 1/34 versus 0%), and low neutrophils (0% versus 3%, 1/33). The criteria for potentially clinically significant laboratory abnormalities are summarised.
- In Stage 2, potentially clinically significant results in haematology parameters were uncommon in both the migalastat-migalastat and placebo-migalastat groups. Potentially clinically significant results for haematology parameters (migalastat-migalastat versus placebo-migalastat) were low haematocrit (9%, 3/33 versus 13%, 4/30), low haemoglobin (3%, 1/33 versus 13%, 4/30), low leucocytes (0% versus 3%, 1/28), and low neutrophils (0% versus 3%, 1/33).
- In the OLE, potentially clinically significant results in haematology parameters were uncommon in both the migalastat-migalastat and placebo-migalastat groups. Potentially clinically significant results for haematology parameters (migalastat-migalastat versus placebo-migalastat) were high eosinophils (0% versus 4%, 1/28), low haematocrit (10%, 3/29 versus 14%, 4/28), and low haemoglobin (0% versus 4%, 1/28).

Study AT1001-012

- In the 18-month treatment period, blood and lymphatic system disorders (SOC) were reported in no subjects in the migalastat group and 1 (5%) subject in the ERT group (anaemia x 1). No treatment-emergent SAEs were reported in either treatment group. There were no clinically meaningful changes in mean values from baseline to month 18 in haematology parameters in either treatment group. Shifts from a normal baseline value through to month 18 were infrequent and not clinically meaningful for the haematology parameters in both treatment groups. Potentially clinically significant haematology laboratory abnormalities were: high eosinophils in 1 (3%) subject in the migalastat group and 1 (5%) subject in the ERT group; low haematocrit in 4 (11%) subjects in the migalastat group and 1 (5%) subject in the ERT group; low haemoglobin in 1 (3%) subject in the migalastat group and 1 (5%) subject in the ERT group; low leucocytes in 1 (3%) subjects in the ERT group; high monocytes in 1 (3%) subject in the ERT group; and low neutrophils in 1 (3%) subject in the ERT group. The criteria for potentially clinically significant laboratory abnormalities are summarised.
- In the safety population (0 to 30 months), there were no blood and lymphatic disorders (SOC) reported in the all migalastat group. There were no clinically meaningful changes in mean values from baseline to month 30 in haematology parameters in the all migalastat group. Shifts from a normal baseline value through to month 30 were infrequent and not clinically meaningful for all haematology parameters in the all migalastat group. In the OLE population, potentially clinically significant haematology laboratory parameters in subjects who had received migalastat were: high eosinophils in 2 (4%) subjects; low haematocrit in 3 (6%) subjects; low haemoglobin in 2 (4%) subjects; low leucocytes in 1 (2%) subject; high leucocytes in 1 (2%) subjects; high monocytes in 2 (4%) subjects; low neutrophils in 1 (2%) subject; and high neutrophils in 1 (2%) subject.

Electrocardiograph findings and cardiovascular safety

Study AT1001-011

Cardiac disorders

- In Stage 1, cardiac disorders (SOC) were reported in 15% (n = 5) of subjects in the migalastat group and 12% (n = 4) of subjects in the placebo group. In the migalastat group, the TEAEs were atrial fibrillation (x 2) and 1 each for tachycardia, right bundle

branch block, cardiomyopathy, mitral valve incompetence, sinus arrhythmia, and ventricular hypokinesia. In the placebo group, the TEAEs were 1 each for tachycardia, AV block first degree, atrial dilatation, and palpitations. There were no serious cardiac disorders (SOC) in Stage 1.

- In Stage 2, cardiac disorders (SOC) were reported in 12% (n = 4) of subjects in the migalastat-migalastat group and 10% (n = 3) of subjects in the placebo-migalastat group. In the migalastat-migalastat group, the TEAEs were 1 each for atrial fibrillation, bradycardia, palpitations and ventricular tachycardia. In the placebo-migalastat group the TEAEs were tachycardia (x 3). Serious treatment-emergent cardiac disorders (SOC) were reported in 1 (3%) subject in the migalastat-migalastat group (1 x ventricular tachycardia) and no subjects in the placebo-migalastat group.
- In the OLE, cardiac disorders (SOC) were reported in 14% (n = 4) of subjects in the migalastat-migalastat group and 14% (n = 4) of subjects in the placebo-migalastat group. In the migalastat-migalastat group, the TEAEs were 1 each for atrial fibrillation (x 3), palpitations (x 2) and cyanosis (x 1). In the placebo-migalastat group, the TEAEs were sinus bradycardia (x 2) and 1 each for palpitations, left bundle branch block, and ventricular extrasystoles. Serious treatment-emergent cardiac disorders (SOC) were reported in 1 (3%) subject in the migalastat-migalastat group (1 x palpitations) and no subjects in the placebo-migalastat group.

ECG results

- In Stage 1, there were no clinically meaningful changes in mean values from baseline to the end of Stage 1 (that is, month 6) for ECG parameters in the treatment groups. No important treatment group differences were noted between the two treatment groups in the mean change from baseline for any ECG parameter. In Stage 1, the frequency of potentially clinically significant abnormalities was low and similar across the two treatment groups. Two (2) subjects in the migalastat group had QTcF values > 450 ms and a > 60 ms increase from baseline at month 6. For 1 subject, this abnormality was observed at month 1, and for the other subject, at months 3 and 6. None of these abnormalities were reported as AEs, and both subjects completed the study.
- In Stage 2, there were no clinically meaningful changes in mean values from baseline to the end of Stage 2 (month 12) in the ECG parameters. In Stage 2, in the Stage 2 OLE population 19% (n = 12) of all subjects had potentially clinically significant high QRS values, and 27% (n = 17) of all subjects had potentially clinically significant high QTcF values. Two (2) subjects in the migalastat-migalastat group and 1 subject in the placebo-migalastat group had QTcF values > 450 ms and a > 60 ms increase from baseline during the study. For 1 subject in the migalastat-migalastat group, this abnormality was observed during Stage 1 (2 incidents), and during Stage 2 (Months 7, 9 and 12). For the other subject in the migalastat-migalastat group, the abnormality was noted in Stage 2 at month 7. For the 1 subject in the placebo-migalastat group, the abnormality was noted in Stage 2 at month 9. None of the abnormalities in the 3 subjects were reported as AEs, and all 3 subjects completed the study.
- In the OLE, 19% (n = 11) of all subjects had potentially clinically significant high QRS values, and 28% (n = 16) of all subjects had potentially clinically significant high QTcF values. QTcF values > 450 ms and a > 60 ms increase from baseline during the study were observed in 1 subject in the migalastat-migalastat group (this subject also had 5 prior incidents of this abnormality in Stages 1 and 2) and 3 subjects in the placebo-migalastat group. For the 1 subject in the migalastat-migalastat group, the finding was observed at months 18 and 24. In the placebo-migalastat group, the finding was observed at month 18 for 1 subject, month 24 for 1 subject, and at an unscheduled visit for 1 subject. None of the findings in the 4 subjects were reported as AEs, and all 4 subjects completed the study.

ECHO (safety)

- The changes in ECHO parameters from baseline were assessed in this study as part of the efficacy assessment. Changes in cardiac ejection fraction by ECHO were reviewed as one of the stopping criteria for discontinuation of individual subjects. No subjects met the mandatory stopping criteria of a 25% decrease in cardiac ejection fraction.

Study AT1001-012

Cardiac disorders

- In the 18-month treatment period, cardiac disorders (SOC) were reported in 14% (n = 5) of subjects in the migalastat group and 14% (n = 3) of subjects in the ERT group. In the 5 subjects in the migalastat group, the TEAEs were palpitations (x 2), bradycardia (x 1), cyanosis (x 1), ventricular extrasystoles (x 1) and ventricular tachycardia (x 1). In the 3 subjects in the ERT group, the TEAEs were palpitations (x 1), arrhythmia (x 1), chronic cardiac failure (x 1). There were two serious TEAEs (1 x ventricular tachycardia in the migalastat group; 1 x chronic cardiac failure in the ERT group).
- In the safety population (0 to 30 months), cardiac disorders (SOC) were reported in 22% (n = 11) of subjects in the all migalastat group. The one TEAE reported in ≥ 2 subjects was palpitations (5, 10%), and TEAEs reported in 1 subject each were angina pectoris, atrial fibrillation, bradycardia, cyanosis, extrasystoles, pericardial effusion, ventricular extrasystoles, and ventricular tachycardia. Serious TEAEs reported in the migalastat-migalastat group were ventricular tachycardia (x 1) and atrial fibrillation (x 1). There was 1 serious TEAE in the ERT-migalastat group (chronic cardiac failure)

ECG

- In the 18-month treatment period, there were no clinically meaningful changes in mean ECG parameters over 18 months in either the migalastat or ERT treatment groups. At screening, more subjects in migalastat group (22%, n = 8) had clinically significant abnormal ECGs compared to the ERT group (10%, n = 2). At all subsequent visits, the frequency of clinically significant abnormal ECGs was lower in the migalastat group compared with the frequency at screening, and the frequency of clinically significant abnormalities was comparable to, or lower than, the frequency observed in the ERT group. At month 18, no subjects in either treatment group had clinically significant abnormal ECGs. At screening, the frequency of non-clinically significant abnormal ECGs was comparable between the two treatment groups (56%, n = 20 in the migalastat group and 52%, n = 11 in the ERT group). The frequency of non-clinically significant abnormal ECGs was higher in the migalastat group (64%, n = 23) compared to the ERT group (48%, n = 10) at month 1 and at all subsequent visits, with the frequencies at month 18 being 78% (n = 28) and 52% (n = 11), respectively.
- At month 18, in the OLE population no subjects in the migalastat-migalastat group or the ERT-migalastat group had clinically significant abnormal ECGs. No clinically significant abnormal ECGs were recorded during subsequent visits (including month 30) in either the migalastat-migalastat or the ERT-migalastat group. At month 18, the frequency of non-clinically significant abnormal ECGs was higher in the migalastat-migalastat group (79%, n = 26) compared to the ERT-migalastat group (53%, n = 8). At month 30, the frequency of non-clinically significant abnormal ECGs was comparable between the migalastat-migalastat group (70%, n = 23) and the ERT-migalastat group (67%, n = 10).

Vital signs and clinical examination findings

Study AT1001-011

- In Stage 1, there were no clinically meaningful changes in mean values from baseline to the end of Stage 1 (Month 6) for any vital signs in the two treatment groups. No clinically important differences were noted between the migalastat and placebo groups in the mean change from baseline through to month 6 for any vital sign. There were no potentially clinically significant abnormalities in systolic BP, diastolic BP or pulse rate in the migalastat group during Stage 1. The percentage of subjects with a potentially clinically significant increase in weight (≥ 7% increase) was similar in the two treatment groups (6% in the migalastat group and 9% in the placebo group).
- In Stage 2, there were no clinically meaningful changes in mean values from baseline to the end of Stage 2 (Month 12) for any vital signs. Potentially clinically significant abnormalities in systolic BP or diastolic BP were uncommon (1 (3%) subject in the migalastat-migalastat group with low systolic blood pressure; 1 (3%) subject in the placebo-migalastat group with high systolic blood pressure), as were potentially clinically significant abnormalities in pulse rate (2 (7%) subjects in the placebo-migalastat group with low values). Potentially clinically significant increase in weight (≥ 7% increase) were reported in 4 (12%) subjects in the migalastat-migalastat group and 4 (13%) subjects in the placebo-migalastat group, and potentially clinically significant decreases in weight (≥ 7%) were reported in 1 (3%) and 2 (7%) subjects, respectively.
- In the OLE, there were no clinically meaningful changes in mean values from baseline to the end of the OLE (Month 24) for any vital signs. Potentially clinically significant abnormalities in systolic BP or diastolic BP were uncommon (decreases in systolic BP in 1 (3%) subject in the migalastat-migalastat group and 1 (4%) subject in the placebo-migalastat group), as were potentially clinically significant abnormalities in pulse rate (decrease in 1 (4%) subject in the placebo-migalastat group). Potentially clinically significant increases in weight (≥ 7% increase) were reported in 5 (17%) subjects in the migalastat-migalastat group and 9 (32%) subjects in the placebo-migalastat group, while potentially clinically significant decreases in weight (≥ 7% decrease) were reported in 2 (7%) subjects and no subjects, respectively.

Study AT1001-012

- In the 18-month treatment period, there were no clinically meaningful changes in mean values from baseline through to month 18 for any vital signs in either the migalastat group or the ERT group. No important differences between the migalastat and ERT groups were noted in the mean change from baseline for any vital sign. Potentially clinically significant abnormalities in vital sign measurements were infrequent during the 18-month treatment period, with the exception of weight. The percentage of subjects with a potentially clinical significant increase in weight (≥ 7% increase) was 11% (n = 4) in the migalastat group and 5% (n = 1) in the ERT group. The percentage of subjects with a potentially clinically significant decrease in weight (≥ 7% decrease) was 17% (n = 6) in the migalastat group and 19% (n = 4) in the ERT group. There were no subjects with potentially clinically significant abnormalities (high or low) for systolic or diastolic blood pressure, and there was 1 subject in the migalastat group with a potentially clinically significant low pulse rate in the migalastat group.
- In the OLE, there were no clinically meaningful changes in mean values from baseline through to month 30 for any vital signs in the OLE population. Potentially clinically significant abnormalities in vital sign measurements were infrequent in the OLE period, with the exception of weight. The percentage of subjects with a potentially clinically significant increase in weight (≥ 7% increase in weight) was 9% (n = 3) in the

migalastat-migalastat group and 33% (n = 5) in the ERT-migalastat group. The percentage of subjects with a potentially clinically significant decrease in weight (≥ 7% decrease in weight) was 18% (n = 6) in the migalastat-migalastat group and 13% (n = 2) in the ERT-migalastat group. There were no potentially clinically significant increases in systolic blood pressure in either the migalastat-migalastat or the ERT-migalastat group, and there was 1 (7%) subject in the ERT-migalastat group with a potentially clinically significant decrease in systolic blood pressure. There were no potentially clinically significant abnormalities (high or low) in diastolic blood pressure in either the migalastat-migalastat or the ERT-migalastat group. There were no potentially clinically significant increases in pulse rate in either the migalastat-migalastat or the ERT-migalastat group. Potentially clinically significant decreases in pulse rate were observed in 6% (n = 2) of subjects in the migalastat-migalastat group and 7% (n = 1) of subjects in the ERT-migalastat group.

Immunogenicity and immunological events

Study AT1001-011

- In Stage 1, no immune system disorders (SOC) were reported in either the migalastat group or the placebo group. In Stage 2, immune system disorders were reported in 1 (3%) subject in the migalastat-migalastat group (1 x drug hypersensitivity) and 1 (3%) subject in the migalastat-placebo group (1 x drug hypersensitivity). In the OLE, no immune system disorders (SOC) were reported in either the migalastat-migalastat group or the placebo-migalastat group. No serious immune disorders (SOC) were reported during the study.

Study AT1001-012

- In the 18-month treatment period, immune system disorders (SOC) were reported in 1 (3%) subject in the migalastat group (1x seasonal allergy) and no subjects in the ERT group. In the safety population (0 to 30 months), immune system disorders (SOC) were reported in 1 (2%) subject in the all migalastat group (1x seasonal allergy). No serious immune disorders (SOC) were reported during the study

Serious skin reactions

Study AT1001-011

- No serious skin disorders (SOC) were reported during the study.
- In Stage 1, skin and subcutaneous disorders (SOC) were reported in 2 (6%) subjects in the migalastat group (1 TEAE each for dry skin and rash) and 5 (15%) subjects in the placebo group (1 TEAE each for dry skin, rash, angiokeratoma, erythema, macular rash, and skin burning sensation).
- In Stage 2, skin and subcutaneous disorders (SOC) were reported in 5 (15%) subjects in the migalastat-migalastat group (1 TEAE each for angiokeratoma, alopecia, eczema, erythema, hypohidrosis, pruritic rash, and skin lesion), and 3 (10%) subjects in the placebo-migalastat group (1 TEAE each for angiokeratoma, hyperhidrosis, and pityriasis).
- In the OLE, skin and subcutaneous disorders (SOC) were reported in 1 (3%) subjects in the migalastat-migalastat group (1 TEAE each for skin lesion and skin ulcer), and 4 (14%) subjects in the placebo-migalastat group (2 TEAEs each for angiokeratoma and erythema, 1 TEAE each for pruritus and rash).

Serious skin reactions

- No serious skin disorders (SOC) were reported during the study.

- In the 18-month treatment period, skin and subcutaneous disorders (SOC) were report in 8 (22%) subjects in the migalastat group and 4 (19%) subjects in the ERT group. In the 8 subjects in the migalastat group, the TEAEs were hyperhidrosis (x3), rash (x2), night sweats (x2) psoriasis (x 1), actinic keratosis (x 1), alopecia (x 1), hyperkeratosis (x 1), pruritus (x 1), skin discolouration (x 1) and skin lesion (x 1). In the 4 subjects in the ERT group, the TEAEs were night sweats (x 1), psoriasis (x 1), acne (x 1) and blister (x 1).
- In the safety-population (0 to 30 months), skin and subcutaneous tissue disorders (SOC) were reported in 11 (22%) subjects in the all migalastat group. The TEAEs were hyperhidrosis (x3), night sweats (x2), rash (x2), actinic keratosis (x 1), alopecia (x 1), hyperkeratosis (x 1), pigmentation disorder (x 1), pruritus (x 1), psoriasis (x 1), skin discolouration (x 1), skin lesion (x 1), skin striae (x 1), skin ulcer (x 1) and stasis dermatitis (x 1).

Post-marketing data

No post-marketing data were submitted. Migalastat was not marketed in any country at the time of submission.

Evaluator's conclusions on safety

It is considered that the safety of migalastat for the proposed indication has been satisfactorily established in the submitted data. Overall, the number of subjects treated with migalastat and the duration of exposure to migalastat are considered to allow adequate characterisation of the safety of migalastat for the treatment of Fabry disease. The safety profile of migalastat is considered to be inferior to placebo, but the differences between the two treatments do not give rise to significant safety concerns. Overall, the safety profile of migalastat is considered to be comparable with the safety profile of ERT, and the differences between the two treatments are considered to be not clinically significant.

In the 20 studies in the migalastat development program, 386 subjects have been exposed to migalastat including 168 subjects with Fabry disease. Of the 168 subjects with Fabry disease exposed to migalastat, 119 have been treated for at least 1 year. Available exposure data collected up to 2 November 2015 for 160 subjects treated with migalastat (all doses) from the Phase II and III studies indicates that the mean duration of exposure is 150 weeks (median 129 weeks), with a range of 0.1 to 507 weeks.

The two pivotal safety studies are the Phase III Studies AT1001-011 and AT1001-012. In these two studies, a total of 115 subjects with Fabry disease have been treated. These subjects included those with and without amenable GLA mutations based on the GLP HEK cell based assay. The primary analysis of safety in the two Phase III studies was on all subjects treated with migalastat, irrespective of amenable GLA mutation status. The safety data in all migalastat treated subjects were consistent with the safety data in subjects with amenable GLA mutations. There is no reason to expect that the safety of migalastat will significantly differ in subjects with Fabry disease with or without amenable GLA mutations.

In Study AT1001-011, in Stage 1 (initial 6-month, randomised, double-blind treatment period), 34 subjects were treated with migalastat with a mean (± SD) exposure of 5.9 ± 0.2 months and 32 subjects were treated with placebo with a mean (± SD) exposure of 6.1 ± 1.5 months. Over the total duration of the study (0-24 months), 66 subjects were exposed to migalastat with a mean (±SD) exposure of 22 ± 6 months. The 66 subjects included 34 in the migalastat-migalastat exposed to migalastat for a maximum of 24 months and 32 in the placebo-migalastat group exposed to migalastat for a maximum of 18 months.

In Study AT1001-012, in the randomised 18-month open-label treatment period 36 subjects were treated with migalastat and 21 subjects were treated with ERT. The mean (±SD) exposure to migalastat in this period was 522 ± 91 days and the mean (±SD) exposure to ERT was 478 ± 106 days. Over the whole duration of the study (0-30 months), the mean (±SD) exposure in the all migalastat group (n = 51) was 756 ± 288 days. The all migalastat group included subjects who had been initially randomised to migalastat (0-18 months) and continued with migalastat during the OLE (18-30 months) and subjects who had been initially randomised to ERT (0-18 months), and switched to migalastat in the OLE (18-30 months).

The mean duration of exposure for the total number of subjects (n = 115) treated in the Phase III Studies AT1001-011, AT1001-012, and AT1001-041 is 142 weeks (range: 5, 277 weeks), based on data at the cut-off date of 2 November 2015. In the long-term extension Study AT1001-041, 85 subjects had enrolled with 13 patients on-going and 71 subjects had entered Study AT1001-042 with 67 on-going as of 2 November 2015. There are no exposure data for Study AT1001-042.

The mean (±SD) age of the patients in Study AT1001-011 (n = 67) and Study AT1001-012 (n = 57) was 42 ± 12 years (range: 16, 68 years) and 49 ± 14 years (range: 18, 72), respectively. The majority of subjects in both studies were < 65 years of age, with only 6 (5%) subjects in the two studies being aged ≥ 65 years. In Study AT1001-011 (n = 67), 64.2% (n = 43) were female and 35.8% (n = 24) were male and in Study AT1001-012, 56.1% (n = 32) were female and 43.9% (n = 25) were male. The majority of the subjects in the two studies were Caucasian (91%) with most of the remaining subjects being Asian. Overall, the subject population in the two pivotal Phase III studies is considered to be representative of the Australian population with Fabry disease likely to be offered treatment with migalastat if the patient has an amenable *GLA* mutation and if the drug is approved.

Study AT1001-011

In Stage 1 (0 to 6 months, placebo-controlled), TEAEs were reported in 91% (n = 31) of subjects in the migalastat group and 91% (n = 30) of subjects in the placebo group. TEAEs reported in ≥ 10% of subjects in either treatment group (migalastat versus placebo) were headache (35% versus 21%), nasophyaryngitis (18% versus 6%), fatigue (12% versus 12%), paraesthesia (12% versus 12%), nausea (12% versus 6%), pyrexia (12% versus 3%), and pain in extremity (0% versus 12%). TEAEs reported in ≥ 10% of subjects in the migalastat group and in ≥ 5% more subjects than in the placebo group were headache (35% versus 21%), nasophyaryngitis (18% versus 6%), pyrexia (12% versus 3%), and nausea (12% versus 6%). The only TEAE reported in ≥ 10% of subjects in the placebo group and in ≥ 5% more subjects than in the migalastat group was pain in extremity (12% versus 0%).

In Stage 2 (6 to 12 months, open-label migalastat), TEAEs were reported in 79% (50/63) of the total number of subjects treated with migalastat. TEAEs reported in ≥ 10% of the total number of subjects were headache (14%) and procedural pain (11%). In the OLE (12 to 24 months, open-label migalastat), 84% (48/57) of subjects treated with migalastat experienced TEAEs. TEAEs reported in ≥ 10% of the total number of subjects treated with migalastat in the OLE were proteinuria (16%), bronchitis (11%) and headache (11%).

In Stage 1 (0 to 6 months, placebo-controlled), treatment-related TEAEs were reported more frequently in the migalastat group than in the placebo group (44% versus 27%). Treatment-related TEAE reported in ≥ 5% of subjects in either of the two treatment groups (migalastat versus placebo) were nausea (6% versus 0%), diarrhoea (6% versus 0%), dry mouth (6% versus 3%), weight increased (6% versus 0%), torticollis (6% versus 0%), paraesthesia (6% versus 0%), and fatigue (0% versus 6%). In Stage 2 (6 to 12 months, open-label migalastat), 19% (n = 12) of subjects treated with migalastat

experienced treatment-related TEAEs. Treatment-related TEAEs reported in ≥ 5% of subjects treated with migalastat were headache (5%) and incorrect dose administered (5%). In the OLE (12 to 24 months, open-label migalastat), 21% (12/57) of subjects treated with migalastat experienced treatment-related TEAEs and no events were reported in ≥ 5% subjects.

There were no deaths reported during the study. In the overall safety population (n = 67), 26 treatment-emergent SAEs were reported in 19 (28%) subjects. In the overall safety population (n = 67), discontinuations due to TEAEs (both considered unrelated to treatment) were reported in 2 (3%) subjects treated with migalastat (anaplastic large cell lymphoma and amyotrophic lateral sclerosis).

Of the 26 treatment-emergent SAEs reported during the study, 2 events in the placebo-migalastat group were considered to be possibly related to treatment (fatigue and paraesthesia). In Stage 1 (0 to 6 month, placebo-controlled), treatment-emergent SAEs were reported in 6% (n = 2) of subjects in the migalastat group and 12% (n = 4) of subjects in the placebo group. In the migalastat group, the 2 treatment-emergent SAEs were 1 each for post-procedural haematoma and hydronephrosis. Both treatment-emergent SAEs were considered by investigators to be unrelated to the study drug. In the placebo group, the 4 treatment-emergent SAEs were 1 each for bacterial infection, viral meningitis, post-procedural haemorrhage, anaplastic large cell lymphoma. In Stage 2 (6 to 12 months, open-label migalastat), treatment-emergent SAEs were reported in 5 (8%) subjects in the total population treated with migalastat. The only treatment-emergent SAE reported in more than 1 subjects was pulmonary embolism (n = 2). In the OLE (12 to 24 months, open-label migalastat), treatment-emergent SAEs were reported in 11 (19%) subjects in the total population treated with migalastat and no events were reported in more than 1 subject.

Study AT1001-012

In the 18-month, active-controlled treatment period, TEAEs were reported in a similar proportion of subjects in the migalastat and ERT groups (94% (34/36) versus 95% (20/21), respectively). TEAEs reported in ≥ 10% of subjects in the migalastat group versus the ERT group, respectively, were nasophyarngitis (33% versus 33%), headache (25% versus 24%), dizziness (17% versus 10%), influenza (14% versus 19%), abdominal pain (14% versus 10%), diarrhoea (14% versus 10%), nauseas (14% versus 10%), back pain (11% versus 14%), upper respiratory tract infection (11% versus 5%), and urinary tract infection (11% versus 5%).

In the 18-month, active –controlled treatment period, TEAEs reported in ≥ 10% of subjects in either treatment group and in ≥ 5% more subjects in the migalastat group than in the ERT group were dizziness (17% versus 10%), upper respiratory tract infection (11% versus 5%), and urinary tract infection (11% versus 5%). TEAEs reported in ≥ 10% of subjects in either treatment group and in ≥ 5% more subjects in the ERT group than in the migalastat group were cough (24% versus 8%), influenza (19% versus 14%), vomiting (14% versus 8%), sinusitis (14% versus 8%), bronchitis (14% versus 6%), vertigo (10% versus 3%), dry mouth (10% versus 3%), gastritis (10% versus 3%), pain in extremity (10% versus 3%), dyspnoea (10% versus 3%), and procedural pain (10% versus 0%).

In the whole study period (0-30 months), TEAEs were reported in 98% (50/51) of subjects in the all migalastat group. The pattern of TEAEs in the all migalastat group (0-30 months) was consistent with the pattern of TEAEs in the migalastat group (0-18 months). TEAEs reported in ≥ 20% of subjects in the all migalastat group (0-30 months) were nasophyarngitis (41%), headache (31%), influenza (24%), and diarrhoea (22%).

In the 18-month, active-controlled treatment period, treatment-related TEAEs were reported notably more frequently in the migalastat group than in the ERT group (39% (14/36) versus 14% (3/21)). Treatment-related TEAEs reported in ≥ 5% of subjects in

either treatment group (migalastat versus ERT, respectively) were headache (17% versus 0%), dizziness (6% versus 0%), diarrhoea (8% versus 0%), abdominal pain (6% versus 0%), nausea (6% versus 0%), dyspepsia (6% versus 1%), CK increased (6% versus 0%), fatigue (3% versus 5%), dry mouth (0% versus 5%), infusion site inflammation (0% versus 5%), blood glucose increased (0% versus 5%), gamma GT increased (0% versus 5%), glucose urine present (0% versus 5%), and cough 5% versus 0%).

In the whole study period (0 to 30 months), treatment-related TEAEs were reported in 37% (19/51) of subjects in the all migalastat group. The pattern of treatment-related TEAEs in the all migalastat group (0 to 30 months) was consistent with the pattern of treatment-related TEAEs in the migalastat group (0 to 18 months). Treatment-related TEAEs reported in ≥ 5% of subjects in the all migalastat group were headache (14%), diarrhoea (8%), CK increased (6%), and dizziness (6%)

No deaths were reported during the study. No subjects discontinued treatment during the study due to TEAEs. In the 18-month, active-controlled treatment period, a total of 24 treatment-emergent SAES (all unrelated to treatment) were reported in 19% (7/36) of subjects in the migalastat group (9 events) and 33% (7/21) of subjects in the ERT group (15 events). In the whole study period (0-30 months), 20 treatment-emergent SAEs were reported in 31% (16/51) of subjects in the all migalastat group. In the whole study period (0-30 months), 1 treatment-emergent SAE was reported to be possibly related to treatment in the all migalastat group (proteinuria in 1 subject in the migalastat-migalastat group).

Studies AT1001-011 and AT1001-012

No safety issues with possible regulatory impact were identified in subjects treated with migalastat in the two Phase 3 studies : i.e., no hepatic toxicity; no renal toxicity; no haematological toxicity; no significant cardiac disorders or changes in ECG parameters including QTc prolongation; no significant immune system disorders; no serious skin reactions (including no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis); no clinically meaningful laboratory abnormalities relating to haematological parameters, liver function tests, renal function tests, or other clinical chemistry parameters; and no clinically significant changes in vital signs.

In special populations: the safety profile of migalastat appeared to be generally similar in males and females, and the reported differences are considered to be not clinically significant: the number of patients aged > 65 years was too small to compare the safety of migalastat in this population with the safety of migalastat in subjects aged ≤ 65 years; there were no safety data in subjects aged < 16 years of age, but migalastat is not being proposed for registration in subjects younger than 16 years of age; the number of non-Caucasian subjects was too small to adequately access the efficacy of migalastat in this population; the safety of migalastat appeared to be similar in subjects with baseline moderate renal impairment and subjects with baseline mild renal impairment/normal renal function, but subject numbers in the moderate renal impairment group were too small to allow definitive conclusions to be made; there were no safety data in subjects with severe baseline renal impairment and no separate safety data in subjects with mild baseline renal impairment; and there were no safety data in subjects with baseline hepatic impairment.

Study AT1001-041 long-term safety

There were data for 85 subjects enrolled in the long-term safety study (AT1001-041), continuing treatment with migalastat. The 85 subjects are from the three feeder studies (FAB-CL-205, AT1001-011, AT1001-012). Of the 85 subjects enrolled in *study AT1001-041*, 81% (n = 69) had experienced at least one TEAE. The TEAEs reported in this study were consistent with those reported in the two Phase 3 studies, and no new safety signals associated with migalastat emerged with long-term treatment. TEAEs, reported in ≥ 10%

of subjects were diarrhoea (16%, n = 14), arthralgia (13%, n = 11), fatigue (12%, n = 10), headache (12%, n = 10), pain in extremity (12%, n = 10), and nasophyaryngitis (11%, n = 9). Of the 662 TEAEs reported in the study, 56 were assessed to be related to treatment. Treatment-related TEAEs reported in ≥ 2 patients were diarrhoea (4, 5%), dizziness (2, 2%), fatigue (2, 2%), glomerular filtration rate decreased (2, 2%), urinary tract deficiency (2, 2%), and vitamin deficiency. All other treatment-related TEAEs were each reported once, and consisted of a variety of events.

There were 31 treatment-emergent SAEs reported by 22 subjects, none of which were related to migalastat. The treatment-emergent SAEs were: cardiac disorders (atrial fibrillation x 2; angina pectoris x 1); gastrointestinal disorders (abdominal pain upper x 1; hiatus hernia x 1; pancreatitis x 1); general disorders and administration site conditions (death x 1; device malfunction x 1); hepatobiliary disorder (hepatic infarction x 1); infections and infestations (pneumonia x2; lobar pneumonia x 1); injury poisoning and procedural complication (foot fracture x 1); musculoskeletal and connective tissue disorders (muscle spasms x 1; musculoskeletal chest pain x 1); neoplasms, benign, malignant and unspecified, including cysts and polyps (breast cancer metastatic x 1; malignant melanoma x 1; meningioma x 1; papillary thyroid cancer x 1; thyroid neoplasm x 1); nervous system disorders (brain stem ischaemia x 1; pre-syncope x 1); not coded (insertion of implantable cardioverter defibrillator x2); psychiatric disorder (conversion disorder x 1); renal an urinary disorders (urinary calculus x 1); reproductive and breast disorders (priapism x 1; uterine polyp x 1); and skin and subcutaneous tissue disorders (angioedema x 1).

There 2 deaths in the study; 1 (1%) subject died from a TEAE (Stage III Breast Cancer) during the study deemed to be unrelated to treatment; 1 (1%) subject was found dead at home (unknown cause, unrelated to treatment), the subject's medical history included transient ischaemic attack, obesity, type 2 diabetes mellitus, hypercholesterolemia, cardiac stent placement, triple bypass surgery, and cardiac pacemaker insertion. These two deaths were the only deaths reported in the migalastat clinical program at the time of the submission. Discontinuations as of 2 November 2015 due to TEAEs were reported in 1 (1.2%) subject (metastatic squamous cell carcinoma considered to be unrelated to treatment).

First round benefit-risk assessment

First round assessment of benefits

The benefits of treatment with migalastat for patients with Fabry disease with amenable GLA mutations based on the GLP HEK assay have been adequately demonstrated in 1 pivotal Phase 3 study comparing migalastat 150 mg QOD with ERT over 18 months of randomised, open-label, treatment (study AT1001-012), and in 1 supportive Phase 3 study comparing migalastat 150 mg QOD with placebo over 6 months randomised, double-blind treatment in a post-hoc analysis undertaken after unblinding of the data (study AT1001-011). In both Phase 3 studies, long-term durability of response with migalastat 150 mg QOD was satisfactorily demonstrated. In addition, the long-term data from study AT1001-014 demonstrated that the $eGFR_{CKD\text{-}EPI}$ remained stable over an average of 36 months in subjects from study AT1001-011 continuing in the long-term extension study, while reductions from baseline in LVMi were observed in subjects with normal LV function and with LVH.

The available data indicate that the benefits of treatment with migalastat are limited to those patients with an amenable GLA mutation. Therefore, if migalastat is approved for registration it will be essential to confirm that all potential patients have an amenable GLA

mutation prior to initiating treatment. As of 27 October 2015, the GLP HEK assays was the only existing method available to identify the target patient population.

It is noted that inter-subject variability in all baseline efficacy parameters was high in both Study AT1001-011 and Study AT1001-012, suggesting that the clinical phenotype of Fabry disease in the subject population in these studies is heterogeneous. Furthermore, it is noted that inter-subject variability in the efficacy endpoints following treatment with migalastat, ERT and placebo was high. High baseline inter-subject variability in the efficacy variables and high post-treatment inter-subject variability in the efficacy outcomes suggests that there is likely to be considerable individual variability in response to treatment in patients with Fabry disease and amenable *GLA* mutations treated with migalastat. The submitted data have not identified a particular subgroup of patients with Fabry disease and amenable GLA mutations for whom treatment with migalastat is likely to be most beneficial. However, the disease burden was high in the total population with amenable GLA mutations in the two studies, with the majority of subjects having disease involving two or more organ systems (91%, 97/107).

There are limited data on the benefits of migalastat in elderly subjects. In study AT1001-011, the mean age of the 67 enrolled subjects was 42.2 years (range: 16, 68 years). In study AT1001-012 the mean age of the 57 enrolled subjects was 48.9 years (range: 18, 72 years), with only 5 subjects being aged > 65 years. The sponsor states that "elderly subjects are not expected to respond differently to Galafold than younger patients", but provides no data supporting this claim.

The benefits associated with migalastat treatment in the proposed patient population are described below. The results refer to subjects with amenable *GLA* mutations based on the GLP HEK assay, unless otherwise stated.

Renal benefits

Fabry disease is associated with progressive decline in renal function, which can lead to ESRD. Therefore, improvement or stabilisation of renal function is considered to be a clinically important treatment outcome. In Study AT1001-012, 66% of patients had baseline $mGFR_{iohexol}$ < 90 mL/min/1.73 m^2, and 48% of patients had baseline $eGFR_{CKD\text{-}EPI}$ < 90 mL/min/1.73 m^2. In Study AT1001-011, 52% of patients had baseline $mGFR_{iohexol}$ < 90 mL/min/1.73 m^2, and 50% of patients had baseline $eGFR_{CKD\text{-}EPI}$ < 90 mL/min/1.73 m^2. Baseline 24-hour urine protein levels ≥ 100 mg/24 hr were present in 79% of patients in Study AT1001-012 and in 84% of patients in Study AT1001-011. These findings indicate that a high proportion of the Phase III patients had abnormal kidney parameters (abnormal GFR and presence of proteinuria) at baseline.

GFR parameters

- In Study AT1001-012 (mITT population), the annualised rates of change for $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ from baseline to month 18 in the migalastat group (n = 34) were comparable with the results in the ERT group (n = 18). The difference between the two groups (migalastat minus ERT) in the LS mean annualised changes from baseline to month 18 for $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ were +0.63 mL/min/1.73 m^2 (in favour of migalastat) and -1.1 mL/min/1.73 m^2 (in favour of ERT), respectively. The 95% CIs for the migalastat annualised rates of change from baseline to month 18 for $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ were entirely enclosed with the corresponding 95% CIs for ERT. The co-primary endpoints, $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$, met the criteria for comparability of annualised means within 2.2 mL/min/1.73 m^2 per year and > 50% overlap of 95% CIs.
- In study At1001-012 (OLE population), in the migalastat-migalastat group (n = 31), the mean annualised rates of change from baseline to month 30 in GFR parameters were: -1.7 mL/min/1.73 m^2 (95% CI, -2.7, -0.8) for $eGFR_{CKD\text{-}EPI}$; -2.3 mL/min/1.73 m^2

(95% CI, -4.0, -0.6) for eGFRMDRD; and -2.7 mL/min/1.73 m² (95% CI, -4.8, -0.7) for mGFRiohexol. The results for the eGFR parameters remained stable over 30 months treatment with migalastat.

- In Study AT1001-011 (ITT population), in the Stage 1 (post-hoc) analysis eGFRCKD-EPI and eGFRMDRD did not change notably from baseline to month 6, and there were no clinically meaningful differences between the migalastat and placebo groups. The mean (± SD) annualised changes from baseline at month 6 in eGFRCKD-EPI in the migalastat group (n = 28) and the placebo group (n = 20) were 0.3 ± 17.05 and 2.0 mL/min/1.73 m², respectively. The mean (± SD) annualised changes from baseline at month 6 in eGFRMDRD in the migalastat group (n = 28) and the placebo group (n = 20) were 4.60 ± 30.175 and 1.88 ± 16.058 mL/min/1.73 m², respectively. In the OLE population, the mean (± SEM) annualised changes in eGFRCKD-EPI and eGFRMDRD from baseline at month 24 were -0.30±0.663 and 0.79 ± 1.027 mL/min/1.73 m², respectively, in subjects treated with migalastat (n = 41) for 18 or 24 months
- In Study AT1001-011 (ITT population), in the Stage 1 (post-hoc) analysis the mean annualised reduction from baseline at month 6 in mGFRiohexol was greater in the migalastat group (n = 28) than in the placebo group (n = 20): -14.11 ± 38.632 versus -1.78 ± 22.763 mL/min/1.73 m², respectively. In the OLE population, in subjects treated with migalastat (n = 37) for 18 or 24 months the mean (± SEM) annualised change in mGFRiohexol at month 24 was -1.51 ± 1.327 mL/min/1.73 m². The results indicate that mGFRiohexol remained stable over 18 or 24 months treatment with migalastat.
- In Study AT1001-011, the mean annualised reductions at month 24 in eGFRCKD-EPI and mGFRiohexol after 18 or 24 months of treatment with migalastat were greater in male subjects than in female subjects, and greater in subjects with baseline urine protein > 1000 mg/24 h.
- In subjects from study AT1001-011 continuing treatment with migalastat in the long-term extension study AT1001-041, eGFRCKD-EPI remained stable over an average of 36 months (range: 18, 54 months). The mean annualised rate of change in eGFRCKD-EPI over this period in subjects continuing treatment (n = 41) was -0.77 (95% CI: -1.9. 0.39) mL/min/1.73 m². Measured GFR (mGFRiohexol) was not assessed in study AT1001-041.

Renal histology

- There were no data on renal histology in Study AT1001-012. Therefore, all data relating to renal histology are from Study AT1001-011. The results from this study indicated that migalastat can reduce the renal burden arising from IC inclusions in renal cells, and that the reduction is durable.
- In Study AT1001-011 (ITT population), the Stage 1 (post-hoc) analysis showed that migalastat (n = 25) statistically significantly reduced the mean (±SD) number of IC GL-3 inclusions compared with placebo (n = 20) from baseline to month 6: -0.250 ± 0.5126 versus +0.071 ± 0.5627, respectively; difference in LS means = -0.3 (95% CI: -0.6, -0.1), p = 0.0078.
- In Study AT1001-011, the Stage 2 (pre-specified) analysis showed that in subjects in the placebo-migalastat group who switched from placebo to migalastat at month 6 (n = 20) the change from baseline in the mean (±SD) number of IC GL-3 inclusions at month 12 (n = 17) was statistically significantly lower than at month 6: -0.243 ± 0.4038 versus +0.071 ± 0.5627, respectively; difference in LS means = -0.320 (95% CI: -0.5719, -0.0677), p = 0.014. In subjects in the migalastat-migalastat group, changes in the mean number of IC GL-3 inclusions were similar for baseline to month 6 and baseline to month 12.

- In Study AT1001-011, in the MMRM analysis in the mITT population during Stages 1 and 2 (n = 45) there was a statistically significant greater percentage of ICs with zero GL-3 inclusions after 6 months treatment with migalastat compared with 6 months treatment with placebo: difference in LS means = 5.7% (95% CI: 1.20, 10.11); p = 0.014.
- In Study AT1001-011, in an exploratory qualitative assessment of GL-3 inclusions in renal cells (other than ICs) based on paired samples, after 12 months treatment with migalastat (migalastat-migalastat group) subjects in the Stage 2 population (n = 27) had reductions in GL-3 inclusions of 22%, 48% and 26% in podocytes, mesangial cells, and endothelial cells, respectively. No subjects experienced increases in GL-3 inclusions in podocytes, mesangial cells, or endothelial cells after 12 months treatment with migalastat. The exploratory results suggest that migalastat can reduce the GL-3 burden in podocytes, mesangial, and endothelial renal cells.

24-hour urine protein, albumin and creatinine

Most subjects in Studies AT1001-011 and AT1001-012 had proteinuria at baseline. In Study AT1001-012, 33 (58%) subjects had proteinuria ≥ 100 mg / 24 h. In Study AT1001-011, 44 (66%) subjects had proteinuria > 150 mg/24 h, 22 (33%) subjects had proteinuria > 300 mg/ 24 h, and 6 (9%) subjects had proteinuria > 1000 mg/24 h. In the majority of subjects with baseline proteinuria < 300 mg/24 h, proteinuria remained stable during treatment with migalastat for 18 to 24 months. However, migalastat does not appear to have a beneficial effect on higher levels of proteinuria (≥ 300 mg/24 h). In a *post-hoc* analysis in which the effect of migalastat was stratified by sex and baseline proteinuria, change in eGFR showed more improvement in patients with low and moderate levels of proteinuria at baseline, especially in women (see below).

Table 8: Annualised eGFR slopes stratified by sex and 24-hour urine protein level at baseline in migalastat treated patients.

Sex	24-h urine protein (g)	Study AT1001-011 Migalastat treated $eGFR_{MDRD}$ (mean ± SEM)	Study AT1001-011 Migalastat treated $eGFR_{CKD-EPI}$ (mean ± SEM)
Males	<0.1 (Low)	No patients	No patients
	0.1-1.0 (Moderate)	+1.0 (1.4) n=12	-0.03 (0.9) n=12
	>1.0 (High)	−5.9 (1.8) n=2	−6.5 (2.0) n=2
Females	<0.1 (Low)	+0.3 (1.4) n=7	+0.2 (1.4) n=7
	0.1-1.0 (Moderate)	+1.8 (2.0) n=18	+0.2 (1.2) n=18
	>1.0 (High)	−1.3 (2.8) n=2	−1.8 (2.4) n=2

- In Study AT1001-012 (mITT population), the mean (±SD) baseline 24-hour urine protein level was 259.6 ± 422.22 mg/day in the migalastat group and 417.4 ± 735.45 mg/day in the ERT group. The mean (±SD) increase from baseline to month 18 was lower in the migalastat group than in the ERT group (49.2 ± 199.53 and 194.5 ± 690.77 mg/day, respectively). The mean (±SD) change from baseline to month 18 in the 24-hour urine albumin:creatinine ratio was smaller in the migalastat group than in the placebo group (5.8 ± 19.66 and 14.3 ± 40.20 mg/mmol, respectively).

- In Study AT1001-012, in the OLE population the mean (±SD) baseline and month 30 24-hour urine protein levels in the migalastat-migalastat group were 269 ± 440 mg/day and 350 ± 599 mg/day, respectively. The data indicate that the mean 24-hour urine protein levels remained relatively stable from baseline to month 30 in subjects treated with migalastat over this period. The mean (±SD) baseline and month 30 24-hour urine albumin-creatinine ratios in the migalastat-migalastat group were 19.0 ± 38.4 and 38.5 ± 100.5 mg/mmol, respectively.
- In Study AT1001-011 (ITT population), in the Stage 1 (post-hoc) analysis the LS mean 24-hour urine protein concentration increased from baseline to month 6 to a notably greater extent in the migalastat group (n = 28) than in the placebo group (n = 22), but the difference in the LS means was not statistically significant (+69.3 versus +9.6 mg/24 h; p = 0.5234.
- In Study AT1001-011 (ITT population), in the Stage 1 (post-hoc) analysis the LS mean 24-hour urine creatinine concentration increased from baseline to month 6 in the migalastat group (n = 28) and decreased in the placebo group (n = 22), but the difference in the LS means between the two groups was not statistically significant (+0.082 versus -0.567 mmol/24 h; p = 0.3848).
- In Study AT1001-011 (ITT population), in the Stage 1 (post-hoc) analysis the LS mean 24-hour urine albumin concentration increased from baseline to month 6 in the migalastat group (n = 28) and decreased in the placebo group (n = 22), but the difference in the LS means between the two groups was not statistically significant (+90.153 versus -23.90 mg/24 h; p = 0.1325).
- In study AT1001-001, in the OLE population (pre-specified) in both the migalastat-migalastat and the placebo-migalastat groups there were increases from baseline to month 24 in 24-hour urine protein (139.3 and 251.1 mg/24 h, respectively) and albumin (106.6 and 184.0 mg/24 h, respectively), while mean changes from baseline to month 24 in 24-hour urine creatinine were negligible in both treatment groups.
- In Study AT1001-011, there was a mean increase from baseline to month 24 in the 24-hour urine albumin:creatinine ratio (11.2 mg/mmol) and the 24-hour protein: creatinine ratio (15.5 mg/mmol).

Cardiac benefits – cardiac function measured by ECHO

- The sponsor comments that left ventricular hypertrophy is the most common manifestation of cardiac disease associated with Fabry disease. In untreated patients with Fabry disease, progressive increases in LVMi occur. Therefore, improvement or stabilisation in LVMi is a clinically relevant treatment benefit for patients with Fabry disease.
- In Study AT1001-012 (mITT), the mean (±SD) baseline LVMi was 95.3 ± 22.8 g/m^2 in the migalastat group and 92.9 ± 25.7 g/m^2 in the ERT group, and at month 18 the mean (±SD) LVMi values were 89.4 ± 22.8 g/m^2 and 90.6 ± 36.7 g/m^2, respectively. The mean LVMi decreased from baseline to month 18 by -6.6 g/m^2 (95% CI: -11.0, 2.1) in the migalastat group and by -2.0 g/m^2 (95% CI: -11.0, 7.0) in the ERT group. At baseline, 34% of subjects had LVH (LVMi > 95 g/m^2 for males and > 115 g/m^2 for females). The LVMi decreased from baseline to month 18 in both males and females in the migalastat group (mean change: males, -9.4 g/m^2; females, -4.5 g/m^2). The ANCOVA analysis of subjects with abnormal LVMi at baseline showed a trend towards a greater decrease from baseline to month 18 in LVMi in the migalastat group, compared to the ERT group (difference in LS means, -10.4 g/m^2).
- In Study AT1001-012, the mean (±SD) baseline LVEF was 64 ± 3% in the migalastat group and 61 ± 4% in the ERT group, and the mean (±SD) LVEF at month 18 was 63 ± 4% in the migalastat group and 60±8% in the ERT group. The mean (±SD) change

from baseline to month 18 was 1±2% in the migalastat group and -0.5 ± 4% in the ERT group. No clinically relevant changes in the LVEF from baseline to month 18 were observed in either treatment group.

- In Study AT1001-012, in the OLE population the mean (±SD) LVMi at baseline (n = 30) in the migalastat-migalastat group was 94.7 ± 22.4 g/m^2 and at month 30 (n = 29) was 89.3 ± 20.3 g/m^2. In subjects with LVH at baseline, the mean (+SD) LVMi at baseline in the migalastat-migalastat group (n = 11) was 116.4 ± 20.9 g/m^2 and at month 30 (n = 10) was 105.6 ± 18.6 g/m^2. The results indicate that LVMi improved over 30 months treatment with migalastat in all subjects and in subjects with baseline LVH. In all amenable subjects in the migalastat-migalastat group the mean (±SD) LVEF was 64±3% at baseline and 64±4% at month 30. Other ECH0 parameters in the migalastat-migalastat group remained stable from baseline to month 30.
- In Study AT1001-011 (ITT population), in the Stage 1 (post-hoc) analysis no notable shifts from baseline to month 6 were observed for either the migalastat or the placebo group for the ECHO parameters of LVMi, LVM, fractional shortening, left ventricular ejection fraction, or left ventricular posterior wall thickness. The mean (±SD) baseline LVMI was 91.7 ± 27.9 g/m^2 in the migalastat group and 97.7 ± 32.2 g/m^2 in the placebo group, and the mean (±SD) change from baseline to month 6 was 0.2 ± 7.8 g/m^2 and -0.8 ± 6.7 g/m^2 respectively. The mean (±SD) baseline LVEF was 64±5% in the migalastat group and 64±5% in the placebo group, and the mean (±SD) change from baseline to month 6 was 0.05 ± 3% and 0.04 ± 3%, respectively.
- In Study AT1001-011, in the Stage 2 (pre-specified) analysis no notable shifts from month 6 to month 12 were observed in ECHO parameters in subjects in the migalastat-migalastat and placebo-migalastat groups. All subjects with amenable GLA mutations had normal fractional shortening at baseline, month 6 and month 12. More than 90% of subjects had normal LVEFs at baseline and at 6 months, and 97% of subjects had a normal LVEF at month 12.
- In Study AT1001-011, the mean (±SD) baseline LVMi was 96.5 ± 32.9 g/m^2 for all subjects with amenable GLA mutations (n = 44) and 138.9 ± 37.1 g/m^2 for subjects with GLA amenable mutations and LVH (n = 11). After 18 or 24 months of migalastat treatment, the mean change from baseline to month 24 in LVMi was -7.7 g/m^2 (95% CI: -15.4, -0.01) in all subjects (n = 27) and -18.6 g/m^2 (95% CI: -38.2, 1.0) in subjects with LVH at baseline (n = 8).
- In subjects from Study AT1001-011 continuing treatment with migalastat in the long-term extension Study AT1001-041, further reductions in LVMi were demonstrated following treatment with migalastat for 42 to 48 months. The mean reductions in LVMi from baseline to 48 months were -12.2 g/m^2 (95% CI: -28.1, 3.6) in all subjects (n = 12) and -35.1 g/m^2 (95% CI: -86.8, 16.6) in subjects with LVH at baseline (n = 3).

Gastrointestinal benefits – assessed by GSRS

- The sponsor comments that gastrointestinal effects are an early and prominent manifestation of Fabry disease, and that patients commonly suffer from debilitating gastrointestinal symptoms, including diarrhoea, nausea, fecal incontinence, vomiting, abdominal pain, and constipation. Therefore, improvement in gastrointestinal signs and symptom represent an important clinical outcome in patients with Fabry disease.
- There was no assessment of gastrointestinal benefits associated with migalastat in Study AT1001-012. However, an assessment of the effects of migalastat on gastrointestinal symptoms using the GSRS instrument was undertaken in Study AT1001-01.
- In Study AT1001-011, in Stage 1 (post-hoc) there was a significant decrease in symptoms of diarrhoea from baseline to month 6 in the migalastat group compared to

the placebo group. There were no significant differences between the two groups in symptoms of constipation, reflux, abdominal pain, or indigestion. In subjects with reflux at baseline there was a significant improvement in symptoms at month 6 compared to placebo. In the OLE extension group, there were notable improvements from baseline at month 24 in diarrhoea and indigestion symptoms in all subjects treated with migalastat for 18 or 24 months and in subjects with these symptoms at baseline.

Patient reported outcomes – SF-36 v2 and BPI

- In Study AT1001-012, SF-36 v2 and BPI scores remained stable throughout the 18 month active-controlled treatment period in both the migalastat and ERT groups. In addition, in subjects in the OLE population SF-36 v2 and BPI scores remained stable from baseline through to month 30 in both the migalastat-migalastat and ERT-migalastat groups.
- In Study AT1001-011, in subjects with abnormal baseline values improvements in the SF-36 v2 were found at month 24 in subjects treated with migalastat for 18 or 24 months for the vitality subscale (mean increase, 4.0) and the general health domain (mean increase, 4.5). No notable changes from baseline or from month 6 through to month 24 were observed for any other SF-36 v2 subscales or norm-based subscales or for the physical and mental components. No notable changes from baseline or from month 6 were observed for either treatment group in the BPI short form at any time point.

Plasma lyso-Gb3 concentration

- The sponsor comments that plasma lyso-Gb3 is now recognised as an important marker of Fabry disease severity. The sponsor notes that plasma lyso-Gb3 levels have been found to be markedly increased in the plasma of male subjects with Fabry disease, compared to healthy subjects. The sponsor also notes that plasma lyso-Gb3 levels have been reported to be elevated in symptomatic females with Fabry disease.
- The sponsor commented that in Study AT1001-011 a majority of subjects had baseline plasma lyso-Gb_3 levels comparable with those from a cohort of male and female Fabry patients with the classic phenotype reported in the literature. However, in Study AT1001-012, the assessment of baseline plasma lyso-Gb_3 levels was confounded by prior treatment with ERT immediately before baseline assessments.
- In Study AT1001-012 (mITT population), the mean (± SD) baseline plasma lyso-Gb3 concentration was 9.1 ± 10.82 nmol/L in the migalastat group (n = 34) and 17.7 ± 20.78 nmol/L in the ERT group (n = 18). The mean (±SD) change from baseline to month 18 was +1.7 ± 5.5 nmol/L in the migalastat group and -1.9 ± 5.0 in the ERT group. The results indicate that baseline concentrations were low in both treatment groups and remained stable over 18 months of treatment. No notable difference was observed between the migalastat and ERT groups in the mean change from baseline to month 18. The 30 month data in the migalastat-migalastat group (n = 31) in the OLE population indicates that plasma lyso-Gb3 concentrations remained stable from baseline to month 30 (mean ± SEM change = +3.6 ± 2.50 nmol/L). Overall, the data from Study AT1001-012 indicate that migalastat and ERT have comparable effects on plasma lyso-Gb3 levels and that the effects of migalastat on this parameter are durable.
- In Study AT1001-011, the results for plasma lyso-Gb3 levels in subjects with available samples (n = 31) in the ITT population showed a statistically significantly greater mean (±SD) reduction from baseline to month 6 in the migalastat group compared to the placebo group (-11.22 ± 20.196 versus +0.58 ± 8.548 nmol/L; difference in LS means = -11.4 (95% CI: -18.7, -4.1), p = 0.0033. In Stage 2, in subjects (n = 13) in the

placebo-migalastat group with available samples in the ITT population the mean (±SD) reduction in plasma lyso-Gb3 level from month 6 to month 12 (that is, migalastat treatment) was statistically significantly greater than from baseline to month 6 (i.e., placebo treatment): -15.49 ± 22.199 versus +0.58±8.548 nmol/L, respectively; mean ± SD difference = -16.06 ± 28.117 nmol/L, p < 0.0001 (ANCOVA).

Composite clinical benefits

- In Study AT1001-012 (mITT population), the percentage of subjects who had a renal, cardiac, or cerebrovascular event or death (composite clinical outcome) during the 18 month treatment period was 29% in the migalastat group and 44% in the ERT group. The percentage of subjects who had a renal event was 24% and 33%, respectively, and the percentage of subjects who had a cardiac event was 6% and 17%, respectively. Only 1 cerebrovascular event occurred (transient ischemic attack in the ERT group), and no subjects died during the 18 month treatment period. No subjects in the migalastat group had events in 2 or more different categories, while 2 subjects in the ERT group had events in 2 or more different categories (both subjects had events in the cardiac and renal categories).
- In Study AT1001-012, percentage of subjects in the OLE population who had a composite clinical outcome through to month 30 was 32% in the migalastat-migalastat group. The percentage of subjects with a renal event or cardiac event was 29% and 3%, respectively. No cerebrovascular events occurred, and no subjects died. No subjects in the migalastat-migalastat group with amenable mutations had events in 2 or more different categories
- In Study AT1001-011, a post-hoc analysis of the composite clinical in GLA amenable subjects in Stage 1 (month 0 to 6, placebo-controlled treatment period) showed that 21% (6/28) of subjects in the migalastat group had an event compared to 18% (4/22) of subjects in the placebo group. All events in both groups were renal events, with no cardiac or cerebrovascular events being reported in either treatment group.

First round assessment of risks

The submitted safety data suggest that the risks of treatment with migalastat for the treatment of Fabry disease are acceptable and are comparable to those associated with ERT for treatment of this condition. In the 20 studies in the migalastat development program, 386 subjects have been exposed to migalastat including 168 subjects with Fabry disease. Of the 168 subjects with Fabry disease exposed to migalastat, 119 have been treated for at least 1 year. The longest exposure up to 2 November 2015 was 9.8 years in 1 patient from Study FAB-CL-205 who continued treatment in the long-term safety Study AT1001-041.

Based on the total number of subjects with Fabry disease exposed to migalastat (n = 168) and the "rule of threes" it can be reasonably inferred that the sample size is large enough to identify adverse reactions occurring with an incidence of approximately ≥ 1% (i.e., common or frequent), but is too small to reliable detect adverse reactions occurring with an incidence of < 1%. In the combined data from studies AT1001-011 and AT-1001-012, the lowest identified incidence of treatment-related TEAEs with migalastat was 0.9%. Furthermore, the number of subjects treated with migalastat for at least 1 year (n = 119) is too small to fully characterise the risks of long-term treatment. However, based on the totality of the available safety data significant adverse events associated with long-term treatment appear to be unlikely. In the two Phase 3 studies there were only 6 subjects aged > 65 years and the oldest subject in the studies was aged 72 years. Therefore, there are uncertainties regarding the safety of migalastat in patients aged > 65 years, although there is no reason to assume that it will be markedly different from patients aged < 65 years.

While the number of subjects with Fabry treated with migalastat in the submitted dataset is small it needs to be considered in the context of the rarity of the disease being treated. No serious safety issues with migalastat were identified and the safety profile of the drug does not appear to be inferior to that of ERT. Therefore, it is considered that the safety of migalastat for the treatment of Fabry disease has been adequately characterised in the submitted data. Further information relating to uncommon, rare and very rare adverse reactions associated with the drug is most likely to emerge from post-marketing safety data. It is noted that the sponsor proposes that Australian patients treated with migalastat be entered on an international registry. If migalastat is approved, then this should be a condition of registration for the drug.

There were no deaths in Study AT1001-012 or Study AT1001-011 in the 115 subjects treated with migalastat through to 30 months. There have been two deaths reported in subjects treated with migalastat in the clinical development program, both of which occurred in the long-term extension Study AT1001-041 (n = 85) and both of which were considered by investigators to be unrelated to the study drug (1 death in a female with Stage III Breast Cancer; and 1 death due to unknown cause in a male with multiple cardiovascular risk factors).

In Study AT1001-012, a total of 16 (31%) subjects in the all migalastat group (n = 51) experienced 20 treatment-emergent SAEs during the study (0-30 months). Treatment-emergent SAEs following migalastat experienced by ≥ 2 subjects were chest pain (n = 2) and obesity (n = 2). Other treatment-emergent SAEs reported in 1 subject were pneumonia, proteinuria, suicidal ideation, endocarditis, embolic stroke, ventricular tachycardia, perineal abscess, haemoptysis, phaeochromocytoma, upper limb fracture, bile stone, hernia eventration, abdominal pain, transient ischaemic attack, vision blurred, hypoaesthesia, vertigo, chronic cardiac failure, atrial fibrillation, and dyspnoea. Subjects could have experienced more than 1 treatment-emergent SAEs and events could have been reported more than once in the same subject. The only treatment-emergent SAEs reported to be treatment-related was proteinuria in 1 subject.

In Study AT1001-011, a total of 19 (28%) subjects in the safety population treated with migalastat (n = 67) experienced 26 treatment emergent SAEs during the study (0-24 months). Treatment-emergent SAEs following migalastat experienced by ≥ 2 subjects were pulmonary embolism (n = 2) and procedural complications (n = 2) (post-procedural haematoma (x 1); post-procedural haemorrhage (x 1)). Other treatment-emergent SAEs reported in 1 subject were malaise, amyotrophic lateral sclerosis, cerebral haemorrhage, pneumothorax, hydronephrosis, palpitations, ventricular tachycardia, constipation, transient ischaemic attack, fatigue, paraesthesia, bone cyst, anaplastic large cell lymphoma, syncope, abdominal pain lower, deep vein thrombosis, non-cardiac chest pain, viral meningitis, multiple fractures, helicobacter gastritis, and bacterial infection. Subjects could have experienced more than 1 treatment-emergent SAEs and events could have been reported more than once in the same subject. There were two treatment-emergent SAEs reported to be treatment-related, and both occurred in the same subject (fatigue and paraesthesia).

Treatment-related TEAEs for migalastat pooled from studies AT1001-011 and AT100-12 showed that the most commonly reported event was headache (10.4%), with no other events being reported in ≥ 10% of subjects. Treatment-related TEAEs reported in ≥ 1% to ≤ 10% of migalastat treated subjects in the pooled data included diarrhoea (7.8%), paraesthesia (5.2%), nausea (5.2%), dizziness (4.3%), rash (2.6%), vertigo (2.6%), abdominal pain (2.6%), constipation (2.6%), dry mouth (2.6%), fatigue (2.6%), incorrect dose administers (2.6%), creatine kinase increased (2.6%), weight increased (2.6%), hypoaesthesia (1.7%), depression (1.7%), proteinuria (1.7%), dyspnoea (1.7%), epistaxis (1.7%), pruritus (1.7%), defecation urgency (1.7%), dyspepsia (1.7%), muscle spasms (1.7%), myalgia (1.7%), and torticollis (1.7%). There were a number of treatment-related

TEAEs reported in < 1% of migalastat treated subjects in the pooled data (each event occurring with an incidence of 0.9%). Treatment related TEAEs reported in migalastat treated patients in the pooled data from studies AT1001-011 and AT100-12 are summarised.

In both Study AT1001-011 and Study AT1001-012, the majority of TEAEs were mild to moderate in severity and did not result in treatment discontinuation. In the overall safety population in Study AT1001-001 (n = 67) including patients treated for up to 24 months, discontinuations due to TEAEs (both considered unrelated to treatment) were reported in 2 (3%) subjects treated with migalastat (anaplastic large cell lymphoma and amyotrophic lateral sclerosis). No subjects in Study AT1001-012 in the all migalastat group (n = 51) treated for up to 30 months discontinued treatment due to TEAEs. In the long-term Study AT1001-041, 1 (1.2%) subject treated with migalastat discontinued due to a TEAE (metastatic squamous cell carcinoma, unrelated to treatment). Overall, the data suggest that the TEAEs reported in association with migalastat resolved either spontaneously or with supportive and/or symptomatic treatment.

In Study AT1001-012 (0-18 months), TEAEs were reported in a similar proportion of subjects in the migalastat and ERT groups (94% (34/36) versus 95% (20/21), respectively). TEAEs reported in ≥ 10% of subjects in the migalastat group were nasopharyngitis (33%), headache (25%), dizziness (17%), influenza (14%), abdominal pain (14%), diarrhoea (14%), nauseas (14%), back pain (11%), upper respiratory tract infection (11%) and urinary tract infection (11%). TEAEs reported in ≥ 10% of subjects in either treatment group and in ≥ 5% more subjects in the migalastat group than in the ERT group were dizziness (17% versus 10%), upper respiratory tract infection (11% versus 5%), and urinary tract infection (11% versus 5%). TEAEs reported in ≥ 10% of subjects in either treatment group and in ≥ 5% more subjects in the ERT group than in the migalastat group were cough (24% versus 8%), influenza (19% versus 14%), vomiting (14% versus 8%), sinusitis (14% versus 8%), bronchitis (14% versus 6%), vertigo (10% versus 3%), dry mouth (10% versus 3%), gastritis (10% versus 3%), pain in extremity (10% versus 3%), dyspnoea (10% versus 3%), and procedural pain (10% versus 0%).

In Study AT1001-012 (0-30 months), TEAEs were reported in 98% (50/51) of subjects in the all migalastat group. The pattern of TEAEs in the all migalastat group (0-30 months) was consistent with the pattern of TEAEs in the migalastat group (0-18 months). TEAEs reported in ≥ 20% of subjects in the all migalastat group (0-30 months) were nasopharyngitis (41%), headache (31%), influenza (24%), and diarrhoea (22%).

In Study AT1001-011 (0-6 months), TEAEs were reported in the majority of subjects in both the migalastat and placebo groups (91% (n = 31/34) versus 91% (30/33), respectively). TEAEs reported in ≥ 10% of subjects in the migalastat group were headache (35%), nasophyaryngitis (18%), fatigue (12%), paraesthesia (12%), and nausea (12%). TEAEs reported in ≥ 10% of subjects in the migalastat group and in ≥ 5% more subjects than in the placebo group were headache (35% versus 21%), nasophyaryngitis (18% versus 6%), pyrexia (12% versus 3%), and nausea (12% versus 6%). The only TEAE reported in ≥ 10% of subjects in the placebo group and in ≥ 5% more subjects than in the migalastat group was pain in extremity (12% versus 0%).

In Study AT1001-011, TEAEs in the Stage 2 population (6-12 months) were reported in 79% (50/63) of the total number of subjects treated with migalastat and in the OLE population (12-24 months) TEAEs were reported in 84% (48/57) of the total number of subjects treated with migalastat. In the 6-12 month period, TEAEs reported in ≥ 10% of the total number of subjects were headache (14%) and procedural pain (11%). Data presented by the sponsor indicates that procedural pain in the migalastat group in Study AT1001-011 was primarily associated with renal biopsies undertaken in order to assess the GL-3 burden. In the 12-24 month period, TEAEs reported in ≥ 10% of the total number of subjects treated with migalastat were proteinuria (16%), bronchitis (11%) and

headache (11%). There was a decrease in the incidence of TEAEs in subjects treated with migalastat over the period from 6 to 24 months compared to the period from 0 to 6 months.

In the two Phase 3 studies (AT1001-011; AT1001-012), no safety issues with possible regulatory impact were identified in subjects treated with migalastat: i.e., no hepatic toxicity; no renal toxicity; no haematological toxicity; no significant cardiac disorders or changes in ECG parameters including QTc prolongation; no significant immune system disorders; no serious skin reactions; no clinically meaningful laboratory abnormalities relating to haematologic parameters, liver function tests, renal function tests, or other clinical chemistry parameters; and no clinically significant changes in vital signs.

In the two Phase 3 studies (AT1001-011; AT1001-012), the following safety issues in special populations were noted: the safety profile of migalastat appeared to be similar in males and females, and the reported differences are considered to be not clinically significant; the number of patients aged > 65 years was too small to compare the safety of migalastat in this population with the safety of migalastat in subjects aged ≤ 65 years; there were no safety data in subjects aged < 16 years of age, but migalastat is not being proposed for registration in subjects younger than 16 years of age; the number of non-Caucasian subjects was too small to adequately access the efficacy of migalastat in this population; the safety of migalastat appeared to be similar in subjects with baseline moderate renal impairment and subjects with baseline mild renal impairment/normal renal function, but subject numbers in the moderate renal impairment group were too small to allow definitive conclusions to be made; there were no safety data in subjects with severe baseline renal impairment and no separate safety data in subjects with mild baseline renal impairment; and there were no safety data in subjects with baseline hepatic impairment.

In the long-term extension Study AT1001-041, 69 (81%) of the 85 subjects experienced at least one TEAE. The TEAEs reported in this study were consistent with those reported in the two Phase 3 studies, and no new safety signals associated with migalastat emerged with long-term treatment. TEAEs, reported in ≥ 10% of subjects were diarrhoea (16%, n = 14), arthralgia (13%, n = 11), fatigue (12%, n = 10), headache (12%, n = 10), pain in extremity (12%, n = 10), and nasophyaryngitis (11%, n = 9). Of the 662 TEAEs reported in the study, 56 were assessed to be related to treatment. Treatment-related TEAEs reported in ≥ 2 patients were diarrhoea (4, 5%), dizziness (2, 2%), fatigue (2, 2%), glomerular filtration rate decreased (2, 2%), urinary tract deficiency (2, 2%), and vitamin deficiency (2, 2%). All other treatment-related TEAEs were each reported once, and consisted of a variety of events.

In the long-term Study AT1001-041, there were 31 treatment-emergent SAEs reported by 22 subjects, none of which were related to migalastat. The treatment-emergent SAEs were: cardiac disorders (atrial fibrillation x 2; angina pectoris x 1); gastrointestinal disorders (abdominal pain upper x 1; hiatus hernia x 1; pancreatitis x 1); general disorders and administration site conditions (death x 1; device malfunction x 1); hepatobiliary disorder (hepatic infarction x 1); infections and infestations (pneumonia x 2; lobar pneumonia x 1); injury poisoning and procedural complication (foot fracture x 1); musculoskeletal and connective tissue disorders (muscle spasms x 1; musculoskeletal chest pain x 1); neoplasms, benign, malignant and unspecified, including cysts and polyps (breast cancer metastatic x 1; malignant melanoma x 1; meningioma x 1; papillary thyroid cancer x 1; thyroid neoplasm x 1); nervous system disorders (brain stem ischaemia x 1; pre-syncope x 1); not coded (insertion of implantable cardioverter defibrillator x 2); psychiatric disorders (conversion disorder x 1); renal and urinary disorders (urinary calculus x 1); reproductive and breast disorders (priapism x 1; uterine polyp x 1); and skin and subcutaneous tissue disorders (angioedema x 1).

First round assessment of benefit-risk balance

The benefit-risk balance for migalastat for the treatment of adult adolescent patients aged 16 years and older with Fabry disease and an amenable GLA mutation is considered to be favourable.

The primary benefits of migalastat treatment in subjects with Fabry disease and amenable GLA mutations relate to stabilisation of renal function (that is, GFR, proteinuria), reduction in renal IC GL-3 substrate burden, reduction in plasma levels of the disease substrate lyso-Gb3, stabilisation and improvement in cardiac function (that is, reduction in LVMi) and improvement in gastro-intestinal symptoms of diarrhoea, reflux and indigestion. In general, the benefits of migalastat were observed in patients remaining on treatment for up to 54 months.

It can be reasonably inferred that improvement in long-term stabilisation of renal function (that is, GFR, proteinuria) together with reduction in renal IC GL-3 substrate burden is likely to delay end-stage renal disease. In addition, it can also be reasonably inferred that reduction in LVMi will contribute to decreased cardiac complications associated with the disease. However, the renal and cardiac benefits observed with migalastat treatment in the Phase III studies are surrogate measures for the primary outcomes of clinical interest, namely, decreased renal and cardiac morbidity and mortality. Therefore, while it is considered reasonable to infer that improvements in renal and cardiac morbidity and mortality are likely to occur in patients treated with migalastat based on the favourable outcomes of the surrogate measures, there are no data confirming that this is actually the case. While studies could be designed to assess whether migalastat has beneficial effects on renal and cardiac morbidity and mortality in patients with Fabry disease, these are unlikely to be undertaken due to the rarity of the condition.

The risks of treatment with migalastat are considered to be acceptable. Discontinuations due to adverse events associated with migalastat were uncommon, and no deaths related to treatment with the drug were reported in the clinical program. Furthermore, no safety issues with possible regulatory impact were identified in subjects treated with migalastat: i.e., no hepatic toxicity; no renal toxicity; no haematological toxicity; no significant cardiac disorders or changes in ECG parameters including QTc prolongation; no significant immune system disorders; no serious skin reactions; no clinically meaningful laboratory abnormalities relating to haematological parameters, liver function tests, renal function tests, or other clinical chemistry parameters; and no clinically significant changes in vital signs. Overall, migalastat appeared to be safe and reasonably well tolerated at the proposed dose and dosage regimen.

First round recommendation regarding authorisation

Approval of Galafold (migalastat HCl) is recommended for the long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.

It should be a condition of approval that patients treated with migalastat be included in an appropriate registry.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of migalastat for the proposed usage are unchanged from those identified in the first round assessment.

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of migalastat for the proposed usage are unchanged from those identified in the first round assessment.

Second round assessment of benefit-risk balance

The benefit-risk benefit balance of migalastat for the proposed usage is favourable.

Second round recommendation regarding authorisation

Approval of Galafold (migalastat HCl) is recommended for the long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.

It should be a condition of approval that patients treated with migalastat be included in an appropriate registry.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[19]

The sponsor has submitted EU-RMP version 01 (dated 5 July 2016; data lock point (DLP) 23 October 2014) and Australian Specific Annex (ASA) version 1.0 (24 May 2016) in support of this application. The sponsor in its post-first round response submitted EU-RMP version 02 (not dated; DLP 23 October 2014) and ASA version 2.0 (not dated) in support of this application.

The sponsor submitted EU-RMP version 2.1 (dated 21 March 2017, DLP. 25 November 2016) and ASA version 2.1 (dated 21 March 2017) in support of this application.

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below (corrected after the sponsor's post-first round response with changes highlighted in yellow below).

[19] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 9: Summary of safety concerns.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	No Identified Risks	–	–	–	–
Important potential risks	Lack of efficacy in case of use in patients with non-amenable mutations	ü	–*	ü	–
	Male infertility (reversible)	ü	ü	ü	–
Missing information	Use in pregnant or breast-feeding women	ü	ü	ü	–
	Use in older patients >74 years	ü	–*	ü	–
	Use in patients with severe renal impairment (GFR <30 mL/min/m^2)		–*		–
	Long term treatment (> 1 year)	ü	ü	ü	–

* Listed in Table 2 and Table 4 in ASA version 1.0 as having additional pharmacovigilance activities. The Sponsor confirmed in its Section 31 response that this was incorrect. Additional pharmacovigilance activities in the form of the patient registry (highlighted in yellow) is proposed for the important potential risk of male infertility (reversible) and the missing information categories of long term treatment beyond one year and use in pregnant and lactating women.

Additional pharmacovigilance activities include two ongoing studies (Study AT1001-041 Study AT1001-042) and a patient registry.

No additional risk minimisation activities are proposed.

New and outstanding recommendations from second round evaluation

There are no outstanding issues post-second round.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The sponsor provided an updated EU-RMP and ASA in its response. Therefore, the suggested wording is:

> *Implement EU-RMP (version 2.1, dated 21March 2017, data lock point 25 November 2016) with Australian Specific Annex (version 2.1, dated 21 March 2017) and any future updates as a condition of registration.*

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator has no objection to approval of migalastat on the basis of chemistry and quality. The manufacturing process, packaging, quality control, biopharmaceutics, shelf-life and storage conditions have been assessed and are considered acceptable. Responses

to the questions raised in the sponsor's post-first round response have been received and are considered acceptable. The sponsor has accepted and incorporated changes to the PI arising from the evaluation.

Nonclinical

The evaluator has no objection to approval of migalastat following assessment of the nonclinical dossier. The pharmacological studies support its use for the proposed indication and did not identify any clinically relevant off-target binding sites. The safety pharmacology and repeat dose toxicity studies did not reveal any treatment-related adverse effects of concern. Migalastat is not considered to have any genotoxic or carcinogenic potential.

Nonclinical studies demonstrated transient, reversible infertility in male rats at subclinical relative exposures. Complete reversibility was noted after 4 weeks off-dose. Fertility in female rats was not affected.

The proposed pregnancy category of B3 is considered appropriate based on the observed embryofetal toxicity in rabbits.

Amendments to the draft PI proposed by the evaluator following the round 1 evaluation have been accepted and incorporated into the PI.

Clinical

The clinical evaluator recommends approval of migalastat (Galafold) for the long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation. The clinical evaluator also recommends it should be a condition of approval that patients treated with migalastat be included in an appropriate registry. The sponsor confirmed in the response to the second round evaluation report that patients treated with Galafold will be given the option to enrol in an appropriate registry study.

The clinical dossier documented a full clinical development program for migalastat comprising 20 studies relating to pharmacology, clinical efficacy and safety:

- 10 Phase I studies evaluating the clinical pharmacology and initial safety and tolerability of migalastat.
- 5 Phase II studies evaluating the safety and tolerability of various migalastat doses and dosage regimens in subjects with Fabry disease.
- 1 Phase II study in subjects with Fabry disease evaluating the pharmacokinetic drug-drug interaction between co-administered migalastat and agalsidase.
- 2 Phase III studies which were identified by the sponsor as being the pivotal efficacy and safety studies (Study AT1001-011 migalastat versus placebo; Study AT1001-012 migalastat versus ERT).
- 2 Phase III studies which were open-label long-term extension trials and enrolled subjects who had successfully completed selected Phase II and III studies.

Pharmacology

Pharmacokinetics

Migalastat is rapidly absorbed following oral administration, reaching peak concentration (t_{max}) in about 3 hours. Absolute bioavailability is 75%. Migalastat is well distributed into

tissues, with a volume of distribution in healthy subjects ranging from 77 L to 133 L. Exposure to migalastat is dose proportional over the dose range 75 mg to 1250 mg (linear PK). Migalastat is predominantly eliminated unchanged via the kidneys, with metabolism by dehydrogenation and O-glucuronide conjugation only a minor route of elimination. The pharmacokinetics in healthy subjects and patients with Fabry disease are similar. Migalastat is not metabolised by CYP450. A specific hepatic PK study was not performed because migalastat is predominantly eliminated unchanged via the kidneys.

Influence of food

Administration of migalastat in association with food decreased the bioavailability of migalastat by approximately 40% when compared with the fasting state (clinical Studies FAB-CL-103 and AT1001-016). The Study AT1001-016 demonstrated a reduction in migalastat bioavailability of approximately 40% when administered 1 hour before or after a light meal. The clinical evaluator considers that the sponsor's proposal for a 2-hour fasting window before and after food is considered acceptable based on the PK data and the efficacy data from the pivotal Phase III Study AT1001-011.

Renal impairment

Migalastat exposures for subjects with mild, moderate and severe renal impairment were 1.2-, 1.8- and 4.3-fold greater than subjects with normal renal function (Study AT1001-015). Terminal elimination half-life values were 6.4, 7.7, 22.1 and 32.2 hours for subjects with normal renal function and mild, moderate and severe renal impairment respectively. Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) were excluded from the Phase III studies. The sponsor proposes that migalastat is not recommended in patients with severe renal impairment. No dosage adjustment is proposed for patients with mild or moderate renal impairment. The clinical evaluator is satisfied with the sponsor's assessment that no dosage adjustment is required for patients with moderate renal impairment because significant accumulation following every other day administration is not anticipated in patients with mild or moderate renal impairment based on analysis of the pharmacokinetic data and adverse event profile.

Pharmacodynamics

The PD effects of migalastat were investigated in 5 Phase II studies in subjects with Fabry disease. These studies measured leucocyte α-Gal A activity, urine GL-3 levels, renal histological changes (interstitial capillary GL-3) and functional changes (cardiac, renal, neurological). In general, the biochemical parameters associated with the disease improved to a greater extent in patients with amenable mutations compared to patients with non-amenable mutations.

In the male population, baseline α-Gal A activity was low in all subjects. An increase in α-Gal A activity following treatment with migalastat was generally observed in subjects with amenable mutations. Urine GL-3 generally decreased from baseline in male subjects with amenable mutations. This trend was not observed in male subjects with non-amenable mutations.

Baseline α-Gal A activity was notably higher in female subjects than in male subjects, due to the expression of both wild-type and mutant α-Gal A in females. There were increases in α-Gal A activity in female subjects with and without migalastat-amenable GLA mutations following migalastat treatment. However, α-Gal A activity is considered not to be a reliable measure of the effect of migalastat on the mutant form of α-Gal A in women with Fabry disease because migalastat increases wild-type enzyme activity as well as mutant form activity. Changes in disease substrate provide a more reliable assessment of pharmacodynamics in females. In Study FAB-CL-204, urine GL-3 decreased from baseline following migalastat treatment in all 5 females with amenable mutations.

Dosage selection for the Phase III studies was based on the findings from nonclinical and clinical studies. The 150mg QOD regimen was considered to have the most favourable benefit/risk ratio. In study FAB-CL-205, when subjects were switched from 150mg QOD to other dosage regimens (250mg or 500mg, 3 days on/4 days off), no further increases in leucocyte α-Gal A activity or reductions in urine GL-3 were observed. Additionally, a higher rate of treatment-related AEs was observed at the 250mg and 500mg doses compared to the 150mg dose. The sponsor considered that 150mg QOD provided the best balance of substrate reduction (urine GL-3) and safety in subjects with amenable GLA mutations.

Efficacy

Two Phase III studies have been identified as the pivotal efficacy and safety studies: Studies AT1001-011 and AT1001-012.

Study AT1001-011 was a randomised, double-blind, placebo-controlled study to evaluate the efficacy, safety and pharmacodynamics of migalastat in patients with Fabry disease with amenable mutations. Stage 1 was randomised, double-blind and placebo-controlled (migalastat 150mg QOD or matching placebo) from month 0 to 6. Stage 2 was open-label, migalastat treatment 150mg QOD from month 7 to 12. An open-label extension phase of migalastat treatment 150mg QOD ran from month 13-24.

The study included male and female patients aged 16 to 74 years with a diagnosis of Fabry disease and an amenable mutation identified by the Clinical Trial HEK. Subjects were required to be ERT naïve or not to have received ERT for at least 6 months before screening. The mean age of the study population was 42 years, with the majority being female (64%) and white (97%). The mean time since diagnosis was 6.3 years. 25% had previously been treated with ERT.

Amenable mutations were initially identified by an in vitro Clinical Trial Human Embryonic Kidney (HEK) cell-based assay developed by Amicus Therapeutics. Following completion of enrolment into Study AT1001-011, the assay was validated by a third-party laboratory in compliance with current regulatory guidance and Good Laboratory Practice regulations. The validated assay is referred to as the GLP HEK assay. The sponsor stated that the GLP HEK assay was similar to the preliminary HEK assay, but included modifications to increase the level of quality control, rigor, precision and consistency. The use of the GLP HEK assay changed the classification of 17 enrolled subjects with amenable mutations based on the Clinical Trial HEK assay to non-amenable mutations. Six of these 17 had been randomised to migalastat, 11 to placebo. The Stage 1 analyses of responsive subjects based on the Clinical Trial HEK assay were termed pre-specified, and the Stage 1 analyses of amenable subjects based on the GLP HEK assay were termed post-hoc. Both pre-specified and post-hoc results for Stage 1 data were reported.

Of the 67 subjects entering Stage 1, 34 (100%) in the migalastat group and 30 (91%) in the placebo group completed Stage 1. 60 subjects completed Stage 2, comprising 31 (94%) in the migalastat-migalastat group and 29 (97%) in the placebo-migalastat group. A total of 54 subjects completed the open-label extension, comprising 27 (93%) in the migalastat-migalastat group and 27 (96%) in the placebo-migalastat group. The Stage 1pre-specified primary efficacy endpoint was the percentage of subjects with a ≥ 50% reduction from baseline in the average number of renal IC GL-3 inclusions. This primary efficacy endpoint was not met. The pre-specified response rate was higher in the migalastat group (41%) than in the placebo group (28%), but the difference between the two groups was not statistically significant ($p = 0.3$).

Stage 1 pre-specified secondary efficacy endpoints included change in IC GL-3 inclusions, urine GL-3, eGFRCKD-EPI, eGFRMDRD, mGFRiohexol and 24-h urine protein, albumin, and creatinine. Although there were some trends in favour of the migalastat group compared

to placebo, none of the pre-specified secondary endpoints were statistically significant. The Stage 1 post-hoc analysis demonstrated a statistically significant reduction in the average number of IC GL-3 inclusions in the migalastat group (39% decrease) compared to the placebo group (14% increase). The post-hoc analysis also demonstrated a statistically significant greater percentage of ICs with zero GL-3 inclusions after 6 months of treatment with migalastat than with placebo.

The sponsor undertook a statistical comparison of annualised changes in eGFR in migalastat-treated subjects with those reported in the literature for untreated patients. This comparison demonstrated statistically significant differences in the annualised rate of change in eGFR favouring migalastat compared to untreated patients from the published literature. This analysis demonstrated stabilisation of renal function in migalastat-treated subjects compared to published reports of renal function in untreated patients. In Stage 2, subjects who switched from placebo to migalastat demonstrated a statistically significantly decrease in the average number of IC GL-3 inclusions from month 6 to month 12. In the open label extension, renal function remained stable over 18 to 24 months of migalastat treatment.

The effect of migalastat on cardiac function was assessed primarily by changes in LVMi on echocardiography. No difference in LVMi was demonstrated between migalastat and placebo at month 6. At the completion of Study AT1001-011, following treatment with migalastat for 18 to 24 months, the mean changes in LVMi from baseline were -7.7 g/m^2 (95% CI: -15.4, -0.01) in all subjects (n = 27) and -18.6 g/m2 (95% CI: -38.2, 1.0) in subjects with LVH at baseline (n = 8). Subjects who continued in the long-term extension study AT1001-041 achieved further decreases in LVMi.

Statistically significant reductions in plasma lyso-Gb3 were observed after 6 months of treatment for subjects randomised to migalastat in Stage 1 and for subjects switching from placebo to migalastat in Stage 2.

Gastrointestinal symptoms were assessed using GSRS subscales. In the Stage 1 post-hoc analysis, significant improvements in diarrhoea symptoms were observed with migalastat compared to placebo, and significant improvements were observed in reflux symptoms in subjects with baseline reflux symptoms. In the open label extension, significant improvements in symptoms of diarrhoea and indigestion were observed in subjects treated with migalastat for 18 to 24 months.

Study AT1001-012 was a randomised, open-label, active-controlled study to compare the efficacy and safety of migalastat to ERT (agalsidase α or agalsidase β) in subjects with Fabry disease with amenable mutations who have been treated with ERT for at least 12 months. In Period 1, subjects were randomised 1.5:1 to receive treatment with migalastat HCl 150mg QOD or continue ERT for 18 months. Period 2 was an optional 12-month open-label extension (OLE) period in which subjects who were randomised to ERT for Period 1 were switched to migalastat and patients randomised to migalastat for Period 1 continued on migalastat.

The two primary efficacy endpoints were the annualised rates of change for mGFRiohexol and eGFRCKD-EPI from baseline to month 18. Although this was an open-label study, the selection of objective GFR measures as the two primary endpoints mitigates the potential bias of an open-label study.

This study was not powered to demonstrate non-inferiority. The rarity of Fabry disease and the limited number of subjects who could be enrolled in the trial meant that a non-inferiority analysis was not feasible. Negotiations with EMA led to the development of pre-specified criteria to enable a descriptive comparison of the GFR results. The two pre-specified comparability criteria were:

- difference between the mean annualised change in GFR for migalastat and ERT within 2.2 mL/min/1.73m^2 per year; and
- > 50% overlap of the 95% CI for migalastat and ERT.

A total of 60 patients were randomised. There were 26 male and 34 female subjects with a mean age of 48 years (range 18 to 72 years). 51 (85%) were classified as white and 7 (12%) as Asian.

36 subjects were randomised to migalastat treatment and 24 to ERT for 18 months. 33 continued in the migalastat-migalastat group and 15 continued in the ERT-migalastat group. 30 completed migalastat-migalastat and 12 completed ERT-migalastat, so there was a higher discontinuation rate in the ERT cohort.

The assessment of *GLA* mutation status during enrolment for all subjects was based on the Clinical Trial HEK assay but subjects were reassessed using the GLP HEK assay prior to the database lock for the 18-month randomised treatment period. The efficacy analyses for this study were performed on subjects assessed as having amenable mutations by the GLP HEK assay. Of the 60 patients randomised, 56 had amenable mutations. Two subjects in each treatment group had their *GLA* mutation status changed from amenable to non-amenable based on the GLP HEK assay.

After 18 months, the mean annualised change in eGFR$_{CKD-EPI}$ was -0.40 for migalastat and -1.03 for ERT (difference = 0.63) and the mean annualised change in mGFR$_{iohexol}$ -4.35 for migalastat and -3.24 for ERT (difference = -1.11). The differences in the mean annualised change in GFR between migalastat and ERT were within 2.2 ml/min/1.73m^2 per year and there was complete overlap of the 95% CI for migalastat with the 95% CI for ERT, so the pre-specified comparability criteria were met for both mGFR$_{iohexol}$ and eGFR$_{CKD-EPI}$. These results for the two primary efficacy endpoints demonstrated that migalastat treatment is comparable to ERT.

There were multiple secondary endpoints, including mGFR$_{iohexol}$, eGFR$_{MDRD}$, 24-hour urine protein, composite clinical outcome, change in ECHO parameters LVMi and LVEF, plasma lyso-Gb$_3$ levels, WBC α-Gal A activity and patient-reported outcomes. The secondary endpoints for GFR were comparable for migalastat and ERT. LVMi decreased from baseline to month 18 in both treatment groups, but to a greater extent in the migalastat group. Plasma lyso-Gb$_3$ remained low and stable on migalastat. There was a lower percentage of composite clinical outcomes in the migalastat group (29%) compared to the ERT group (44%). The BPI short form and SF-36 v2 remained stable throughout the 18-month treatment period in both treatment groups.

There was durability in the renal and cardiac responses to migalastat during the open label extension (up to 30 months).

Safety

386 subjects have been exposed to migalastat in the clinical development program, including 168 subjects with Fabry disease, 119 of whom have been treated for at least 1 year.

The two pivotal Phase III Studies AT1001-011 and AT1001-012 are considered to be the pivotal safety studies. The safety data from these two studies are most relevant because the migalastat dosage regimen and the Fabry patient population reflect the proposed usage of the drug in Australia. These studies also allow comparative assessment of the safety of migalastat against placebo and ERT. 85 subjects subsequently enrolled in the long-term safety Study AT1001-041.

TEAEs for migalastat pooled from Studies AT1001-011 and AT1001-012 showed that the most commonly reported event was headache (10.4%), followed by diarrhoea (7.8%),

paraesthesia (5.2%), nausea (5.2%) and dizziness (4.3%). The majority of TEAEs were mild to moderate in severity and did not result in treatment discontinuation.

In Study AT1001-011, a total of 19 (28%) subjects treated with migalastat (n = 67) experienced 26 treatment emergent SAEs during the study period (24 months), two of which were considered to be possibly related to treatment (fatigue and paraesthesia). Two subjects discontinued treatment due to TEAEs, both considered unrelated to treatment (anaplastic large cell lymphoma, amyotrophic lateral sclerosis). In study AT1001-012, a total of 16 (31%) subjects in the all migalastat group (n = 51) experienced 20 treatment-emergent SAEs during the study period (30 months), one of which was considered to be possibly related to treatment (proteinuria). No subjects discontinued treatment due to TEAEs.

No safety issues of significant regulatory concern were identified in subjects treated with migalastat in the two pivotal Phase 3 studies. No deaths occurred in the two pivotal Phase 3 studies.

85 subjects from the three feeder Studies FAB-CL-205, AT1001-011, and AT1001-012 enrolled in the long-term safety Study AT1001-041. The TEAE profile reported in this study is consistent with the two pivotal Phase III studies, and no new safety signals associated with migalastat have emerged with long-term treatment. Two deaths were reported in this study but both were deemed unrelated to the study drug.

Risk management plan

The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised earlier.

The PI contains a precaution that migalastat is not recommended for patients with severe renal insufficiency, defined as eGFR < 30 mL/min/1.73m^2.

Risk-benefit analysis

Delegate's considerations

Quality

The chemistry and quality of migalastat have been assessed and the evaluator is satisfied that the chemistry and quality of migalastat are satisfactory for approval. The chemistry and quality issues in the Product Information have been satisfactorily addressed.

Nonclinical

The evaluator recommends approval on nonclinical grounds. The nonclinical issues in the Product Information have been satisfactorily addressed.

Efficacy

The Phase III Study AT1001-011 failed to achieve its pre-specified primary and secondary stage 1 endpoints, but the results of the other pivotal Phase III Study AT1001-012, the post-hoc analysis of stage 1 of Study AT1001-011 and the analyses of stage 2 and the open label extension of Study AT1001-011 have demonstrated the efficacy of migalastat for the treatment of patients 16 years and older with a confirmed diagnosis of Fabry disease and who have an amenable mutation. Study AT1001-012 used pre-specified criteria to demonstrate comparability in efficacy between migalastat and ERT.

The failure to achieve the pre-specified primary and secondary endpoints for stage 1 of Study AT1001-011 may have been influenced by the 17 subjects (25%) who were initially

recruited to the study on the basis of having an amenable mutation but were subsequently reclassified by the GLP HEK assay as having a non-amenable mutation.

The benefits of migalastat demonstrated in the Phase III studies include stabilisation of renal function, decrease in LVMi, reduction in renal IC GL-3 substrate burden, reduction in plasma lyso-Gb3 and improvement in gastro-intestinal symptoms of diarrhoea, reflux and indigestion. The studies have not demonstrated that treatment with migalastat reduces renal and cardiac morbidity and mortality.

The study populations in the two pivotal studies are broadly representative of the Australian population, so the efficacy data from these studies can reasonably be extrapolated to the general Australian population of patients aged ≥ 16 years with Fabry disease and an amenable mutation.

Amenable mutations

The benefits of treatment with migalastat are limited to patients with an amenable mutation. At the time of the submission, 841 different genetic mutations had been linked to Fabry disease. 600 of these mutations had been assessed by the GLP HEK assay, with 268 confirmed as amenable mutations and 332 as non-amenable. The amenable mutations identified in subjects in the Phase III studies are a subset of these 268 amenable mutations. The efficacy of migalastat has not been demonstrated for all known amenable mutations but it is biologically plausible that the results achieved in these studies would be consistent with the results achievable for all amenable mutations. The small study numbers and the variety of amenable mutations in the study populations did not permit efficacy analyses for specific mutations or mutation subgroups.

Genotyping for Fabry disease is provided at the National Referral Laboratory at the Women and Children's Hospital, Adelaide.

Safety

The safety profile of migalastat has been satisfactorily established from the submitted data. Although the number of subjects with Fabry disease treated with migalastat in the clinical studies is small, it needs to be considered in the context of the rarity of the disease being treated. No serious safety concerns with migalastat have been identified. The safety profile of the drug appears acceptable and does not appear to be inferior to that of ERT. Uncommon, rare and very rare adverse effects may not have been identified in these studies because of the size of the study populations. Post-market safety monitoring would be important to identify emergent uncommon, rare and very rare adverse effects.

Nonclinical studies demonstrated reversible infertility in male rats at subclinical relative exposures. No effect on fertility was demonstrated in female rats. The effect of Migalastat on fertility in humans has not been studied. The sponsor has proposed to implement a register of migalastat patients to provide additional pharmacovigilance in relation to the potential risk of male infertility.

RMP

The RMP and ASA are considered satisfactory. A patient registry will provide additional pharmacovigilance.

Overall

The quality, nonclinical and clinical evaluators have recommended approval of migalastat for the proposed indication. The quality, safety and efficacy of migalastat for the proposed indication are supported by the data in the submission. Fabry disease is a rare, progressive, inherited disorder associated with life-threatening complications and premature mortality. ERT is the only currently approved treatment and carries the administrative burden of fortnightly intravenous infusions and risks of infusion-related reactions and immune responses. Migalastat, being an orally administered medicine, offers

an alternative treatment option to ERT with comparable efficacy. Pending further advice from ACM, the delegate proposes to register migalastat (Galafold) for the proposed indication.

Data deficiencies

The pivotal Study AT1001-012 was not powered to demonstrate non-inferiority. Following negotiation with EMA, pre-specified comparability criteria were developed to facilitate a descriptive comparison of GFR results for migalastat and ERT as the primary efficacy endpoints. This approach was taken because Fabry disease is rare and the study population was not large enough to allow a non-inferiority analysis.

The introduction of the GLP HEK assay after commencement of the pivotal Phase 3 studies resulted in some subjects having their mutation status re-classified from amenable to non-amenable.

The Phase III studies excluded patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and women who were pregnant or breastfeeding, so there are not adequate clinical efficacy and safety data for these populations. Migalastat is not recommended for these patient groups. Children aged under 16 years were not evaluated in this submission and are not included in the proposed indication.

Conditions of registration

The following is proposed as a condition of registration:

- Implement EU-RMP (version 2.1, dated 21 March 2017, data lock point 25 November 2016) with ASA (version 2.1, dated 21 March 2017) and any future updates.

Questions for the sponsor

The sponsor is requested to address the following issues in the pre-ACM response:

- The Galafold (migalastat) amenability table in the draft PI includes c.217C>T, c.C218T, A73V whereas the table in the European SmPC includes c.218C>T, c.C218T, A73V. Is this a transcription error in the draft PI?
- c.728T>G is not in the correct numerical sequence in the Galafold (migalastat) amenability table in the draft PI.
- Will the GLP HEK assay be used in clinical practice to assess a patient's amenability to migalastat or will the patient's amenability be determined solely by his/her known genotype? If the GLP HEK assay will be used in clinical practice, what will be its availability in Australia?

Summary of issues

Issues arising from this submission include:

Efficacy

- Study AT1001-012 demonstrated comparability to ERT based on pre-specified criteria. The primary and secondary pre-specified endpoints for stage 1 of Study AT1001-011 were not met but these outcomes may have been influenced by the 17 subjects who were re-assessed during the course of the study as non-amenable by the GLP-HEK assay. Benefits over placebo were demonstrated in the post-hoc stage 1, stage 2 and OLE analyses. The main outcomes demonstrated in these studies include stabilisation of renal function, decrease in LVMi, reduction in renal IC GL-3 substrate burden, reduction in plasma lyso-Gb3 and improvement in gastro-intestinal symptoms of diarrhoea, reflux and indigestion. The studies have not demonstrated that treatment with migalastat reduces renal and cardiac morbidity and mortality.

Amenable mutations

- Subjects in the Phase III studies expressed a variety of amenable mutations. The amenable mutations evaluated in these studies represent a subset of all known amenable mutations (as confirmed by the GLP-HEK assay).

Proposed action

The Delegate has no reason to say, at this time, that the application for Galafold should not be approved for registration.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

- What is the committee's view on the efficacy outcomes from the Phase 3 studies?
- Is the committee satisfied that the table of amenable mutations listed in the PI appropriately defines the target population for migalastat?
- To what extent would variability in phenotypic expression of amenable mutations be likely to impact on the efficacy of migalastat for individual patients and what would be the likely relevance of this in clinical practice?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor provides comments on the evaluations in the following sections:

- A brief summary of information on the GLP HEK amenability assay (based on information included in the dossier), to provide background on the use of the GLP HEK amenability assay and the applicability of the data from clinical trials to the lists of amenable and non-amenable mutations in the PI.
- A response to the three questions posed by the Delegate in the Overview.

Section 1

- ***The applicability of the data observed in clinical trials to the list proposed in the Australian Prescribing Information***

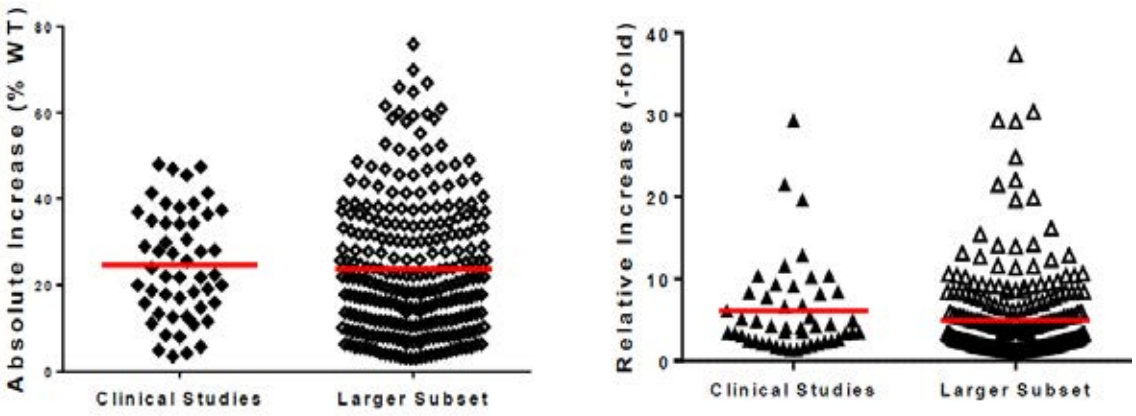
The subset of amenable mutant forms of α-Gal A in Phase II and III clinical studies was compared to all known Fabry disease-associated amenable mutant forms.

The following parameters were used to compare the two groups of amenable mutations:

- Mean absolute increase and α-Gal A activity fold over baseline in response to 10 μmol/L migalastat (shown as red lines in figure below)
- The proportion of amenable mutations grouped by phenotype
- Mean baseline α-Gal A activity
- The proportion of conservative and non-conservative amino acid substitutions
- The locations of the mutations within the structure of the GLA gene
- The locations of substituted amino acid residues within the structure of α-Gal A

Comparability was shown between the subset of amenable mutations in the Phase III clinical studies and the larger subset number of known amenable mutations.

Figure 2: Absolute increase and α-Gal A Activity;Fold over Baseline of Phase II and III clinical study amenable mutant forms compared to the larger subset that met the amenable mutation criteria



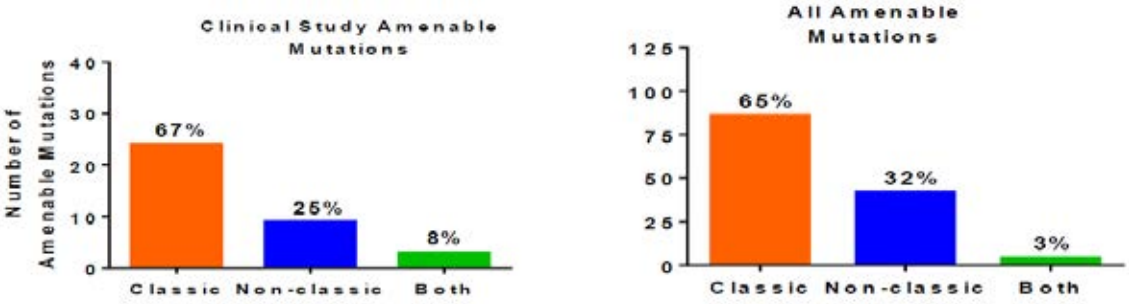
These analyses showed that the characteristics of the amenable mutant forms of α-Gal A from patients in Phase II and III clinical studies were similar to those for all amenable mutant forms. These results demonstrate that the amenable mutant forms evaluated in Phase II and III clinical studies are representative of all amenable mutant forms identified by the GLP HEK assay.

· ***Phenotypic expression of amenable mutations***

The patients in the migalastat clinical studies represent the range of genotypes and phenotypes in Fabry disease in general, and the positive effects of migalastat were demonstrated across these patient types. Thus, the various phenotypic expressions of amenable mutations would not affect the efficacy of migalastat in clinical practice.

The majority of amenable mutant forms in migalastat clinical studies are associated with classic Fabry disease. However, a significant minority was associated with non-classical Fabry disease (figure below).

Figure 3: Clinical study amenable mutations are comparable to all amenable mutations



An analysis of baseline disease severity revealed that 86% of the patients enrolled in the Phase III studies had substantial disease burden at baseline, based on having two or more organ systems affected by the disease. The clinical manifestations observed in patients in the migalastat Phase III studies reflect the general Fabry disease population and are comparable to the patients in the ERT registries and pivotal Phase III studies.

The beneficial effects of migalastat on eGFRCKD-EPI, mGFRIohexol, and LVMi were found in both males with the classical presentation and the 'other' subgroup consisting of non-classical male patients and female patients. Given the positive effects observed in all types of patients in Phase III, it can be concluded that all patient phenotypes benefit from treatment with migalastat.

Analyses of pharmacodynamic and clinical responses to migalastat in patients with the same amenable mutations were conducted for white blood cell α-Gal A activity, plasma lyso-Gb3, and LVMi. In these comparisons, patients with the same amenable mutations (2 to 5 patients represented per same amenable mutation) demonstrated similar responses across phenotypic parameters (for example gender, disease severity), indicating that patients with the same amenable mutation would be expected to have similar clinical responses regardless of phenotype.

Section 2

Response to question 1

- ***The Galafold (migalastat) amenability table in the draft PI includes c.217C>T c.C218T, A73V whereas the table in the European SmPC includes c.218C>T, c.C218T, A73V. Is this a transcription error in the draft PI?***

The sponsor confirms that this is a transcription error, the correct listing should read: c.218C>T, c.C218T, A73V.

Response to question 2

- ***c.728T>G is not in the correct numerical sequence in the Galafold (migalastat) amenability table in the draft PI.***

The sponsor confirms that the listing for c.728T>G is not in numerical order. The correct order is following c.725T>C.

Response to question 3

- ***Will the GLP HEK assay be used in clinical practice to assess a patient's amenability to migalastat or will the patient's amenability be determined solely by his/her known genotype? If the GLP HEK assay will be used in clinical practice what will its availability be in Australia?***

The sponsor confirms that the GLP HEK assay will not be used in clinical practice to confirm a patient's amenability to migalastat; rather, the patient's amenability will be determined solely on his/her known genotype. GLA genotyping, which is performed as standard of care when diagnosing Fabry disease, is required to initiate treatment with migalastat. Following the process below, a Health Care Professional (HCP) can determine whether or not a patient has a mutation amenable to treatment with migalastat, based on the results of the GLP HEK assay for that genotype.

It should be noted that since the GLP HEK assay is not used in clinical practice, it does not need to be available in Australia.

The following steps take place when determining the amenability of a patient. This process is working effectively in the EU (where Galafold has been approved since May 2016) and will be implemented in markets where migalastat is approved:

- If the patient's genotyping is not already known, perform GLA genotyping.
- Review the Galafold Amenability Table (which is based on the GLP HEK amenability assay) in the package insert and confirm if the patient's mutation is present on the amenable or non-amenable table.
- If the mutation is amenable, the HCP can prescribe migalastat.
- If the mutation is not present on either the amenable or non-amenable tables, the HCP will contact Amicus via the medical information contact details provided. If the mutation has not yet been tested, Amicus will test the mutation in the HEK Amenability Assay which is run centrally at Cambridge Biomedical in the US. No patient samples are required for the HEK Amenability Assay.

- Once testing of the new mutation in the HEK Amenability Assay has been completed and amenability has been determined, a treatment decision can be made.
- Newly identified mutations will be subsequently added to the tables in the PI via a regulatory submission.

Advisory Committee Considerations[20]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Galafold capsules containing 123 mg of migalastat to have an overall positive benefit-risk profile for the indication:

> *Migalastat is indicated for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.*

Proposed conditions of registration

ACM agreed with the delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

ACM agreed with the Delegate to the proposed amendments to the PI.

Specific advice

ACM advised the following in response to the Delegate's specific questions on the submission:

1. *What is the committee's view on the efficacy outcomes from the Phase III studies?*

The ACM agreed that given the rareness of the disorder, the efficacy outcomes from the Phase III studies including the number of patients studied were acceptable. ACM noted that stabilisation of disease in this particular condition is accepted as beneficial.

2. *Is the committee satisfied that the table of amenable mutations listed in the PI appropriately defines the target population for migalastat?*

The ACM is satisfied that the list of amenable mutations listed in the product information defines the current target population for Fabry patients who could be treated with migalastat. The ACM noted that the current assay appears effective in identifying amenable mutations. As was shown in the differences between the patients originally enrolled on the basis of their mutation and those found to have amenable mutations based on the GLP HEK assay, rigorous testing of cells containing the mutation is important.

The ACM noted that there is a mechanism for addition to the list of amenable mutations, once these have been robustly demonstrated to actually be amenable to this treatment. The ACM also noted that there is a mechanism for removing from the list any mutations

[20] The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

subsequently determined not to be amenable. The ACM further noted that there should be a clear and transparent process for the sponsor to notify any such changes to the clinical community.

3. *To what extent would variability in phenotypic expression of amenable mutations be likely to impact on the efficacy of migalastat for individual patients and what would be the likely relevance of this in clinical practice?*

The ACM noted that there are factors other than the actual GLA mutation that impact on the disease. A number of modifier genes are involved in all genetic conditions; some in the disease pathway, others in immune and cell signalling pathways. The ACM agreed that it is likely for practical purposes that the ability of migalastat to increase enzyme activity will in itself be beneficial for the patient, irrespective of any other factors.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Galafold (migalastat (as hydrochloride)) 123 mg hard capsule blister pack indicated for:

> *Galafold is indicated for long-term treatment of adult and adolescent patients 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in the section on Mechanism of Action).*

Specific conditions of registration applying to these goods

- The migalastat EU-RMP, version 2.1, dated 21 March 2017, data lock point 25 November 2016 with ASA (version 2.1, dated 21 March 2017), included with the submission, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Galafold approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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