Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for migalastat

Proprietary Product Name: Galafold

Sponsor: Amicus Therapeutics Pty Ltd

First round: September 2016

Second round: February 2017

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 the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of 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
Cmax	maximum observed concentration
CMI	Consumer Medicines Information
Cmin	minimal observed concentration
CYP450	cytochrome P450
ECG	electrocardiogram
ECHO	echocardiography
eGFR	estimated glomerular filtration rate
eGFR CKD-	estimated glomerular filtration rate based on the Chronic

Abbreviation	Meaning
EPI	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
LC-MS/MS	liquid chromatography with tandem mass spectrometry method

Abbreviation	Meaning
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
Tmax	time of occurrence of Cmax
UGT	uridine 5'-diphospho-glucuronosyltransferase
WT	wild type

1. Introduction

This is a submission for a new chemical entity (NCE) for the treatment of Fabry disease.

2. 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.

2.1. Guidance

A pre-submission meeting was held between the TGA and the sponsor. 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.***

Comment: 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.***

Comment: 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.***

Comment: 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, 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 did not include any requests for additional information or revision to the proposed dossier content.

3. Contents of the clinical dossier

3.1. Scope 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 [AT1001-011 migalastat versus placebo; 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

3.2. 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.

Comment: 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.

3.3. 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.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The PK of migalastat have been evaluated 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 (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 [FAB-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, 2, and 3 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 1: 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	9 9 23 23

PK topic	Subtopic	Study ID	N *
		AT1001-011	62
	Hepatic impairment	No studies	-
	Renal impairment	AT1001-015	32
	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.

4.1.1. 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 were comprehensive and allowed adequate characterisation of the PK of migalastat in plasma, urine and feces.

4.1.2. 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.

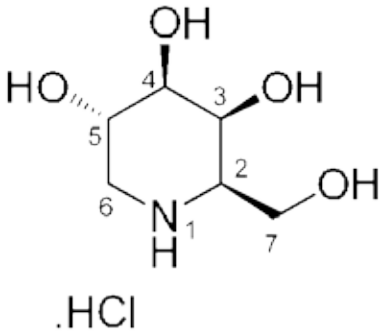
4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

The structural formula of migalastat HCl is provided below. The molecular formula is $C_6H_{13}NO_4$.HCl. The molecular mass of migalastat HCl is 199.63 and the molecular mass of

migalastat free base is 163.17. Migalastat is reported to contain 4 stereogenic centres, and is stated to be the isomer with the 2R,3S,4R,5S configuration as proven by single crystal X-ray crystallography.

Figure 1: Structural formula of migalastat HCl.



General properties physicochemical properties of interest:

- *Description:* Migalastat hydrochloride is a white to almost white crystalline solid.
- *Solid state form:* It is reported that comprehensive solid state form screening of migalastat hydrochloride has identified one solid state form (Form 1). Form 1 is reported to be crystalline, anhydrous and non-solvated. Migalastat hydrochloride is stated not to form hydrates or solvates.
- *pka:* pka of 7.47±0.01 has been determined experimentally for the protonated secondary amine, at concentrations of 34 to 49 µM under aqueous conditions.
- *pH:* 4.7 for a 1% aqueous solution at ambient temperature.
- *Partition coefficient at 25°C:* The partition coefficient (log D [octanol/water]) was determined to be -5.2 to -0.8 over the pH range 3 to 9, with the log D being -1.4 at pH 7. The results indicate that migalastat is predominantly water soluble rather than lipid soluble.
- *Solubility:* Migalastat hydrochloride is described as being freely soluble between pH 1.2 and pH 7.5 in aqueous media.
- *Particle size:* 90th percentile in the range of 470-846 µm is reported to have been determined by sieve analysis for batches of migalastat HCl during drug development.

4.2.1. Pharmacokinetics in healthy subjects

4.2.1.1. Absorption

Sites and mechanism of absorption

The sponsor reports that migalastat HCl is very soluble across the physiological pH range. Aqueous solubility in excess of 500 mg/mL at 15°C to 25°C and intrinsic dissolution rates in excess of 26 mg cm^2 min^{-1} in water and in 0.1 M hydrochloric acid have been reported. Due to its reported high solubility and low passive permeability, migalastat HCl is stated to be a Biopharmaceutics Classification System (BCS) Class III compound (i.e., high solubility, low permeability). However, despite its low permeability migalastat is stated to be well absorbed, which the sponsor considers to be probably due to paracellular processes [study7AMICP1, study 9AMICP2].

In the clinical studies, the absorption of migalastat was investigated in 6 healthy male subjects following single-dose administration of [^{14}C]-radiolabelled migalastat HCL 150 mg (oral aqueous solution) [Study AT1001-014]. Absorption was rapid with the median t_{max} being 4 hours (range: 2, 6 hours) for both [^{14}C]-radioactivity and plasma migalastat. The mean (SD)

terminal half-life (t1/2) was 7.68 (6.90) hours for [^{14}C]-radioactivity and 6.34 (2.50) hours for plasma migalastat.

In *Study ATT1001-014*, chromatographic analysis of plasma extracts indicated that the major circulating drug component in human plasma was migalastat accounting for approximately 77% of the plasma radioactivity. The geometric mean plasma [^{14}C]-radioactivity to plasma migalastat ratio for the AUCinf values was 0.59, indicating that the majority of the total radioactivity in the plasma was parent compound and that metabolism occurred.

In vitro bi-directional permeability studies using monolayer cultures of Caco-2 cells expressing the human multidrug resistance P-glycoprotein (P-gp) were reported to show no significant interaction between migalastat and P-gp mediated transporters (study 7AMICP1; study 9AMICP2). The results indicate that migalastat is not a substrate for P-gp.

Migalastat *in vitro* was reported to be a low affinity substrate for, and inhibitor of, the sodium glucose co-transporters SGLT1 and SGLT2 that control intestinal glucose absorption (SGLT1 [study 2011N125700_00; study 2011N125739_00]; SGLT2 [study OPT-2015-091; study OPT-2015-090]). The *in vitro* results from these studies are consistent with the clinical study in healthy subjects that showed co-administration of migalastat HCl 150 mg with a high-concentration glucose drink had no clinically significant effect on the bioavailability of migalastat [Study AT1001-0016].

4.2.1.2. Bioavailability

Absolute bioavailability

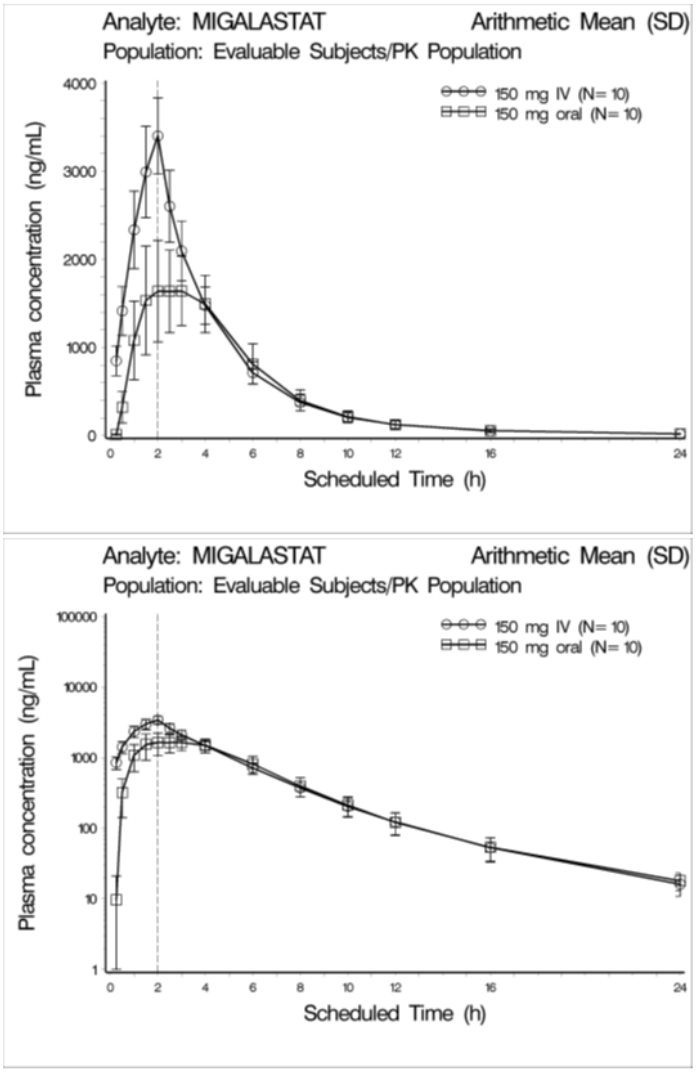
The absolute bioavailability of migalastat was evaluated in one study in 10 healthy volunteers [AT1001-018]. In this study, the absolute bioavailability of migalastat, based on the AUC0-inf was 74.6% (90% CI: 67.2, 82.7), following a single oral 150 mg dose of migalastat HCl. The results are summarised below. The plasma concentration (arithmetic mean) – time profiles following IV and oral administration for the linear and semi-logarithmic plots are summarised below.

Table 2: AT1001-018 – Summary statistical analysis of bioavailability (Cohort 4), 10 subjects treated with the oral capsule and the IV formulation in a crossover design.

Parameter	Geometric Least Square Means				Percentage Test/Reference	
	Test		Reference		Estimate	90% CI
AUC0-t	Oral 150 mg	9777	IV 150 mg	13167	74.3	67.0, 82.3
AUC0-inf	Oral 150 mg	9881	IV 150 mg	13253	74.6	67.2, 82.7

CI = confidence interval; IV = intravenous; PK = pharmacokinetic. PK parameters were compared using an ANOVA with treatment (oral or IV), period and sequence a fixed factors, and subject within sequence as a random factor. The data were ln-transformed and back transformed after the analysis to obtain ratios.

Figure 2: AT1001-018 – Arithmetic mean (linear and semi-logarithmic) plasma concentration-time profiles of migalastat after single oral and IV doses of 150 mg migalastat HCl (Cohort 4).



The PK parameters following oral and IV dosing are summarised below. The geometric mean plasma migalastat Cmax and AUC0-inf values were approximately 1.9-fold and 1.3-fold higher, respectively, after IV administration relative to oral administration. The median tmax value was 1.93 hours after the IV dose and 2.75 hours after the oral dose.

Table 3: AT1001-018 – Pharmacokinetic parameters for migalastat in plasma following oral and IV administration, crossover (n = 10).

PK Parameter*	150 mg oral (N=10)	150 mg IV (N=10)
C_{max}[a] (ng/mL)	1786 (25.9%)	3378 (12.6%)
t_{max}[b] (h)	2.75 (1.50 - 4.00)	1.93 (1.93 - 2.00)
AUC_{0-t}[a] (h·ng/mL)	9777 (25.7%)	13167 (14.9%)
$AUC_{0-\infty}$[a] (h·ng/mL)	9881 (25.6%)	13253 (15.0%)
t½[c] (h)	7.28 (59.2%)	4.54 (44.8%)
CL_T[c,d] (L/h)	12.8 (26.1%)	9.34 (14.6%)
V_Z[c,d] (L)	123 (46.0%)	59.4 (33.7%)
V_{ss}[c,e] (L)		30.2 (15.0%)

a. For Cmax, AUC0-t, and AUC0-∞ geometric mean (CV%) are presented. b. For tmax median and (minimum - maximum) are presented. c. For t½, CLT, Vz, and Vss arithmetic mean (CV%) are presented. d. CLT and Vz for IV treatment and CLT/F and Vz/F for oral treatment. e. Vss was calculated for IV treatment only.

Bioavailability relative to an oral solution or micronised suspension

There was one study [FAB-CL-103] with relative bioavailability data comparing an oral capsule formulation (single-dose 100 mg [4 x 25 mg capsules]) to an oral solution (100 mg [100 mg/10 mL]). This study showed that the relatively bioavailability of the capsule to the solution was approximately 98%, based on the AUC0-t and AUC0-inf values, and approximately 97% based on the Cmax values. The 90% CIs of the geometric LSM ratios for the AUC and Cmax values were enclosed entirely within the interval 80% to 125%, indicating that the capsule and solution formulations are bioequivalent. The results are summarised below.

Table 4: FAB-CL-103 – Summary of PK results (GLSMR) with associated 90% CI) for the oral capsule and the oral solution following administration of a single 100 mg dose to healthy male volunteers (n = 15) in a crossover design.

Parameter	Migalastat HCl Capsule versus Migalastat HCl Solution (GLSMR with 90% CI)
AUC0-t	97.9% (90% CI: 88.7%, 108.1%)
AUC0-inf	97.9% (90% CI: 88.8%, 108.0%)
Cmax	97.1% (90% CI: 86.8%, 108.6%)

Notes: GLSMR = geometric least square mean ratio. PK parameters were compared using an ANOVA with treatment (capsule or solution), period and sequence a fixed factors, and subject nested within sequence as a random factor. The data were ln-transformed and then back transformed after the analysis to obtain ratios.

Bioequivalence of clinical trial and market formulations

There was no clinical bioequivalence study comparing the clinical trial formulation and the proposed marketing formulation of migalastat HCl 150 mg. No formal justification supporting the absence of such a study could be identified in the dossier. The sponsor is requested to submit such a study or submit a formal justification for not doing so.[1]

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

In the summaries, it is stated that the capsules supplied for the blinded phase of the pivotal Phase III study [AT1001-011] were identical to the primary stability batches and proposed commercial formulation in terms of capsule fill composition, but differed in the blue colouring agent in the cap of the capsule shell. The sponsor provided dissolution data and comparative profiles for the Phase III clinical (blinded) batch W004637 and the clinical (open label) / primary stability batch W011176 for migalastat HCl 150 mg capsules. The dissolution profiles of the two formulations were identical and demonstrated complete dissolution at 15, 30 and 45 minutes. Based on this dissolution study it can be reasonably inferred that the migalastat HCl 150 mg capsules used in pivotal Phase III Study AT1001-011 (blinded/open label phases) and the migalastat HCl 150 mg capsules proposed for marketing are bioequivalent.

It was stated in the summaries that migalastat HCL 150 mg capsules have been designed as an immediate release dosage form. Drug substance release from all formulations used in clinical, pivotal clinical and primary stability studies was reported to be rapid and to comply with the proposed commercial specification of not less than 85% dissolved (Q = 80%) at 30 minutes.

Bioequivalence of different dosage forms and strengths

Not applicable. Only one dose form and one dosage strength are being proposed for approval.

Bioequivalence to relevant registered products

Not applicable.

Influence of food

In *study FAB-CL-103*, the effect of a high-fat breakfast on the bioavailability a single 100 mg dose of migalastat HCl (4 x 25 mg capsules) within 30 minutes of food was assessed in 14 healthy male subjects. The study showed that the bioavailability of migalastat was significantly reduced when migalastat HCl capsules were given with a high fat meal compared to fasting administration. The bioavailability of migalastat in the fed state was reduced by approximately 37% relative to the fasting state based on the AUC0-inf values, and by approximately 40% based on the Cmax values. The 90% CIs of the geometric LSM ratios for the AUC and Cmax values were not enclosed entirely within the interval of 80% to 125%, indicating that migalastat HCl capsules are not bioequivalent when administered in the fasting and fed states. The tmax was delayed by approximately 28% when the capsules were administered with food (i.e., from 3.067 to 3.929 hours). The fed versus fasting ratios for AUC and Cmax are summarised below.

Table 5: FAB-CL-103 – Geometric least mean square ratios, with associated 90% CIs, for the oral capsule in the fasting and fed states following administration of a single 100 mg dose f migalastat HCl to healthy male volunteers (n = 15) in a crossover design.

Parameter	Migalastat HCl Capsule Fed versus Fasting (GLSMR with 90% CI)
AUC0-t	62.5% (90% CI: 56.5%, 69.2%)
AUC0-inf	62.8% (90% CI: 56.8%, 69.4%)
Cmax	59.6% (90% CI: 53.1%, 66.9%)

Notes: GLSMR = geometric least square mean ratio. PK parameters were compared using an ANOVA with treatment (capsule fed or fasting), period and sequence a fixed factors, and subject nested within sequence as a random factor. The data were ln-transformed and then back transformed after the analysis to obtain ratios.

In *Study AT1001-106*, the effect of meal type and timing on the PK of migalastat were assessed in a single centre (USA) randomised, open-label, 5-period, crossover study in healthy subjects of both genders. In each of the treatment periods, subjects were randomly assigned to receive a single dose of migalastat HCl 150 mg as follows: fasting (Treatment A, reference); with the simultaneous consumption of a glucose drink (Treatment B); 1 hour before a high-fat meal (Treatment C); 1 hour before a light meal (Treatment D); or 1 hour after a light meal (Treatment

E). Blood samples for PK analyses were collected over 24 hours after single-dose administration during each period. There was a minimum 7-day washout between each period. A total of 20 subjects were enrolled and 19 completed the study. The results of the statistical analysis are summarised below.

Table 6: AT1001-016 – Effect of meal and timing with respect to dosing on the PK of migalastat, ratios are bases on geometric LSM estimates of exposure.

Parameter (unit)	Treatment[1]	n	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90% CI of the Ratio
AUC(0-inf) (h•ng/mL)	A	19	9835.95	–	–	–
	B	19	8497.48	B/A	0.864	0.771-0.968
	C	19	6165.57	C/A	0.627	0.559-0.702
	D	19	5703.58	D/A	0.580	0.518-0.650
	E	19	5924.40	E/A	0.602	0.538-0.675
AUC(0-t) (h•ng/mL)	A	19	9727.84	–	–	–
	B	19	8390.66	B/A	0.863	0.769-0.968
	C	19	6056.09	C/A	0.623	0.555-0.699
	D	19	5609.48	D/A	0.577	0.514-0.647
	E	19	5836.75	E/A	0.600	0.535-0.673
Cmax (ng/mL)	A	19	1579.14	–	–	–
	B	19	1426.64	B/A	0.903	0.799-1.021
	C	19	1340.30	C/A	0.849	0.751-0.959
	D	19	1295.79	D/A	0.821	0.726-0.927
	E	19	956.36	E/A	0.606	0.536-0.684

AUC0-∞ = area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; CI = confidence interval; Cmax = maximum observed concentration; GLSM = geometric least-squares mean. 1. A = 150 mg migalastat HCl in the fasting state. B = 150 mg migalastat HCl with simultaneous consumption of high-concentration glucose drink. C = 150 mg migalastat HCl 1 hour before consumption of a high-fat meal. D = 150 mg migalastat HCl 1 hour before consumption of a light meal. E = 150 mg migalastat HCl 1 hour after consumption of a light meal.

Significant reductions in mean AUC0-inf of approximately 37%, 42%, and 40% (treatment comparisons C/A, D/A, and E/A, respectively) were observed for the different meal types and timing when each was compared with the fasting state (Treatment A). Significant reductions in mean Cmax of approximately 15%, 18%, and 39% (treatment comparisons C/A, D/A, and E/A, respectively) were observed for the different meal types and timing when each was compared with the fasting state (Treatment A). Clinically insignificant reductions in migalastat Cmax and AUC0-inf (10% and 14%, respectively) were observed when a high concentration glucose drink (50 g glucose) was administered concomitantly with 150 mg migalastat HCl (B/A).

No difference in median migalastat tmax (compared to the fasting state) was observed after co-administration of a glucose drink or when migalastat HCl was administered 1 hour after the consumption of a light meal (3.0 hours for each of the three treatments). Statistically significant increases in the rate of absorption (median tmax) were observed when migalastat was administered 1 hour before consumption of a high-fat meal compared to the fasting state (1.5 versus 3 hours; p = 0.0007), and 1 hour before consumption of a light meal compared to the fasting state (2.0 vs. 3.0 hours; p<0.0001).

Dose proportionality

In *study FAB-CL-101*, mean Cmax values for migalastat generally increased dose proportionally over the dose range 25 mg to 675 mg, while mean AUC0-t values for migalastat generally increased dose proportionally over the dose range 75 mg to 675 mg and more than dose proportionally over the dose range 25 mg to 75 mg. The results are summarised below. The dose proportionality results of from this study should be interpreted cautiously due to the small number of subjects at each dose level (n = 6).

Table 7: FAB-CL-101 – PK parameters for migalastat following ascending single-doses of migalastat HCl.

Dose Level (mg)	AUC_{0-t}* (mcg*h/L) (n=6)	AUC_{inf}* (mcg*h/L) (n=6)	C_{max}* (mcg/L) (n=6)	t_{max} (h) (n=6)	$t_{1/2}$ (h) (n=6)	CL/F (L/h) (n=6)	Varea/F (L) (n=6)
25	1092 (34.2)	1129 (33.6)	201 (35.5)	3.00 (21.1)	3.04 (15.7)	18.95 (34.5)	81.16 (27.2)
75	4661 (9.0)	4730 (8.6)	685 (16.7)	2.92 (41.2)	4.05 (16.4)	13.0 (8.3)	76.47 (22.7)
225	11177 (59.8)	11353 (59.2)	1997 (56.1)	3.17 (23.8)	4.62 (15.4)	18.63 (65.1)	133.09 (83.6)
675	35275 (22.3)	35675 (22.4)	6492 (24.4)	2.67 (30.6)	4.19 (7.3)	15.78 (21.9)	94.27 (15.8)

*Geometric mean and geometric CV% were used to present the AUC(0-t), AUCinf and Cmax parameters.

In *study FAB-CL-104*, three migalastat dose levels in healthy subjects were studied in order to assess dose proportionality (500 mg [n = 6], 1250 mg [n = 6] and 2000 mg [n = 6]). There was no dose proportionality between the 1250 mg and 2000 mg doses, indicating less than dose proportional exposure. However, there was a dose proportional relationship between 500 mg and 1250 mg. The PK results are summarised below.

Table 8: FAB-CL-104 – Plasma PK parameters following single ascending doses of migalastat HCl oral solution.

Pharmacokinetic Parameter	500 mg (N=6)	1250 mg (N=6)	2000 mg (N=6)
AUC_{0-t} (ng•hr/mL)	27144 (40)	75108 (29)	72794 (27)
$AUC_{0-\infty}$ (ng•hr/mL)	27428 (40)	76091 (29)	73838 (27)
C_{max} (ng/mL)	5028 (39)	14342 (32)	13844 (42)
t_{max} (hr)	3.01 (1.50, 5.00)	3.50 (2.50, 4.02)	2.51 (2.50, 3.50)
$t_{½}$ (hr)	4.29 (0.28)	4.28 (0.32)	4.79 (0.52)

In *study FAB-CL-104*, the results of the planned power model dose proportionality analysis and of an *ad hoc* ANOVA analysis, are shown below. The power model produced wide 95% CIs for the slopes, but the CIs for both Cmax and AUCinf contained 1. The results are consistent with dose proportionality, but should be interpreted cautiously due to the wide 95% CIs. Since exposure did not appear to be proportional over the entire dose range studied (i.e., no proportionality between 1250 mg and 2000 mg), an *ad hoc* ANOVA analysis was performed comparing the two lower doses, 500 mg and 1250 mg. The ANOVA model was used to construct 90% CIs for the dose normalised mean ratio 500 /1250 mg for Cmax and AUCinf. The ANOVA comparisons produced 90% CIs which fell outside of the 0.85 to 1.25 target range. However, unity was included in the 90% CI, which suggests dose proportionality between the 500 mg and 1250 mg doses.

Table 9: FAB-CL-104 – Proportionality models.

	Power Model (500 mg to 2000 mg)			ANOVA Model (comparison 500 mg versus 1250 mg		
PK Parameter	Slope (b)	SE	95% CI for slope	Ratio	SE	90% CI for mean ratio (500/1250)
Cmax (ng/mL)	0.787	0.16	0.439, 1.14	0.88	0.20	0.611, 1.26
AUCinf	0.769	0.15	0.461, 1.08	0.90	0.90	0.632, 1.28

	Power Model (500 mg to 2000 mg)			ANOVA Model (comparison 500 mg versus 1250 mg		
(ng.h/mL)						

In *study MGM115806*, dose proportionality following single-dose migalastat HCl (50 mg [n = 14], 150 mg [n = 13], 450 mg [n = 13]) was assessed in healthy Japanese male subjects. Using a power model, the three doses tested were generally dose-proportional for the exposure parameters. The slope parameters for the three doses approximated 1, and the 90% CI for the 3 slope estimates included 1.

Table 10: MGM115806 – Summary of dose proportionality of single-dose migalastat PK parameters using power model.

Parameter	Slope	90% Confidence Interval	
		Lower	Upper
C_{max}	0.954	0.769	1.14
AUC_{0-t}	1.09	0.917	1.27
$AUC_{0-\infty}$	1.09	0.914	1.26

AUC_{0-t}=area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration;
$AUC_{0-\infty}$=area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time;
C_{max}=maximum observed concentration

Bioavailability during multiple-dosing

In *study FAB-CL-102*, the multiple-dose PK of migalastat in healthy subjects was assessed in 2 cohorts treated with migalastat 50 mg BD or 150 mg BD for 7 days. In each of the 2 cohorts, 6 subjects received migalastat HCl and 2 subjects received placebo. The PK results for Day 1 and Day 7 are summarised below.

Table 11: FAB-CL-102 – Day 1 mean (CV%) of PK parameters.

Dose Level	AUC_{0-t} (mcg•h/L) (n=6)	AUC_{inf} (mcg•h/L) (n=6)	C_{max} (mcg/L) (n=6)	t_{max} (h) (n=6)	$t_{1/2}$ (h) (n=6)	CL/F (L/h) (n=6)	V_{area}/F (L) (n=6)
50 mg BID	1897 (48.0)	2017 (47.8)	344 (40.9)	2.92 (36.6)	2.56 (14.6)	22.1 (47.6)	84.6 (57.4)
150 mg BID	8955 (40.5)	9482 (40.2)	1723 (46.6)	3.08 (36.1)	2.44 (5.5)	13.9 (49.9)	48.4 (46.2)

Geometric mean and Geometric CV% were used to present the AUC0-t, AUCinf and Cmax, whereas arithmetic means were used to estimate the other parameters.

Table 12: FAB-CL-102 – Day 7 mean (CV%) of PK parameters.

Dose Level	$AUC_{0-\tau}$ (mcg•h/L) (n=6)	C_{max} (mcg/L) (n=6)	C_{min} (mcg/L) (n=6)	t_{max} (h) (n=6)	Flux1 (%) (n=6)	Flux2 (%) (n=6)
50 mg BID	3259 (25.6)	617 (35.1)	60.5 (22.7)	2.50 (35.8)	206 (17.0)	967 (37.1)
150 mg BID	10680 (33.6)	1659 (40.5)	224 (32.1)	2.92 (29.4)	163 (20.5)	670 (32.1)

Geometric mean and Geometric CV% were used to present the AUC0-t, AUCinf and Cmax, whereas arithmetic means were used to estimate the other parameters. Flux 1 = [Cmax-Cmin]/[Css,av] x 100; Flux 2 = [Cmax-Cmin]/[Cmin] x 100.

Dose linearity was assessed using appropriate ANOVA models. On Day 1, the mean AUC0-t and Cmax values increased in a more than a dose proportional manner between 50 mg to 150 mg. However, increases in AUC0-τ and Cmax values were dose proportional on Day 7 for the 50 mg BD and 150 mg BD doses. The results for the dose linearity assessment for the Day 1 versus Day 7 comparison are summarised below. For the 50 mg dose, the ratio (AUC0-τ/AUCinf) and the 90% CI were not within the 80-125% acceptance range. Therefore, dose linearity could not be concluded for the 50 mg dose following multiple BD dosing. For the 150 mg dose, the 90% CI for the ratio (AUC0-τ/AUCinf) was not within the 80-125% acceptance range. However, the ratio approximated 100% (i.e., unity) and was enclosed within the 90% CI, which suggests approximate PK linearity at the 150 mg dose level following multiple BD dosing.

Table 13: FAB-CL-102 – Dose linearity assessment, AUC values described by geometric mean.

Dose Level	AT-1001 Exposure*		Statistical analysis
	AUC_{inf} Day 1	$AUC_{0-\tau}$ Day 7	Ratio (90% Confidence interval)
50 mg BID	2017	3259	161.59% (140.26–186.17%)
150 mg BID	9482	10680	112.64% (97.77–129.77%)

A steady state analysis was performed on the ln-transformed pre-dose Cmin concentrations at -48, -24 and 0-hour (corresponding to Days 5, 6 and 7), with back transformation to obtain the geometric means. The statistical analysis compared the Cmin at each of the three time points for each dose (Helmert's contrasts) and found that steady state had not been reached by Day 7 of migalastat BD dosing (50 mg or 150 mg). This finding is unexpected given that in this study the half-life of both the 50 mg and 150 mg doses was short (2.56 h and 2.44 h, respectively). No accumulation ratios were calculated for either dose. However, given that steady state had not been reached by Day 7, accumulation ratios based on Day 7 and Day 1 exposures in *study FAB-CL-102* might be unreliable. Nevertheless, significant accumulation of migalastat following multiple oral administration is unlikely, given the short terminal phase half-life of the drug. The geometric mean of Cmin by dose and time are summarised below.

Table 14: FAB-CL-102 – Geometric mean of Cmin by dose and time (Days 5, 6, and 7).

Dose Level	Time	C_{min}* (mcg/L)
50 mg BID	-48-hour	56.568
	-24-hour	51.333
	0-hour	63.561
150 mg BID	-48-hour	177.567
	-24-hour	158.063
	0-hour	194.905

*Geometric Mean of Cmin by Dose and Time (Days 5, 6 and 7)

4.2.1.3. Distribution

Volume of distribution

In *Study AT1001-018*, in healthy volunteers (n = 10) the mean (CV%) volume of distribution (Vz) was 59.4 L (33.7%) L following single-dose IV migalastat HCl 150 mg and was 123 L (46.0%) L following single-dose oral migalastat HCl 150 mg. 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.

In *study FAB-CL-101*, the apparent volume of distribution (Vz/F) of migalastat following oral administration of migalastat (solution) in healthy subjects ranged from 76.5 to 133 L, with the

mean (SD) values for Vz/F being 81.2 (22.1) L, 76.5 (17.4) L, 133 (111) L and 94.3 (14.9) L following doses of 25, 75, 225, and 675 mg, respectively.

Plasma protein binding

In vitro protein binding evaluation using equilibrium dialysis over a concentration range of 1 to 100 µM (i.e. 163 to 16300 ng/ml free base) showed that migalastat did not bind to plasma proteins [study 0332-145-02].

Erythrocyte distribution

In the ADME study [AT1001-014], geometric mean [^{14}C] blood/plasma ratios were relatively constant between 2 and 6 hours post-dose (ranging between 0.76 and 0.82). The mean [^{14}C] blood/plasma ratio then increased to 1.12 at 24 hours post-dose. No [^{14}C] blood/plasma ratio could be calculated at 48 hours post-dose. Overall, these 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.

Tissue distribution

There were no data on tissue distribution in humans. In a nonclinical study in Sprague-Dawley rats, migalastat was reported to be widely distributed in the brain, heart, kidneys, liver, muscle, skin and spleen following a dose of 50 mg/kg administered by oral gavage [study XBL08605]. The same study also showed that migalastat can penetrate the blood-brain barrier. In a pre- and post-natal study in Sprague-Dawley rats, it was reported that there was placental transfer of 6% to 11% migalastat into the fetus of pregnant rats and significant excretion into milk of lactating rats with milk-to-plasma ratios ranging from 2.5 to 8.1 [Study AA94762].

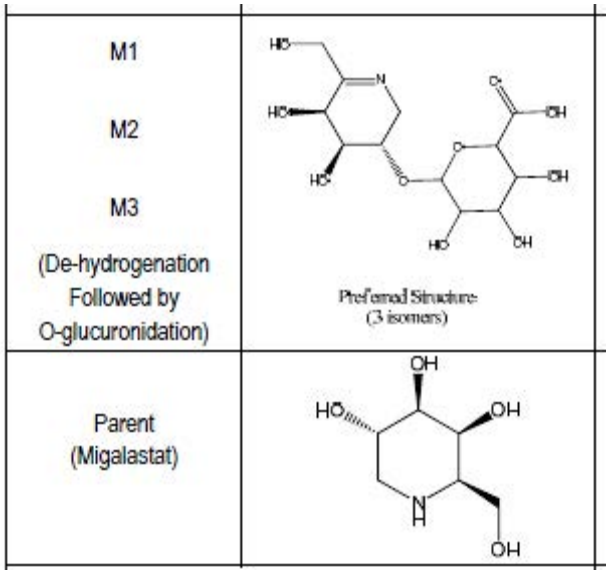
4.2.1.4. Metabolism

Sites of metabolism and mechanisms / enzyme systems involved

Migalastat was reported not to be metabolised by CYP450 enzymes *in vitro* in human hepatocytes at concentrations of 1 and 100 µM [^{14}C]-migalastat [study 0322-145-01]. There were no clinical studies investigating the effect of CYP450 enzymes on the metabolism of migalastat.

In *Study AT1001-014*, three minor dehydrogenated O-glucuronide conjugated metabolites of migalastat were identified (M1, M2, and M3). The sponsor reports that metabolism of migalastat via dehydrogenation and O-glucuronide conjugation was a minor route of clearance representing approximately 4% of the dose in human urine. The proposed structure of the three metabolites (3 isomers) are summarised below.

Figure 3: At1001-014 – Parent compound (migalastat) and proposed structure if the metabolites



Non-renal clearance

Non-renal clearance of migalastat appears to be clinically insignificant. It is assumed that the liver is the primary site of the metabolism of migalastat to the three minor dehydrogenated O-glucuronide conjugated metabolites identified in humans [AT1001-014].

Metabolites identified in humans: active and other

The metabolites of migalastat HCl were characterised in the mass-balance study in 6 healthy male subjects [AT1001-014]. Three minor dehydrogenated O-glucuronide conjugated metabolites of migalastat were identified (M1, M2, and M3). The sponsor postulates that the contribution of these metabolites to the overall pharmacological and toxicological profiles of migalastat is likely to be negligible, given the very low levels of these metabolites. This is considered to be a reasonable conclusion.

Pharmacokinetics of metabolites

There were no data on the PK of the three minor dehydrogenated O-glucuronide conjugated metabolites identified in humans.

Consequences of genetic polymorphism

There were no data were on the consequences of genetic polymorphisms of CYP450 enzymes on the metabolism of migalastat. However, given that the *in vitro* data demonstrated that migalastat is not metabolised by CYP450 enzymes it can be predicted that the effect of genetic polymorphisms on metabolism will be insignificant.

4.2.1.5. Excretion

Routes and mechanisms of excretion

In *study FAB-CL-101*, total clearance ranged from 13.0 to 19.0 L/h across the dose range 25 to 625 mg in healthy subjects, while the mean renal clearance ranged from 5.90 to 7.66 L/h (comparable to the normal filtration rate). The results from this study indicate that non-renal clearance ranged from 7.1 to 11.3 L/h.

In the absolute bioavailability study [AT-1001-018], mean (CV%) CL following IV administration of migalastat HCl 150 mg (n = 10) was 9.34 L/h (14.6%) and mean (CV%) CL/F following oral administration of migalastat HCl 150 mg (n = 10) 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.

The mass balance study [AT1001-04] demonstrated that the major route of [^{14}C]-radioactivity excretion following oral dosing was via the urine (77.2%), with unchanged migalastat being the predominant component. The other notable components identified in the urine were three dehydrogenated O-glucuronide conjugated metabolites (M1, M2 and M3). In a pooled sample extract, unchanged migalastat, M1, M2 and M3 accounted for approximately 80%, 3%, 1% and 2% of the sample radioactivity, which equated to approximately 55% (unchanged migalastat) and 4% (combined metabolites) of the administered dose. Approximately 5 % of the total sample radioactivity in the urine was unassigned components. All quoted values were stated to be best estimates as the metabolite peaks in the radio-chromatogram were small and not fully baseline resolved.

The high percentage of dose excreted in urine (approximately 77%) indicates that migalastat was well absorbed following oral administration. The remainder of the administered [^{14}C]-radioactivity was excreted in feces (20.4%). Unchanged migalastat was the only drug related component observed in feces extracts. Duodenal bile was stated to contain insufficient levels of radioactivity to warrant further investigation.

Mass balance studies

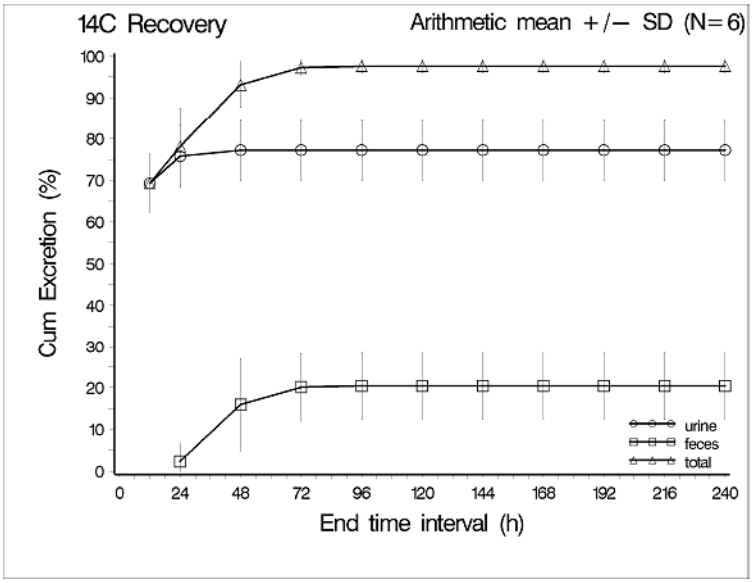
Overall, in the mass balance study [AT1001-014] the mean total recovery of [^{14}C]-radioactivity in urine and feces was 97.6 % of the administered dose of 150 mg migalastat HCl. No [^{14}C]-radioactivity was detected in expired air samples. The total collection period to determine the excretion balance of percentage of drug related material recovered in urine, bile and feces was up to 240 hours following administration. All 6 subjects had reached maximum total recovery at 96 hours post dose (Day 5). The [^{14}C]-radioactivity and migalastat excretion parameters are summarised below, and the cumulative excretion values over the duration of the collection period are summarised below.

Table 15: AT1001-014 – Summary of [^{14}C]-radioactivity percentages collected in the urine and feces and summary of the urinary excretion parameters for migalastat.

Radioactivity [^{14}C]	Ae_{urine} (%)	Ae_{feces} (%)	Ae_{total} (%)
Arithmetic mean (range)	77.2 (67.1 - 85.8)	20.4 (11.9 - 33.5)	97.6 (95.7 - 100.6)
Urine Migalastat	**Ae_{urine} (%)**	**Ae_{urine} (mg)**	**CL_R (L/hr)**
Arithmetic mean (range)	64.5 (57.0 - 70.4)	79.1 (69.9 - 86.3)	7.32 (4.49 - 9.09)

N = number; AE_{urine} = amount of radioactivity or migalastat excreted in urine, Ae_{feces} = amount of radioactivity excreted in feces, Ae_{total} = total amount of radioactivity excreted in urine and feces, CLR = renal clearance .

Figure 4: AT1001-014 – Arithmetic (SD) mean profile of cumulative [^{14}C]-radioactivity excretion in urine and feces and total recovery.



The PK parameters of [^{14}C]-radioactivity and migalastat in plasma (n = 6) are summarised below. The arithmetic mean (SD) [^{14}C]-radioactivity profiles for migalastat in plasma and blood and the migalastat plasma concentration profiles are summarised below. 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 three dehydrogenated O-glucuronide metabolites of migalastat (M1, M2, and M3) accounted for 13% of the total radioactivity in the plasma and approximately 9% of the total radioactivity in the plasma was assigned. Total recovered radioactivity in the plasma (unchanged migalastat, metabolites, unassigned) accounted to 99% of radiolabelled dose recovered in the plasma.

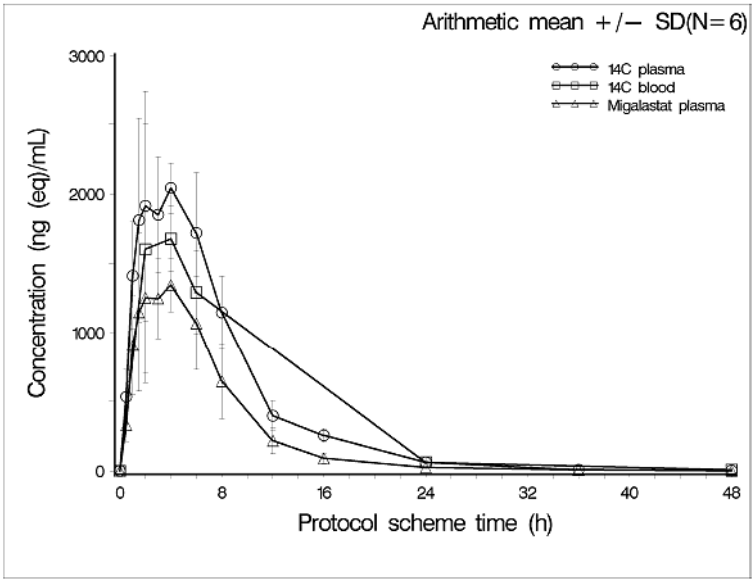
At all time points through to 48 hours, [^{14}C]-concentrations in plasma were higher than migalastat concentrations in plasma. After the maximum peak plasma concentrations at 4 hours post-dose, mean migalastat and [^{14}C]-plasma concentrations decreased in a biphasic manner. Migalastat was detectable in all 6 subjects up to 24 hours (Day 2) after dosing, and was detectable in only 1 out of 6 subjects at 48 hours post dose (Day 3). [^{14}C]-radioactivity was detectable in all subjects up to 24 hours (Day 2) after dosing, and was detectable in only 1 subject after 72 hours post dose (Day 4). Subject 4 showed one radioactive sample just above the LLoQ again (13.9 ng eq/mL) at 240 hours post dose (Day 11), while from Day 5 onwards these levels were below the LLoQ. Therefore, the sponsor considered that this value was implausible value and it was excluded from the PK analysis.

Table 16: Summary statistics of PK parameters of radioactivity and migalastat in plasma (n = 6).

Analyte	C_{max} [a] (ng {eq}/mL)*	t_{max} [b] (h)	$AUC_{0\text{-last}}$ [a] (ng {eq}.h/mL)*	$AUC_{0\text{-inf}}$ [a] (ng {eq}.h/mL)*	$t_{1/2}$ [c] (h)
Radioacitivity [^{14}C]	2246 (27)	4.00 (2.00-6.00)	18718 (14)	18849 (14)	7.68 (6.90)
Plasma Migalastat	1516 (27)	4.00 (2.00-6.00)	10957 (22)	11029 (22)	6.34 (2.50)

[a] Geometric mean (CV%)
[b] Median (range)
[c] Arithmetic mean (SD)
h = hour; N = number; * {eq} only applies to [^{14}C]

Figure 5:AT1001-014 – Arithmetic (SD) mean concentration- time profiles for migalastat in plasma and [^{14}C]-radioactivity in plasma and whole blood, linear scale.



Renal clearance

In the mass balance *Study AT1001-014*, the mean renal clearance in 6 healthy male subjects was 7.32 L/h (range: 4.49, 9.09 L/h). The renal clearance of migalastat was similar to the normal glomerular filtration rate (i.e., 7.3 L/h and 7.5 L/h, respectively). In *Study AT1001-014*, the majority of the administered [^{14}C]-radioactivity was excreted in urine (77.2%), and unchanged migalastat accounted for 64.5% (range: 57.0%, 70.4%) of the administered dose. The results indicate the renal clearance is the major route of elimination of orally administered migalastat.

4.2.1.6. Intra and inter individual variability of pharmacokinetics

Based on the data for the migalastat HCl 150 mg oral capsule proposed for registration, inter-subject variability based on the coefficients of variation (CV%) following single-dose fasting administration for the plasma migalastat AUCinf values were 25.7% and 27.1% and for the plasma Cmax values were 25.9% and 33.8% (studies MFM116050 and AT1001-18). These results suggest moderate inter-subject variability in the exposure parameters for migalastat. There were no data in the submission relating to intra-subject variability.

4.2.2. Pharmacokinetics in the target population

The PK of migalastat in patients with Fabry disease was assessed in 4 clinical studies [FAB-CL-201, FAB-CL-204, FAB-CL-205, and AT-1001-011].

Study FAB-CL-201 (n = 9, males) and *study FAB-CL-204* (n = 9, females) were conventional PK studies in which blood was collected for determination of plasma migalastat using a dense sampling schedule following single and multiple oral dosing. In addition, both studies include assessment of the urinary PK parameters of migalastat. In both studies, the PK parameters of migalastat were calculated using standard non-compartmental methods. The PK results from these two studies have been evaluated and the results discussed below.

Study FAB-CL-205 included limited PK data in 23 patients (n = 14 male, n = 9 female) with Fabry disease assessing plasma concentrations of migalastat taken at trough and 3 hours post-dose at selected time-points. The results of this study have been briefly reviewed below.

In Study AT1001-011 (the pivotal Phase III study), sparse sampling for plasma PK analysis was undertaken pre-dose and at 4 time-points after dosing (2, 3, 4 and approximately 8 hours). The PK data from this study were pooled with other data for analysis using population PK methods. The PK data from this study have been evaluated in the review of the PPK report.

4.2.2.1. Study FAB-CL-201

Study FAB-CL-201 was a Phase II, open-label, multicentre, 12-week study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of migalastat in patients with Fabry disease. The study consisted of a 4-week screening period and a 12-week treatment period with an optional extension period of 36 or 84 weeks. A total of 9 male patients with Fabry disease were enrolled and received repeated doses of migalastat HCl 25, 100, and 250 mg BD in a dose-escalation fashion over the first 6 weeks, followed by 6 weeks treatment with migalastat HCl 25 mg BD. Subjects who did not enter an optional treatment extension were to enter a 2-week follow-up period. Subjects who entered the optional treatment extension period received a total daily dose of 50 mg migalastat HCl (initially 25 mg BD, then 50 mg QD). An additional six subjects enrolled under Amendment 3 failed screening and none of these subjects continued into the treatment phase. The study included single-dose and multiple-dose PK data.

The PK data set included 9 eligible enrolled male patients with Fabry disease. The mean age of the 9 patients was 36.7 years (range: 17, 58 years), with race being classified as White for 8 patients and other for 1 patient. The mean (SD) duration of Fabry disease was 6.4 (10.02) years, with a range of 0.3 to 31.4 years.

Blood samples for plasma PK analyses were collected on Days 1, 15, and 29 (single-dose PK) and Days 14, 28, and 42, and Week 24 (multiple-dose PK). The timing of the blood samples collected for PK analysis on Days 1, 14, 15, 28, 29, and 42 were before the morning dose and after dosing at 0.5, 1, 2, 3, 4, 5, 6, 8 and 10 hours. In addition, blood samples were collected for trough (Cmin) determination for steady-state assessment at the following times in relation to the morning dose on Days 14, 28 and 42: -14 to -12 hours (i.e., before the evening dose on Days 13, 27, and 41) and 0 hours (i.e., just before the morning dose). The plasma PK results are below.

Table 17: Single-dose PK for migalastat in plasma following after first dose of 25, 100, and 250 mg.

PK Parameters	Study Day* and Dose (BID)		
	Day 1 (25 mg)	Day 15 (100 mg)	Day 29 (250 mg)
Geometric Mean (CV%)			
AUC_{0-t} (ng*hr/mL)	1008.40 (30.8)	3952.53 (32.7)	10431.22 (32.7)
AUC_{0-12} (ng*hr/mL)	1052.96 (29.9)	4217.95 (32.0)	10880.66 (32.4)
AUC_{0-inf} (ng*hr/mL)	1115.66 (28.9)	4487.41 (33.3)	11492.88 (31.9)
C_{max} (ng/mL)	204.25 (31.3)	883.54 (37.6)	2305.06 (37.1)
Arithmetic Mean (CV%)			
$t_{1/2}$ (hr)	2.45 (19.8)	2.55 (17.9)	2.39 (13.4)
CL/F (L/hr)	18.97 (27.9)	18.95 (26.1)	18.60 (34.2)
V_{area} /F (L)	67.30 (32.2)	69.41 (29.4)	64.33 (35.1)
Median (Min-Max)			
t_{max} (hr)	2.00 (1.92-4.00)	2.51 (1.00-3.00)	3.00 (2.00-4.08)

CV% = coefficient of variation
* Days 1, 15 and 29 – After first dose at 25, 100 or 250 mg BID AT1001

Table 18: Multiple-dose PK for migalastat in plasma following multiple (BD) oral doses.

PK Parameters	Study Day and Dose (BID)		
	Day 14* (25 mg)	Day 28* (100 mg)	Day 42* (250 mg)
Geometric Mean (CV%)			
AUC_{τ} (ng*hr/mL)	1360.69 (32.9)	5643.50 (25.3)	12244.47 (26.0)
C_{max} (ng/mL)	263.18 (46.4)	1071.29 (30.3)	2185.30 (33.6)
Arithmetic Mean (CV%)			
$t_{1/2}$ (hr)	2.69 (25.9)	2.63 (11.6)	2.69 (16.6)
CL/F (L/hr)	15.72 (32.6)	14.90 (26.5)	17.17 (25.2)
Accumulation Ratio**	1.43 (40.8)	1.39 (27.1)	1.19 (37.3)
Median (Min-Max)			
t_{max} (hr)	3.00 (2.00-5.00)	3.00 (1.02-5.00)	3.00 (1.08-4.08)

* The fourteenth day of dosing at 25, 100 or 250 mg BID.
** Accumulation Ratio is the ratio of AUC_{τ} on Day 14 to $AUC_{0\text{-}12}$ on Day 1.
CV% = coefficient of variation

The single-dose migalastat plasma PK data showed that the migalastat was rapidly absorbed with median tmax values ranging from 2 to 3 hours over the dose range of 25 to 250 mg. Mean elimination half-life values were similar over the dose range studied (2.39 to 2.55 hours). The mean CL/F values remained constant over the dose range studied (18.60 to 18.97 L/h), as did mean Varea/F values (64.33 to 69.41 L).

The multiple-dose plasma PK data showed that migalastat was rapidly absorbed, with the median tmax value being 3 hours at each of the doses studies over the 25 to 250 mg. Mean elimination half-life values remained constant over the dose range studied (2.63 to 2.69 hours). Mean CL/F values ranged from 14.9 L/h to 17.2 L/h across the dose range studied. With repeated BD oral administration for 14 days, the accumulation ratios were 1.43, 1.39 and 1.19 at dose levels of 25, 100, and 250 mg, respectively.

Two subjects had evaluable PK data at Day 168 (Week 24) on a total once a day dose of 50 mg during the optional treatment extension. The geometric mean (CV%) Cmax and AUCτ values were 370.85 ng/mL (86.1%) and 2180.19 ng.h/mL (82.6%), respectively. The arithmetic mean (CV%) t1/2 and CL/F values were 2.18 h (21.9%) and 21.24 L/h (66.5%), respectively, and the median tmax was 3.0 h.

Taking dose and dosing interval into account, the PK data following once daily dosing appear to be comparable to the PK data seen after BD dosing, suggesting the extended time on treatment has no apparent effect on the PK of migalastat.

Dose proportionality was evaluated at single and multiple dose for migalastat using a regression approach. Dose proportionality could not be rejected for AUC0-inf and Cmax at single dose on Day 1 and at steady state on Day 14 of BD dosing, because a linear relationship was demonstrated and the 95% CI for the slopes of the ln-transformed PK parameters included the value of 1. These results indicate that systemic exposure increased in a dose proportional fashion as doses increased from 25 to 250 mg on Days 1 and 14. The results for the dose proportionality assessment are summarised below.

Table 19: Geometric mean (CV%) of the PK parameters and slope estimates (95% CIs).

Day	PK Parameter	25 mg (n = 9)	100 mg (n = 8)	250 mg (n = 8)	Dose proportionality slope [95% CI]

Day	PK Parameter	25 mg (n = 9)	100 mg (n = 8)	250 mg (n = 8)	Dose proportionality slope [95% CI]
1 *	AUCinf (ng.h/mL)	1115.66 (28.9)	4487.41 (33.3)	11492.88 (31.9)	1.01 [0.89, 1.14]
	Cmax (ng/mL)	204.25 (31.3)	883.54 (37.6)	2305 (37.1)	1.05 [0.91, 1.20]
14 **	AUCτ (ng.h/mL)	1360.69 (32.9)	5643.50 (25.3)	12244.47 (26.0)	0.96 [0.86, 1.06]
	Cmax (ng/mL)	263 (46.4)	1071.29 (30.3)	2185.30 (	0.93 [0.81, 1.04]

Complete urine output (24-hour urine samples) was collected from each patient during the 12-week treatment period on Days 1, 14, 28, and 42 for analysis of migalastat. Amounts (Ae0-10 µg) excreted after 100 mg BD and 250 mg BD for 14 days appeared to increase proportionately with dose. Percent of dose excreted was similar after 100 mg and 250 mg BD. Renal clearance was similar after 100 mg BD and 250 mg BD, and was comparable to normal glomerular filtration rate. The results are summarised below.

Table 20: FAB-CL-201 - Arithmetic means (CV%) of PK parameters for migalastat in urine after single and multiple (BD) doses.

	Study Day and Dose (BID)			
PK Parameters	Day 1* (25 mg)	Day 14** (25 mg)	Day 28**† (100 mg)	Day 42** (250 mg)
$Ae_{0\text{-}10}$ (µg)	NR	NR	38767.67 (29.0)	91731.51 (28.4)
Fe (%)	NR	NR	47.43 (29.0)	44.89 (28.4)
CL_R (L/hr)	NR	NR	6.84 (18.1)	7.92 (27.9)

*After a single dose on Day 1.
** After repeated twice daily doses for 14 days.
†Subject 03 - 01, after 100 mg BID, had unexpectedly no recovery of AT1001 in urine and was excluded from summary statistics.
NR = not reportable. The LLOQ of the analytical method did not allow sufficient recovery of drug at the 25 mg dose regimens

4.2.2.2. FAB-CL-204

Study FAB-CL-204 was a Phase II, open-label trial in previously untreated female patients with Fabry disease. It comprised a 4-week screening phase, a 12-week treatment phase, and a 36-week treatment extension phase. Samples for plasma and urine PK analysis were collected following the 1st dose (Day 1), the 7th dose (Day 14), and the 42nd dose (Day 84). The study included 9 female subjects with Fabry disease who received single-dose and multiple-dose (every other day) migalastat HCl 50 mg (n = 2), 150 (n = 4), and 250 mg (n = 3). The age of the 9 female subjects ranged from 36 to 62 years; 6 were white, 2 were Hispanic, and 1 was Arab-American. The duration of Fabry disease since diagnosis ranged from 0.6 to 23.7 years. Only one 9 female subjects had Fabry disease diagnosed before the age of 30.

Blood samples were collected for PK analysis on Days 1, 14, and 84 before dosing and after dosing at 0.5, 1, 2, 3, 4, 5, 6, 8, and 10 hours. In addition, blood samples were collected at 12 hours before dosing on Days 14 and 84. Samples for steady-state assessment were collected at Days 14 and 84, using two Cmin points: 1 at 12 hours before the dose on Day 14 and Day 84 (i.e.,

evening of Day 13 and Day 83); and 1 just before the dose on Day 14 and Day 84. The results for the PK parameters on Day 1, Day 14, and Day 84 are summarised below.

Table 21: Study FAB-CL-204 – Migalastat plasma PK parameters on Days 1, 14, and 84.

	AT1001 50 mg QOD n=2	AT1001 150 mg QOD n=4	AT1001 250 mg QOD n=3
Day 1 PK Parameters			
Geometric Mean (CV%)			
AUC_{0-t} (ng*h/mL)	2628.9 (100.4)	8941.6 (32.2.)	13217.2 (30.2)
C_{max} (ng/mL)	519.5 (95.5)	1690.7 (22.0)	2461.4 (43.4)
Median (Range)			
t_{max} (h)	2.00 (2.00, 2.00)	3.50 (1.00, 4.00)	3.00 (2.00, 5.00)
Day 14 PK Parameters			
Geometric Mean (CV%)			
AUC_{0-10} (ng*h/mL)	3191.6 (64.9)	10637.9 (35.6)	14850.6 (9.6)
C_{max} (ng/mL)	600.3 (33.1)	2028.6 (40.0)	2662.7 (22.8)
Median (Range)			
t_{max} (h)	3.17 (2.33, 4.00)	2.96 (2.00, 4.00)	3.00 (3.00, 5.00)
Day 84 PK Parameters			
Geometric Mean (CV%)			
AUC_{0-t} (ng*h/mL)	2300.3 (79.6)	8581.9 (29.7)	9970.3 (37.8)
C_{max} (ng/mL)	500.9 (67.4)	1523.7 (23.3)	1953.8 (49.1)
Median (Range)			
t_{max} (h)	2.00 (2.00, 2.00)	3.50 (2.00, 4.00)	3.00 (3.00, 4.00)

The plasma PK data showed that single and multiple oral doses of migalastat were rapidly absorbed, with median tmax values ranging from 2.0 to 3.5 hours. Trough concentrations were measurable at Day 14 and Day 84, suggesting that a potential longer terminal phase of the PK profile than that measured may be present (see below).

Table 22: FAB-CL-204 – Arithmetic mean (CV%) pre-dose (trough) migalastat plasma concentrations (ng/mL) on Day 14 and Day 84.

Dose Level	Day 14	Day 28
50 mg (n = 2)	BLQ (5.88 ng/mL)	11.3 ng/mL (n = 1)
150 mg (n = 4)	11.3 ng/mL (57.7%)	8.9 ng/mL (83.8%)
250 mg (n = 3)	26.4 ng/mL (35.7%)	15.1 ng/mL (27.9%)

Following repeat oral administration of migalastat HCL 50 mg, 150 mg, or 250 mg every other day, plasma exposures (AUC0-10 and Cmax) did not deviate significantly from dose proportionality across the dose range studied (see Table 24, below). However, while the results of the dose proportionality analysis showed slope estimates close to 1 (indicating no significant deviation from dose proportionality), the 90% CIs for the estimates were wide (reflecting the small number of patients in each dose group). Therefore, no conclusive claims regarding dose proportionality can be made based on the data from the analysis. No marked accumulation of migalastat was observed over 84 days of once every other day oral dosing.

Table 23: FAB-CL-204 – Geometric mean (CV%) of the PK parameter, and slope estimates (95% CI).

Day	PK Parameters	Geometric Means (CV%)			Dose Proportionality Slope (95% CI) in ln-scale
		50 mg (n=2)	150 mg (n=4)	250 mg (n=3)	
1	AUC_{0t} (ng·h/mL)	2628.9 (100.4)	8933.4 (32.3)	13222.4 (30.2)	1.02 (0.46 ; 1.57)
	C_{max} (ng/mL)	519.5 (95.5)	1690.7 (22.0)	2461.4 (43.4)	0.98 (0.43 ; 1.52)
14	AUC_{0-10} (ng·h/mL)	3191.6 (64.9)	10637.9 (35.6)	14850.6 (9.6)	0.97 (0.52 ; 1.41)
	C_{max} (ng/mL)	600.3 (33.1)	2028.6 (40.0)	2662.7 (22.8)	0.94 (0.51 ; 1.38)
84	AUC_{0-10} (ng·h/mL)	2300.3 (79.6)	8581.9 (29.7)	9970.3 (37.8)	0.94 (0.38 ; 1.50)
	C_{max} (ng/mL)	500.9 (67.4)	1523.7 (23.3)	1953.8 (49.2)	0.86 (0.35 ; 1.38)
Reference: Appendices 2.1.1, 2.1.2, and 2.1.3					

Complete urine output was collected from each subject for analysis of migalastat at the following time intervals on Days 1, 14, and 84: -14 to 0 hours pre-dose, and then post-dose at 0 to 4, 4 to 8 and 8 to 10 hours. The results for the PK parameters in urine are summarised below. Following repeat once every other day oral dosing 10% to 60% of the migalastat dose was recovered in the urine as unchanged migalastat within 10 hours of dosing (excluding one subject with 193% of the dose suggesting incorrect collection). Mean migalastat renal clearance ranged from 2.97 to 9.65 L/h.

Table 24: FAB-CL-204 – Summary of mean (CV%) PK results for migalastat in urine after single and multiple oral doses once every other day.

Day	PK Parameters	Dose Level		
		50 mg (n=2)	150 mg (n=4)	250 mg (n=3)
1	$Ae_{(0-10)}$ (mcg)	NR	74083 (44.2)	64885 (50.4)
	Fe (%)	NR	60.4 (44.2)	31.8 (50.4)
	CL_R (L/h)	NR	9.65 (75.2)	4.55 (29.2)
14	$Ae_{(0-10)}$ (mcg)	16770*	72991 (59.0)	79410 (31.1)
	Fe (%)	41.0*	59.5 (59.0)	38.9 (31.1)
	CL_R (L/h)	7.99*	9.00 (91.2)	5.46 (38.4)
84	$Ae_{(0-10)}$ (mcg)	4160**	41775 (54.4)	60815 (67.4)
	Fe (%)	10.2**	34.1 (54.4)	29.8 (67.4)
	CL_R (L/h)	2.97**	5.41 (77.0)	7.00 (84.8)

*n=1
** Significantly greater than 100% of the dose was recovered in the urine of Patient 01-01 (193%) suggesting that the urine collection was not conducted correctly. Therefore, the data for this subject were excluded.
NR= not reportable
Reference: AT1001 in Urine Tables 5, 10, and 15

4.2.2.3. Study FAB-CL-205

Study FAB-CL-205 was a Phase II, open-label, non-comparative, long-term extension study for male and female subjects with Fabry disease who had completed the treatment period of one of the four prior Phase II clinical trials. Subjects received the following oral doses of migalastat HCl during the extension period: 150 once every other day; 250 mg (3 days on/4 days off); and 500 mg 3 days on/4 days off. The study enrolled 23 subjects, and all 23 subjects had blood for PK analysis.

Blood samples for plasma migalastat concentrations were taken at trough (pre-dose or Time 0) and at peak (3 hours post-dose) during dose escalation period 1 (DEP 1) (250 mg 3 days on/4 days off) and DEP 3 (500 mg 3 days on/f4 days off). Specifically, trough and peak blood samples were taken just prior to and 3 hours after the 3rd dose during a 3 days on followed by 4 days off dosing regimen. Blood samples for plasma migalastat concentrations were not taken during DEP 1, DEP 4 or DEP 5 when patients were receiving 150 mg migalastat HCl once every other day.

Plasma migalastat concentrations at trough (Time 0) were below the limit of quantification (i.e., < 5.88 ng/mL) for 15 of 23 subjects (65.2%) when receiving the 250 mg migalastat HCl dose regimen, and 3 of 23 subjects (13.0%) when receiving 500 mg migalastat HCl dose regimen. Concentrations below the limit of quantification were set to zero for calculation of the arithmetic mean and median values. Inter-subject variability in trough concentration was high (CV% > 100%) for both the 250 mg and 500 mg regimens.

Plasma concentrations for the pre-dose samples in DEP 1 ranged from 5.94 ng/mL to 313 ng/mL for the 150 mg dose of migalastat. The 3 hour post-dose samples ranged from 908 to 5250 ng/mL for the 250 mg dose of migalastat and 113 to 8500 ng/mL for the 500 mg dose of migalastat. The sponsor states that the low plasma post-dose concentration of 113 ng/mL for the 500 mg dose may be attributed to a laboratory error with the sample labels since the pre-dose plasma concentration level for the 500 mg dose was 5070 ng/mL.

4.2.3. Pharmacokinetics in special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

There was no dedicated PK study in patients with hepatic impairment. However, the mass balance study [AT1001-014] in health subjects (n = 6) showed that migalastat is eliminated predominantly in the urine with metabolism by dehydrogenation and O-glucuronide conjugation being a minor route of elimination. The three glucuronide metabolites (M1, M2, M3) represented approximately 4% of the total sample radioactivity in urine and the unassigned components accounted for approximately 5%. In plasma, the three glucuronide metabolites (M1, M2, and M3) accounted for 13% of the total plasma radioactivity. In addition, *in vitro* data was reported to show that migalastat is not metabolised by CYP450 enzymes. Overall, the data indicate that hepatic impairment is unlikely to have a significant impact on the PK of migalastat. Nevertheless, the sponsor is requested to provide a formal justification of not submitting a dedicated hepatic impairment study.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

The submission include a dedicated PK study assessing the impact of renal impairment on the PK of migalastat in healthy subjects [Study AT1001-015]. In this study, a single-dose of migalastat HCl 150 mg was administered to 8 subjects with normal renal function (CLcr > 90 mL/min), 8 subjects with mild renal impairment (CLcr ≥ 60 to < 90 mL/min), 8 subjects with moderate renal impairment (CLCr ≥ 30 mL/min to < 60 mL/min) and 8 subjects with severe renal impairment (CLcr ≥ 15 mL to < 30 mL/min). No subjects with end stage renal disease (CLCr < 15 mL/min) were included in the study. The PK results for the 4 treatment groups are summarised below.

Table 25: Study AT1001-015 – Geometric mean (CV%) plasma PK parameters of migalastat by renal function.

PK Parameter	Units	Renal Function Group			
		Normal (N=8)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
AUC_{0-t}	(ng·hr/mL)	12306 (27.9)	14389 (31.1)	22126 (42.8)	53070 (27.0)
$AUC_{0-\infty}$	(ng·hr/mL)	12397 (27.7)	14536 (30.7)	22460 (42.2)	56154 (24.9)
C_{max}	(ng/mL)	2100 (26.0)	2191 (28.8)	1868 (32.1)	2078 (45.5)
t_{max}[a]	(hr)	2.50 (1.50, 3.00)	2.50 (1.50, 4.00)	3.00 (1.50, 4.00)	4.27 (3.00, 8.00)
$t_{\frac{1}{2}}$[b]	(hr)	6.42 (1.93)	7.66 (3.02)	22.2 (14.2)	32.3 (7.35)
λ_z	(1/hr)	0.113 (32.9)	0.0965 (40.1)	0.0386 (84.6)	0.0219 (21.2)
CL/F	(L/hr)	12.1 (27.7)	10.3 (30.7)	6.68 (42.2)	2.67 (24.9)
Vd/F	(L)	107 (38.0)	107 (37.7)	173 (102.3)	122 (43.7)
C_{48}[b]	(ng/mL)	5.70 (3.63)	9.34 (7.57)	64.5 (68.1)	334 (126)

[a] Median (Min, Max) presented for t_{max}.
[b] Arithmetic Mean (SD) is presented
Note, below the limit of quantification (BLQ) values were treated as 0 at predose and treated as missing after the last quantifiable concentration in a profile in PK analysis.

Geometric LS mean ratios (90% CIs [renal-impairment/normal]) for AUC0-t were 1.17 (0.89, 1.53), 1.80 (1.37, 2.36), and 4.31 (3.29, 5.65), respectively, for the mild, moderate, and severe renal function groups. The geometric LS mean ratios (90% CIs [renal-impairment/normal]) for Cmax were 1.04 (0.79, 1.38), 0.89 (0.67, 1.18), and 0.99 (0.75, 1.31), respectively, for the mild, moderate, and severe renal function groups.

Overall, the data indicate significantly increased systemic exposure (AUC0-t) in subjects with moderate and severe renal impairment, and notably increased concentrations at 48 hours (C48) in these subjects. The C48 data suggest that significant accumulation of migalastat is likely to

occur in patients with moderate or severe renal impairment following the proposed once every other day dosing regimen. The PK data suggest that treatment with migalastat is not recommended for patients with severe renal impairment, and that a dosage adjustment might be required for patients with moderate renal impairment.[2]

4.2.3.3. Pharmacokinetics according to age

No dedicated PK study was conducted in an elderly population. In the population PK analysis, no clinically relevant impact on exposure of migalastat was found for age.

4.2.3.4. Pharmacokinetics related to genetic factors

No dedicated studies were submitted investigating the impact of genetic factors on the PK of migalastat.

4.2.3.5. Pharmacokinetics in other special population / with other population characteristic

- **Race:** Results from the PK study in healthy Japanese subjects [MGM115806] indicated that the PK in healthy Japanese subjects were similar to the PK in healthy Caucasian subjects.
- **Gender:** The PPK analysis indicates that there is no gender effect on the PK of migalastat.
- **Weight**: The PPK analysis showed that body weight appeared to be a covariate for migalastat clearance. Patients with a low body weight are subject to a higher exposure, while patients with a large body weight are subject to lower exposure. The PPK analysis predicted a less than 2-fold average difference in exposure for body weights between 50 kg and 170 kg. This difference is not considered to be clinically significant.

4.2.4. Population pharmacokinetics (PPK)

4.2.4.1. PPP analysis ID

The submission included one PPK report [MGM116016]. The dossier included the final report prepared by GSK on 17 July 2014, and an amendment to this report prepared by Nuventra Pharma Sciences on 16 April 2015. The amended report was prepared at the request of the sponsor to ensure that the PPK analyses were performed on the final dataset.

Objectives

The objectives of the PPK analysis were: (1) to develop a PPK model that characterised the disposition of migalastat following oral administration; (2) to evaluate the potential effect of selected patient covariates on the PK of migalastat; and (3) to estimate individual patient PK and exposure parameters for subsequent exposure-response analysis for the Phase III *Study AT1001-011*.

PPK pooled studies

The data for the PPK analysis were obtained from 13 Phase I, 2, and 3 studies of migalastat HCl administered orally using a range of doses (unit dose no more than 675 mg of migalastat HCl) and several dosing schedules (QD, BD, QOD, and Q4D) under fasting condition. The 13 studies in the PPK analysis included pooled data from 8 healthy volunteer studies [FAB-CL-101, FAB-CL-102, FAB-CL-103, FAB-CL-104, AT1001-010, AT1001-014, AT1001-016, and MGM115806], 1 renal impairment study [AT1001-015], and 4 studies in subjects with Fabry disease [FAB-CL-201, FAB-CL-204, FAB-CL-205, AT1001-011].

PPK population

The PPK analysis included pooled data from 260 subjects (179 healthy subjects, 81 patients with Fabry disease), with 4447 observations. The median age of the 260 subjects was 36 years

[2] When the evaluation was completed, a recommendation for dosage adjustment in patients with moderate renal impairment was not required.

(range: 16, 74 years), 91 (35%) were female and 169 (65%) were male, 204 (78.5%) were White, 25 (9.6%) were Black, 24 (9.2%) were Asian, and 7 (2.7%) were Other. The median weight of the 260 subjects was 74.0 kg (range: 38, 141) and the median BMI was 25 kg/m^2 (range: 16.3, 51.8 kg/m^2).

Methodology

The PPK analyses was performed in NONMEM (version VII or higher) using the ADVAN4 subroutine and FOCE-I method. Model evaluation was conducted by examination of NONMEM model fitting logs, assessment on model parameter estimates and variances, visual assessment of diagnostic plots. In addition, further model assessments were also conducted using bootstraps and visual predictive checks. Simulation of individual Fabry patient PK profiles and derivation of PK exposure parameters were conducted.

A base PPK model was first developed. This was followed by development of an interim PPK model with covariates incorporated based on data available at that time. A final PPK model (GSK model) was validated in early 2014 based on the data available at that time (prior to the database lock for the pivotal Phase III *Study AT1001-011*). Following release of the database lock for *Study AT1001-011* the sponsor requested Nuventra to develop a final NONMEM dataset for migalastat using confirmed datasets after the database lock and rerun the GSK models. The final PPK model was refined by Nuventra in March 2015 to optimise the model developed by GSK and minimise bias.

In summary, the Nuventra analysis was undertaken: (1) to confirm that the selection of eGFR on apparent oral clearance (CLT/F), body weight on CLT/F, body weight on the apparent oral volume of distribution for the central compartment (V2/F), and Fabry disease on V2/F were able to adequately characterise the plasma concentration-time data from the final dataset; (2) to compare parameter estimates for the model between the GSK and Nuventra NONMEM datasets; and (3) to simulate $AUC_{0\text{-}48}$, C_{max} and C_{48} in Fabry patients receiving migalastat 150 mg every other day at steady-state.

Development of the PPK model

The development of the base PPK model consisted of three main steps. First, the structural model was developed from a two-compartment model with a depot absorption compartment. Estimation of lag-time was also considered. Second, various absorption models were considered since the first order absorption model was unable to estimate C_{max} appropriately. It was found that an absorption function with the absorption rate constant linearly dependent on the time after dosing was able to capture the C_{max}, and was retained in the base model. Third, baseline renal function and body size were included in the base model as it was realised early in PPK modelling that body size and renal function status had significant effects on the plasma PK of migalastat. Based on assessment of model performance, renal function based on baseline eGFR rather than baseline CrCl and body size based on weight (WT) rather than body surface area (BSA) were chosen for the base model.

Covariate modelling was then undertaken, with additional covariate-parameter relationships being explored by inspection of the plots of individual random effects against covariates for clearance (CL), volume of distribution for the central compartment (V2), and the absorption rate (Ka) intercept and the slope. The categorical covariates of interest were sex (male, female), race (white black, Asian, other) ethnicity (Hispanic, non-Hispanic, unknown/not recorded), formulation (solution, capsule 25 mg, capsule 150 mg), Fabry disease status (Fabry disease, healthy subject), administration (single-dose, QD, QOD, Q4D), and the continuous covariates of interest were age, alanine transferase (ALT) level (IU/L), aspartate transferase (AST) level (IU/L), alkaline phosphatase (ALP) level (IU/L), and total bilirubin (TBIL) level (μmol/L).

Each covariate of interest was tested one at a time on each parameter of interest (i.e., CL, V2, Ka intercept, Ka slope). Based on the drop in objective function value (OFV), each covariate was then included in the model in a stepwise fashion. The criterion for the forward inclusion was set

to p-value less than 0.01 and the criterion for the backward elimination was set to p-value greater than 0.001. Relative to the base model, the stepwise covariate search resulted in only one additional statistically significant covariate of Fabry status (i.e., Fabry disease versus healthy subject). Fabry status was statistically significant on the volume of distribution for the central compartment (V2).

The model at this point was considered the interim model. In early 2014, the final PPK dataset was created for the final PPK modelling (GSK) and simulations, utilising the interim PPK model developed from the interim PPK dataset.

The final PPK model

The summary of the parameter estimates from the final Nuventra PPK model are provided below.

Table 26: PPK Analysis – Final Nuventra PPK model parameter estimates with bootstrapped 95% confidence intervals.

	NONMEM	Bootstrap	
Parameter	Estimate (%RSE)	Estimate (%RSE)	95% Confidence Interval
CL_1/F (L/h)	17.1 (0.153%)	17.0 (2.70%)	11.77-22.36
V_2/F (L)	63.6 (0.053%)	63.5 (2.87%)	58.00-69.24
Q/F (L/h)	0.95 (0.052%)	0.949 (0.046%)	0.855 to 1.035
V_3/F (L)	25.7 (0.108%)	25.7 (2.87%)	20.09 to 31.33
K_a (intercept) (h^{-1})	0.26 (0.091%)	0.256 (0.024%)	0.210 to 0.302
K_a (slope)	0.27 (0.089%)	0.270 (0.022%)	0.229 to 0.314
Lag time (h)	0.18 (0.047%)	0.177 (0.008%)	0.161 to 0.192
EGFR-related CL_1/F	0.95 (0.054%)	0.947 (0.050%)	0.849 to 1.043
WT-related CL_1/F	0.44 (0.216%)	0.448 (0.098%)	0.250 to 0.633
WT-related V_2/F	0.65 (0.173%)	0.655 (0.112%)	0.432 to 0.870
Fractional Change in V_2/F related to Fabry disease	-0.28 (0.146%)	-0.274 (0.037%)	-0.347 to -0.204
CL_1/F for those with EGFR>120 mL/min/1.73 m^2	18.6 (0.164%)	18.5 (3.19%)	12.31 to 24.81
Fractional Change in CL_1/F related to Fabry disease	-0.16 (0.243%)	-0.161 (0.036%)	-0.231 to -0.09
IIV on CL_1/F	54.8%	30.1%	26.9% to 33.6%
IIV on V_2/F	57.5%	29.2%	25.4% to 33.0%
IIV on K_a (slope)	92.2%	33.2%	29.1% to 37.1%
IIV on K_a (intercept)	77.5%	59.9%	45.2% to 72.4%
Residual (unexplained) Variability			
Proportional Component (%)	51.0%	25.6	23.9% to 27.2%
Additive Component (ng/mL)	2.85	8.03	7.53 to 8.54

The conclusions from the Nuventra PPK analyses are:

- A two-compartment PPK model with linear time-dependent absorption sufficiently characterised the PK of migalastat in plasma after oral administration.
- Renal function is the most important determinant of variability in the exposure of migalastat, with an average 3-fold range in exposure occurring for eGFR values between 30 and 120 mL/min/1.73 m^2 (i.e., subjects with low eGFR values have higher exposures than subjects with high eGFR values).
- Weight is the second largest determinant of variability in exposure of migalastat, with a less than 2-fold average difference in exposure for body weights between 50 and 170 kg (i.e., subjects with low body weight have higher exposures than subjects with high body weight)
- The predicted exposures in Fabry disease [Study AT1001-011] were similar to the exposures reported for healthy volunteers [Study AT1001-010], but the t1/2 was notable longer in subjects with Fabry disease than in healthy volunteers. The following pharmacokinetic parameters were calculated using the predicted concentration-time data from subjects in studies *AT1001-010, AT1001-011*, and *FAB-CL-205* with the final Nuventra NONMEM model: (1) AUC0-∞ , Cmax, tmax, and t1/2 after a single dose in healthy volunteers in Study AT1001-010; and (2) Cmax, tmax, AUC0-48, t1/2 and C48 in Fabry patients receiving migalastat 150 mg once every other day at steady-state.

Table 27: PPK Report – Predicted parameters in healthy volunteers from Study AT1001-010 (n = 51).

	Cmax (ng/mL)	AUCinf (hŸng/mL)	tmax (h)	t1/2 (h)
Mean	1582	9975	-	3.65
Median (range)	1583 (769, 2560)	9982 (4508, 14915)	2.68 (2.18, 4.18)	3.64 (2.98, 4.55)

Table 28: PPK Report – Predicted parameters in Subjects with Fabry Disease AT1001-011(n = 62).

	Cmax (ng/mL)	AUC0-48 (hŸng/mL)	Tmax (h)	C48 (ng/mL)	t1/2 (h)
Mean	1239	9580	-	10.1	20.6
Median (range)	1186 (503, 2538)	8615 (3518, 23611)	3 (2, 4.5)	7.31 (1.07, 58.6)	20.7 (19.0, 23.5)

Comment: The predicted t1/2 in subjects with Fabry's disease [Study AT1001-010] was notably longer compared to healthy volunteers [Study AT1001-010]. The sponsor is requested to comment on this observation in the s31 first round response.

4.2.5. Pharmacokinetic interactions

4.2.5.1. In vitro findings

In vitro data on the metabolism of migalastat and the potential for drug-drug interactions were provided. The reported results of the *in vitro studies* are summarised below.

- Migalastat was reported not to be metabolised *in vitro* by CYP450 isoenzymes in human hepatocytes at migalastat concentrations of 1 and 100 µM [^{14}C]-migalastat [study 0322-145-01]. Migalastat was reported not to cause significant *in vitro* inhibition of individual CYP450 isoenzymes in human liver microsomes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) [study XT115084], or induce CYP1A2 or CYP3A4 [study XBL07624], or CYP2B6 [study XBL15798] in human hepatocytes. These results suggest that migalastat is unlikely to be involved in any clinically relevant drug-drug interactions involving CYP450 inducers, inhibitors or substrates.
- Bi-directional permeability studies *in vitro* using monolayer cultures of Caco-2 cells expressing the human multidrug resistance P-glycoprotein (P-gp) were reported to show no significant interaction between migalastat and P-gp mediated transporters [study 7AMICP1; study 9AMICP2]. The results indicated that migalastat is not a substrate for P-gp.
- Migalastat was reported not to inhibit BCRP, MDR1, or BSEP human efflux (ABC) transporters, or OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K human uptake transporters [study Amicus-01-02Dec2014]. In addition, it was reported that migalastat is not a substrate for BCRP, MDR1, MATE1, MATE2-K, OAT1, OAT3, or OCT2 transporters [study Amicus-02-28Apr2015; study Amicus-04-03Nov2015].
- Migalastat was reported to be a low affinity substrate for, and inhibitor of, the sodium glucose co-transporters SGLT1 and SGLT2 that control intestinal glucose absorption [SGLT1 - studies 2011N125700_00 and 2011N125739_00; SGLT2 – studies OPT-2015-091 and 2.6.5.21, OPT-2015-090].

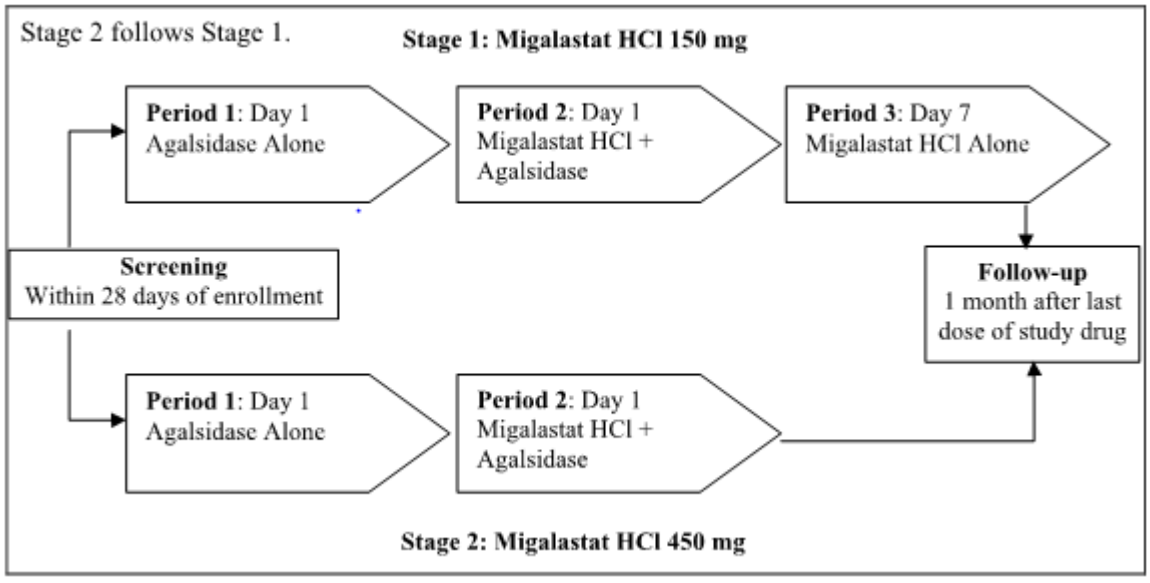
4.2.5.2. In vivo findings

Study AT1001-013

There were no PK drug-drug interactions studies in healthy subjects. There was one PK drug-drug interaction study in adult male patients with Fabry disease involving co-administration of migalastat HCl oral capsules with agalsidase administered by IV infusion [Study AT1001-013]. The *primary objectives* of this study were: (1) to characterise the effects of 150 mg and 450 mg of migalastat HCL administered 2 hours before administration of agalsidase on the safety and plasma PK of agalsidase in subjects with Fabry disease; and (2) to characterise the effect of agalsidase on the safety and plasma PK of 150 mg of migalastat HCl administered 2 hours before administration of agalsidase in subjects with Fabry disease. The *secondary objectives* were to characterise the effects of 150 mg and 450 mg migalastat HCl on the distribution of α–Gal A to skin after administration of agalsidase.

The study was conducted in 2 stages, and these are summarised schematically below. Two dose levels of migalastat HCl (150 mg and 450 mg) were selected to evaluate interaction with each of 3 doses of recombinant agalsidase (0.5 mg/kg agalsidase beta, 1.0 mg/kg agalsidase beta, and 0.2 mg/kg agalsidase alfa). Agalsidase alfa was administered as a 40-minute infusion, and agalsidase beta was administered as a 2-hour infusion.

Figure 6: AT1001-013 – Study design for assessment of drug-drug interaction.



The treatment schedules for the 2 stages are summarised below.

Table 29: AT1001-013 – Treatment schedules for assessment of drug-drug interaction.

	Stage 1	Stage 2
Period 1	Intravenous infusion of 0.2 mg/kg agalsidase alfa, or 0.5 mg/kg or 1.0 mg/kg agalsidase beta	Intravenous infusion of 0.2 mg/kg agalsidase alfa, or 0.5 mg/kg or 1.0 mg/kg agalsidase beta
Period 2	A single 150 mg oral dose (1 capsule) of migalastat HCl 2 hours before initiation of an IV infusion of 0.2 mg/kg agalsidase alfa or 0.5 mg/kg or 1.0 mg/kg agalsidase beta	A single 450 mg oral dose (3 × 150-mg capsules) of migalastat HCl 2 hours before initiation of an IV infusion of 0.2 mg/kg agalsidase alfa or 0.5 mg/kg or 1.0 mg/kg agalsidase beta
Period 3	A single 150 mg oral dose (1 capsule) of migalastat HCl	—

Agalsidase plasma PK parameters measured by α-Gal A enzyme activity (primary PK endpoint): Agalsidase plasma PK parameter values measured by active α–Gal A levels (α-Gal A enzyme

activity) was a primary PK endpoint. The results for the agalsidase plasma PK parameters following agalsidase IV infusion alone and in combination with oral migalastat HCl are summarised below. Overall, the greatest relative increases in α-Gal A activity AUCinf were observed following co-administration of migalastat HCl with agalsidase alfa. Single oral doses of 150 mg and 450 mg migalastat HCl administered in combination with agalsidase increased systemic exposures to agalsidase over the dose range 0.2 mg/kg to 1.0 mg/kg. This effect was greater at lower doses of agalsidase than at higher doses, with the largest mean increase (4.1-fold) occurring at the lowest dose of agalsidase (0.2 mg/kg co-administered with 150 mg migalastat HCl), and the smallest mean increase (2.0-fold) occurring at the highest dose of agalsidase (1.0 mg/kg agalsidase co-administered with either 150 mg or 450 mg migalastat HCl). The average relative increase in α-Gal A activity AUCinf following dosing with agalsidase (either alfa or beta) with co-administration of 150 mg migalastat HCl was 2.9-fold and with co-administration of 450 mg migalastat HCl, was 2.4-fold. The results indicate that the magnitude of the increase in α-Gal A activity was not correlated with migalastat HCl dose.

Table 30: AT1001-013 – Summary of active α-Gal A PK parameters by treatment, PK population.

Treatment Group	C_{max}[a] (nmol/hr/mL)	t_{max}[b] (hr)	$AUC_{infinity}$[a] (hr*nmol/hr/mL)	$t_{1/2}$[c] (hr)	AUC Ratio[a]
0.2 mg/kg agalsidase alfa alone (N = 4)	299.52 (29.08)	0.66 (0.7;1.0)	381.48 (21.56)	4.48 (3.132)	
0.2 mg/kg agalsidase alfa + 150 mg migalastat HCl (N = 4)	511.09 (14.88)	0.66 (0.7;1.0)	1583.90 (28.01)	4.27 (1.536)	4.15 (20.15)
0.2 mg/kg agalsidase alfa alone (N = 4)	358.10 (31.37)	0.66 (0.7;1.0)	672.01 (79.59)	5.15 (3.645)	
0.2 mg/kg agalsidase alfa + 450 mg migalastat HCl (N = 4)	605.20 (25.81)	0.66 (0.7;1.0)	2108.57 (46.69)	5.31 (2.462)	3.14 (38.24)
0.5 mg/kg agalsidase beta alone (N = 5)	508.55 (16.52)	2.00 (2.0;2.3)	1128.90 (19.56)	3.91 (2.054)	
0.5 mg/kg agalsidase beta + 150 mg migalastat HCl (N = 5)	877.31 (25.17)	2.00 (2.0;3.0)	3191.54 (27.48)	3.51 (1.304)	2.83 (30.94)
1.0 mg/kg agalsidase beta alone (N = 3)	1645.96 (26.63)	2.00 (1.5;3.0)	4765.43 (26.26)	5.33 (4.082)	
1.0 mg/kg agalsidase beta + 150 mg migalastat HCl (N = 3)	2291.63 (37.92)	2.22 (2.0;3.0)	9464.36 (30.60)	4.30 (1.712)	1.99 (16.85)
0.5 mg/kg agalsidase beta alone (N = 1)	684.36	3.00	2523.87	6.50	
0.5 mg/kg agalsidase beta + 450 mg migalastat HCl (N = 1)	1351.18	3.00	6197.71	3.49	2.46
1.0 mg/kg agalsidase beta alone (N = 6)	1655.35 (44.44)	2.25 (2.0;4.0)	4931.07 (65.14)	3.11 (1.875)	
1.0 mg/kg agalsidase beta + 450 mg migalastat HCl (N = 6)	2315.55 (31.39)	2.25 (2.0;4.0)	9676.48 (42.94)	4.96 (1.532)	1.96 (53.36)

Abbreviations: α–Gal A = α–galactosidase A; AUC = area under the plasma concentration versus time curve; $AUC_{infinity}$ = area under the plasma concentration versus time curve extrapolated from time 0 to infinity; C_{max} = maximum observed plasma concentration; HCl = hydrochloride; PK = pharmacokinetic; t_{max} = time to maximum observed plasma concentration; $t_{1/2}$ = terminal elimination half-life

[a] Geometric mean (% Coefficient of variation of geometric mean)

[b] Median (Range)

[c] Arithmetic Mean (Standard deviation)

Total α–Gal A protein level: Total α–Gal A protein level was a primary PK endpoint. Unlike the consistent increases observed in plasma α-Gal A enzyme activity with co-administration of migalastat HCl, the co-administration of migalastat HCl with 0.2 mg/kg agalsidase alfa or 0.5 mg/kg or 1.0 mg/kg agalsidase beta had no statistically significant effects on circulating plasma total α-Gal A protein levels, based on AUC0-t and Cmax ratios of geometric point estimates for total α-Gal A protein levels. However, when migalastat HCl was co-administered with 1.0 mg/kg agalsidase beta, the data suggested a dose-dependent trend for migalastat HCl toward increases in circulating plasma total α-Gal A protein levels: i.e., total α-Gal A protein AUC0-t increased by 1.2-fold (90% CI: 0.883, 1.723) following co-administration with 150 mg migalastat HCl relative to 1.0 mg/kg agalsidase beta alone agalsidase beta alone, and by 1.5-fold (90% CI: 1.007, 2.126) following co-administration with 450 mg migalastat HCl relative to 1.0 mg/kg agalsidase beta alone.

Migalastat plasma PK: The plasma migalastat PK parameters of migalastat by treatment are summarised below. The geometric mean AUC0-t for 150 mg migalastat HCl plus agalsidase relative to the geometric mean AUC0-t form150 mg migalastat HCl alone (AUC Frel) was 1.06 (90% CI: 0.81, 1.37). The results indicate that co-administration of migalastat 150 mg HCl and agalsidase has no the significant effect on migalastat exposure relative to administration of migalastat HCl 150 mg alone. The plasma PK of migalastat following oral administration of 450 mg was approximately dose proportional to the 150 mg dose (geometric mean ratio [450 mg/150 mg] AUC Frel = 2.57).

Table 31: AT1001-103 – Summary of plasma migalastat PK parameters by treatment, PK population.

Treatment Group	C_{max}[a] (ng/mL)	t_{max}[b] (hr)	AUC_{0-t}[a] (hr*ng/mL)	$AUC_{infinity}$[a] (hr*ng/mL)	AUC F_{rel}	$t_{1/2}$[c] (hr)
150 mg migalastat HCl + Agalsidase (N = 12)	1625.99 (35.78)	3.04 (2.0;4.4)	13104.50 (40.00)	13520.99 (41.23)	1.06 (31.70)[d]	5.11 (0.845)
150 mg migalastat HCl Alone (N = 12)	1630.11 (32.25)	3.00 (2.0;4.0)	12371.21 (36.19)	12858.27 (37.15)	-	5.08 (0.874)
450 mg migalastat HCl + Agalsidase (N = 11)	3935.34 (30.82)	4.00 (2.0;6.0)	31846.98 (34.50)	33101.26 (35.07)	2.57[e]	4.85 (1.244)

Abbreviations: AUC_{0-t} = area under the plasma concentration versus time curve to t_{last} (last time point at which concentration is quantified); AUC F_{rel} = ratio of relative exposure (eg, AUC_{0-t} following combination therapy to AUC_{0-t} following migalastat HCl alone); $AUC_{infinity}$ = area under the plasma concentration versus time curve extrapolated from time 0 to infinity; C_{max} = maximum observed plasma concentration; HCl = hydrochloride; PK = pharmacokinetic; t_{max} = time to maximum observed plasma concentration; $t_{1/2}$ = terminal elimination half-life

[a] Geometric mean (% Coefficient of variation of geometric mean)

[b] Median (Range)

[c] Arithmetic Mean (Standard deviation)

[d] Geometric mean AUC_{0-t} for 150 mg migalastat HCl + agalsidase/ geometric mean AUC_{0-t} for 150 mg migalastat HCl alone

[e] Geometric mean AUC_{0-t} for 450 mg migalastat HCl + agalsidase/ geometric mean AUC_{0-t} for 150 mg migalastat HCl alone

Effect of migalastat on distribution to skin (secondary endpoint): Following co-administration of agalsidase with 150 mg or 450 mg migalastat HCl, levels of active α-Gal A enzyme in Day 2 skin biopsies demonstrated consistent increases relative to agalsidase alone (19 out of 23 Fabry subjects, 82.6%). Relative to agalsidase alone, increases in active α-Gal A levels in skin following co-administration with migalastat HCl appeared to be migalastat HCl dose-dependent for the 0.2 mg/kg and 0.5 mg/kg agalsidase groups. Relative to baseline, increases in active α-Gal A levels in skin were generally agalsidase dose-dependent.

4.2.6. Clinical implications of *in vitro* findings

The *in vitro* drug-drug interaction findings suggest that migalastat HCl is unlikely to undergo significant PK interactions with co-administered medicines.

4.3. Evaluator's conclusions on pharmacokinetics

4.3.1. 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.

4.3.2. Absorption

The sponsor reports that migalastat HCl is categorised as a BCS Class III compound (i.e., 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 tmax values being approximately 3 hours in the fasted state [studies AT1000-016 and AT1001-018]). Geometric mean AUCinf values were approximately 9800 to 9900 ng·h/mL and geometric

mean Cmax 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 AUC_{inf} 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.

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 AT1001-016. 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. 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.[3]

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].

4.3.3. 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 (i.e. 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 [AT1001-103].

4.3.4. Metabolism

Metabolism is a minor route of clearance for migalastat. I*n 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 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.

4.3.5. 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

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

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).

4.3.6. 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 AUC0-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 (C48) 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 (i.e., 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.[4]

4.3.7. 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.[5]

4.3.8. 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.

4.3.9. 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.

4.3.10. 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 [MGM116016].

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

4.3.11. Race

The PK healthy Japanese subjects [study MGM115806] were similar to the PK of healthy Caucasian subjects.

4.3.12. 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 [MGM116016], which suggests that dosage adjustments based on weight are not required.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

The primary pharmacodynamics (PD) of migalastat were investigated in 5 Phase II studies in 28 subjects with Fabry disease (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 32: 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 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).

Study ID	N	Primary PD Outcome Variables
		• 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.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Migalastat (a low molecular weight iminosugar) is an analogue of the terminal galactose of GL-3. Nonclinical studies have been reported to demonstrate that migalastat acts as a pharmacological chaperone, selectively and reversibly binding with high affinity to the active site of wild-type α-Gal A and specific mutant forms of α-Gal A (amenable mutations). Migalastat binding is reported to stabilise the 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 GL-3 and plasma lyso-Gb3 levels. The sponsor reports that approximately 30% to 50% of patients with Fabry disease have amenable *GLA* mutations, and that the majority of amenable *GLA* mutations are associated with the classic phenotype of the disease. Based on the mechanism of action, it can be anticipated that the primary PD effects of migalastat will be to increase α-Gal A activity in leucocytes and skin and reduce GL-3 levels in plasma, urine, skin and kidneys. These biochemical changes are likely to be associated with functional cardiac, renal and neurological improvements in patients with Fabry disease.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The primary PD effects of migalastat were evaluated in five Phase II PD studies in 27 subjects (18 male, 9 female) with Fabry disease. In general, the primary PD outcome variables in the Phase II studies were secondary and/or exploratory objectives with the primary objectives of the studies being safety and tolerability.

Subjects from four Phase II studies (FAB-CL-201, FAB-CL-202, FAB-CL-204, FAB-CL-203) could continue treatment with migalastat in the Phase II extension study FAB-CL-205. The 27 male and female subjects with Fabry disease included in the PD studies were between 18 and 65 years (inclusive). The male subjects were required to be hemizygous for Fabry disease, while the female patients were required to be heterozygous for the condition. In all subjects, Fabry disease was required to have been confirmed with a documented missense gene mutation (individual or familial).

All Fabry disease patients in the Phase II studies were permitted to have been either previously untreated (i.e., ERT-naive; substrate depletion) or previously treated with ERT. Patients who had been previously treated with ERT underwent a 'wash-out period' (21 to 274 days) prior to starting migalastat. In each of the Phase II studies, subjects were required to have at least minimal or mild disease involving cardiac, renal and/or neurological function.

In the three Phase II studies FAB-CL-201, FAB-CL-202, and FAB-CL-204, prior to protocol amendments subjects were required to have residual α-Gal A activity in lymphocytes of greater than or equal to 3% of normal, with a greater than or equal to 20% increase in activity following incubation with migalastat. However, following protocol amendments all four Phase II studies (FAB-CL-201, FAB-CL-202, FAB-CL-204, FAB-CL-203) required both male and female subjects to have enhanceable (i.e., responsive) α-Gal A enzyme activity in lymphocytes after incubation with migalastat meeting one of the following criteria:

- if residual α-Gal A activity in lymphocytes was less than 1% of normal, then α-Gal A activity after incubation with migalastat was required to be at least 2% of normal;
- if residual α-Gal A activity in lymphocytes was between 1% of normal and less than 3% of normal, then α-Gal A activity after incubation with migalastat was required to be at least 2 times the baseline level;
- if residual α-Gal A activity in lymphocytes was between 3% of normal and less than 10% of normal, then α-Gal A activity after incubation with migalastat was required to be at least 1.3 times the baseline level; or
- if residual α-Gal A activity in lymphocytes was greater or equal to 10% of normal, then α-Gal A activity after incubation with migalastat was required to be at least 3% of normal higher than the baseline level.

Separately from the Phase II study protocols, the sponsor developed an *in vitro* human embryonic kidney (HEK) cell based assay to identify amenable (responsive) mutant forms of α-Gal A that were expected to respond to migalastat *in vivo*. The HEK cell based criteria for amenability took in to account the magnitude of the mutant α-Gal A response to 10 μM migalastat. The concentration of 10 μM was selected because it was the approximate average maximum plasma concentration (C_{max}) measured in humans following a single oral migalastat dose of 150 mg. A minimum magnitude of response (i.e., ≥ 1.2-fold above baseline and an absolute increase ≥ 3% of wild-type α-Gal A) was specified to favour mutant forms α-Gal A that show substantial increases in activity after incubation with migalastat. It was hypothesised that the mutant forms of α-Gal A meeting the *in vitro* criteria would be responsive to migalastat *in vivo*. The sponsor also noted data from the literature indicating that increases of 1% to 5% of wild-type α-Gal A activity *in vivo* are clinically meaningful for the treatment of Fabry disease.

The sponsor compared the mutant α-Gal A responses observed in the HEK cell based assay to the peripheral blood mononuclear cell (PBMC) α-Gal A responses in male subjects from the Phase II studies (representing 19 mutant forms) using several different sets of criteria with varying specified values for a minimum magnitude of response (e.g., ≥ 1.2-, 1.5-, 1.6-, 1.7-, or 1.8-fold above baseline and an absolute increase that is 3%, 4%, or 5% of wild-type α-Gal A). The total number of mutant forms that met these different criteria was calculated based on the entire HEK cell dataset representing more than 300 mutant forms available at the time the criteria were being developed. The two values (1.2-fold and 3% of wild-type α-Gal A) chosen as criteria for amenability showed the highest sensitivity and specificity of the HEK cell based results compared to PBMC α-Gal A responses in male subjects from the Phase II studies (sensitivity=1, specificity=0.88). Therefore, the criteria for amenability based on the HEK cell based assay were that the responsive mutant form of α-Gal A at 10 μM migalastat must show a relative increase in α-Gal A activity that is ≥ 1.2-fold above baseline and an absolute increase that is ≥ 3% of wild-type. For mutant forms with a baseline α-Gal A activity that is below the limit of detection, this criterion is met if the α-Gal A activity at 10 μM migalastat is ≥ 3% of wild-type.

Results of the Phase II PD studies

The Phase II PD studies assessed biochemical changes (α-Gal A activity, urine GL-3 levels), renal histological changes (interstitial cell GL-3) and functional changes (cardiac, renal, neurological) from baseline following treatment with migalastat. In the five Phase II studies, a range of migalastat doses and treatment regimens were explored: i.e., BD (25, 100, 250 mg); per day (50 mg); QOD (50, 150, 250 mg); and 3 days on-4 days off (250, 500 mg). In these studies, 150 mg migalastat QOD resulted in the best balance of substrate reduction (urine GL-3) and safety in subjects with amenable mutations, compared to the other doses and regimens studied. Treatment with 150 mg QOD also resulted in decreases in kidney interstitial capillary GL-3 levels 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 doses, at other intervals (250/500 mg 3 days on-4 days off), no further increases in WBC α-Gal A activity or reductions in urine GL-3 were observed. Additionally, a higher rate of treatment-related AEs was observed at the 250 mg and 500 mg doses. Clinically meaningful improvements in baseline functional abnormalities associated with Fabry disease were not observed in the Phase II PD studies. The key PD results for the five Phase II studies are reviewed below.

Study FAB-CL-201

Study FAB-CL-201 was a Phase II dose-escalation trial in which 9 adult male subjects with Fabry disease each received oral migalastat 25 mg BD, 100 mg BD, and 250 mg BD for 2 weeks. At the end of the 6 weeks dose-escalation phase, subjects received 25 mg migalastat BD for a further 6 weeks. At the completion of the initial 12-week treatment period, subjects could enter an optional extension phase during which they received 50 mg QD through to Week 96. The 9 subjects who were enrolled before protocol amendment 3 were referred to as the eligible-enrolled subjects. These 9 subjects were required to meet the initial criteria for enhanceable α-Gal A enzyme activity referred to above, and provided PD data for migalastat. The study also included 6 subjects who were enrolled after protocol amendment 3 and were referred to as the dosed screen failures. These 6 subjects received migalastat 150 mg QD for 2 weeks during the screening period and failed to demonstrate enhanced α-Gal A enzyme activity after treatment. These 6 dosed screen failures did not proceed to the treatment phase of the study and provided no PD data. The outcomes for the key biochemical PD parameters for the 9 eligible-enrolled subjects are summarised below.

Table 33: FAB-GL-201 – Selected key PD parameters at baseline and end of study (Week 96) or earlier if no end of study data were available; all eligible-enrolled male patients with Fabry disease.

All Male	Dose mg	Migalastat Amenable HEK assay	Previous ERT (last dose days)	α-Gal A leucocyte Baseline	α-Gal A leucocyte Week 96	Urine GL-3 Baseline	Urine GL-3 Week 96	Kidney IC GL-3 Baseline	Kidney IC GL-3 Week 96
	Esc	Yes	No	5.2	20.3	66.5	52.1	-	-
	Esc	Yes	No	4.7	22.8	49.4	39.4	-	-
	Esc	Yes	No	6.6	20.3	64.1	68.3	-	-
	25 BD	Yes	No	10.7	15.9 [W2]	75.5	69.4 [W2]	-	-
	Esc	Yes	No	0.1	0.8 [W24]	4091.0	1290.8 [W24]	-	-
	Esc	Yes	Yes (32)	1.0	12.8	159.0	131.6	-	-
	Esc	Yes	Yes (45)	0.9	1.9	851.9	2266.5	-	-
	Esc	Yes	Yes (69)	0.0	0.1 [W24]	2212.3	1435.0 [W24]	-	-
	Esc	Yes	Yes (21)	0.2	0.2	457.7	2160.8	-	-

Note: α-Gal A leucocyte activity = α-galactosidase A leucocyte activity (nmol 4-MU/hr/mg protein); Urine GL-3 = globotriaosylceramide (total urine [sum of 5 isoforms of GL-3 measured] pmol/nmol PC [phosphatidylcholine]); Kidney IC GL-3 = Kidney interstitial cells (IC) GL-3 (histological quantitative measurement by Barisoni method), not measured since patients in this study did not have renal biopsies. Dose = Esc (escalation regimen). Previous ERT - If yes, days since last dose provided in brackets. If no data available for Week 96, then results for week of with last available data provided [W]. Subject 01-05 discontinued in the first 2 weeks of the study due to hypertension. Subjects 02-05 and 02-04 withdrew consent after 36 and 41 total weeks of treatment, respectively, due to worsening clinical condition.

Comment: Data presented by the sponsor showed that mean (± SD) α-Gal A activity in healthy adult males (n = 29) is 22±5.7 nmol 4-MU/hr/mg protein activity. Based on baseline α-Gal A activity in study FAB-CL-201, eligible-enrolled subjects appeared to be divided into two subgroups, one with a baseline average of approximately 25% of normal activity, and one with a baseline average of approximately 5% of normal activity. Despite these varying levels of baseline α-Gal A activity, all subjects had increases in α-Gal A activity while taking migalastat. At Week 96, leukocyte α-Gal A activity ranged from 0.2 to 22.8 nmol 4-MU/hr/mg protein, which was well above baseline levels for 4 of the 6 subjects with paired Baseline and Week 96 data.

For urine GL-3, the data presented represents the total of the five GL-3 isoforms that were detected. In normal controls the mean ± SD total urine GL-3 was 48.6 ± 13.0 pmol/nmol PC, as measured in 29 healthy male volunteers. Subjects in this study had baseline urine GL-3 levels higher than the average level in healthy volunteers, with 5 of the 9 subjects having baseline levels that were considerably higher than average levels. There were no consistent changes in urine GL-3 levels during treatment with migalastat.

Study FAB-CL-202

Study FAB-CL-202 was a Phase II open-label trial in 4 adult patients with Fabry disease. The study included an initial 12-week treatment period and a 36-week optional extension treatment period. All subjects were treated with migalastat HCL 150 mg QD. The outcomes for selected biochemical PD parameters for the 4 subjects are summarised below.

Table 34: FAB-GL-202 – Key PD parameters at baseline and end of study (Week 48) or earlier if no end of study data were available; all male patients with Fabry disease.

All Male	Dose mg QOD	Migalastat Amenable HEK assay	Previous ERT (last dose days)	α-Gal A leucocyte Baseline	α-Gal A leucocyte Week 48	Urine GL-3 Baseline	Urine GL-3 Week 48	Kidney IC GL-3 Baseline	Kidney IC GL-3 Week 48
	150 mg	N	-	0.14	0.12	2098.9	4050.4	2.3	6.2 [W12]
	150 mg	Y	N	0.24	2.3 [W12]	2935.0	1162.0 [W12]	5.9	0.3 [W12]
	150 mg	Y	N	0.21	BLQ [W36]	2355.6	928.6 [W36]	2.9	None available
	150 mg	Y	N	0.3	6.06	336.2	182.3	0.3	0.3

Note: α-Gal A leucocyte activity = α-galactosidase A leucocyte activity (nmol 4-MU/hr/mg protein); Urine GL-3 = globotriaosylceramide (total urine [sum of 5 isoforms of GL-3 measured] pmol/nmol PC [phosphatidylcholine]); Kidney IC GL-3 = Kidney interstitial cells (IC) GL-3 (histological quantitative measurement by Barisoni method). Previous ERT - If yes, days since last dose provided in brackets. If no data available for Week 48, then results for week of with last available data provided [W]. Subject 01-03 was discontinued for low compliance and did not complete his Week 24 visit. Subject 01-04 discontinued study drug before Week 48 assessment due to drug supply issue.

Comment: The average leucocyte α-Gal A activity in the 4 males in this study was about 1% of normal, based on mean ± SD of 22±5.7 nmol 4-MU/hr/mg protein activity in healthy adult males (n = 29). At Weeks 4, 8, and 12, the 3 subjects with an amenable α-Gal A mutant form based on the HEK assay each showed several fold increases in α-Gal A activity (ranging from 7 to 25 fold). At Week 48, leucocyte α-Gal A activity was markedly greater than at baseline for subject 02-02, who had an amenable α-Gal A mutant form based on the HEK assay, while leucocyte α-Gal A activity was unchanged from baseline for subject 01-02, who had a non-amenable α-Gal A mutant form based on the HEK assay. For subject 02-02, an increase in leucocyte α-Gal A activity was apparent at every visit from Week 4 through Week 48, while for subject 01-02 leucocyte α-Gal A activity remained essentially unchanged at every visit from Week 4 through Week 48.

For urine GL-3, the data presented represents the total of the five GL-3 isoforms that were detected; one additional isoform was measured but not detected in any sample. All values are normalised to the amount of phosphatidylcholine (PC) measured in the same sample. The normal (mean ± SD) value provided by the sponsor for healthy male volunteers was 48.6 ± 13.0 pmol/nmol PC, with a reference range of 22.6 to 74.6 pmol/nmol PC. Subjects in the study had baseline

levels that were 4.5 to 39 times greater than the upper limit of the normal reference range. At Weeks 4, 8, and 12, following treatment with migalastat, decreases in urine GL-3 were seen in all 3 subjects with an amenable α-Gal A mutant form based on the HEK assay. During the optional treatment extension, these decreases in urine GL-3 continued for the subjects who remained on treatment. In the subject with a non-amenable α-Gal A mutant form based on the HEK assay, urine GL-3 levels were greater at Week 48 than at Baseline.

Histological analysis of interstitial capillary GL-3 used the fully quantitative Barisoni method. No categorical scores were assigned, and inclusions per interstitial capillary were counted by two pathologists and these counts were then averaged. After treatment with migalastat, 1 of the 3 subjects with an amenable α-Gal A mutant form based on the HEK assay had a decrease in the average interstitial capillary GL-3 inclusions in their last available biopsy relative to baseline, while 1 of the 3 subjects had no change in average GL-3 inclusions. In the one subject with a non-amenable α-Gal A mutant form based on the HEK assay, the average inclusions per interstitial capillary more than doubled from Baseline to Week 12.

Study FAB-CL-203

Study FAB-CL-203 was a Phase II trial in 5 adult male patients with Fabry disease. The treatment period consisted of two parts: part one was a 24-week treatment phase and part two was an optional 24-week extension of treatment. All subjects received migalastat HCl 150 mg once every other day (QOD) for 24 weeks, and for a further 24 weeks if continuing in the extension part of the study. The outcomes for selected biochemical PD parameters for the 5 subjects are summarised below.

Table 35: FAB-GL-203 – Selected key PD parameters at baseline and end of study (Week 48) or earlier if no end of study data were available; all male patients with Fabry disease.

All Male	Dose mg QOD	Migalastat Amenable HEK assay	Previous ERT (last dose days)	α-Gal A leucocyte Baseline	α-Gal A leucocyte Week 48	Urine GL-3 Baseline	Urine GL-3 Week 48	Kidney IC GL-3 Baseline	Kidney IC GL-3 Week 48
	150 mg	Y	Y (129)	0.05	0.1	3875.9	4765.3	1.4	0
	150 mg	N	Y (162)	0.06	0.1	3565.5	3998.2	2.6	4.3
	150 mg	N	Y (107)	0.14	0.33	1488.7	4347.2	2.9	2.8
	150 mg	Y	N	3.4	7.4	170.0	132.1	0.3	Not Done
	150 mg	Y	Y (43)	0.18	3.13	1159.7	841.1	N/A	0.1

Note: α-Gal A leucocyte activity = α-galactosidase A leucocyte activity (nmol 4-MU/hr/mg protein); Urine GL-3 = globotriaosylceramide (total urine [sum of 5 isoforms of GL-3 measured] pmol/nmol PC [phosphatidylcholine]); Kidney IC GL-3 = Kidney interstitial cells (IC) GL-3 (histological quantitative measurement by Barisoni method). Previous ERT - If yes, days since last dose provided in brackets. If no data available for Week 48, then results for week of with last available data provided [W].

Comment: Data referred to by the sponsor indicate that the mean (± SD) leucocyte activity in healthy adult males is 22 ± 5.7 nmol 4-MU/hr/mg protein. In *study FAB-CL-203*, baseline leucocyte α-Gal A activity ranged from 0.23% to 15.5% of normal. During migalastat treatment, at each visit with measurable α-Gal A activity all 5 subjects had increased leucocyte α-Gal A activity relative to baseline. At Week 48, the highest leucocyteα-Gal A activity relative to baseline was seen in 2 subjects with a migalastat amenable *GLA* mutation. In the remaining subjects at Week 48, an approximately 2-fold increase in activity over baseline was seen, but remained very low relative to normal.

For urine GL-3, the presented data represents the total of the five GL-3 isoforms that were detected; one additional isoform was measured but not detected in any sample. All values are normalised to the amount of phosphatidylcholine (PC) measured in the same sample. The normal mean (± SD) value provided by the sponsor for healthy male volunteers was 48.6 ± 13.0 pmol/nmol PC, with a reference range of 22.6 to 74.6 pmol/nmol PC. All subjects in the study had baseline urine GL-3 values that were notably greater than the upper reference range for healthy subjects. Subject [information redacted] had the lowest urine GL-3 at baseline, which was consistent with his high baseline leucocyte α-Gal A activity. For urine GL-3, during treatment with migalastat there was a trend to increase in 3 subjects and a trend to decrease in 2 subjects. The decreases were observed in subjects RF-01 and RF-03, who both had migalastat amenable *GLA* mutations and demonstrated the greatest increases in leucocyte, kidney and skin α-Gal A activity following treatment with migalastat. By Week 48, these 2 subjects each showed an approximately 25% decrease in urine GL-3 relative to baseline.

Histological analysis of interstitial capillary GL-3 used the fully quantitative Barisoni method. No categorical scores were assigned, inclusions per interstitial capillary were counted by two pathologists and these counts were then averaged. Overall, there was no consistent trend towards decreased average interstitial capillary GL-3 inclusions from baseline to last available biopsy.

Study FAB-CL-204

Study FAB-CL-204 was a Phase II study in 9 female patients with Fabry disease. The trial included an initial 12-week treatment period and a 36-week optional treatment extension. All subjects were stratified (high or low α-GAL A activity, as measured in an *ex vivo* lymphocyte assay) and then randomly allocated to received one of three oral doses of migalastat HCl (50, 150, or 250 mg) once every other day (QOD). The outcomes for selected key biochemical PD parameters s are summarised below.

Table 36: FAB-GL-204 – Selected key PD parameters at baseline and Week 48 or earlier if no end of study data were available; all female patients with Fabry disease.

All Female	Dose mg QOD	Migalastat Amenable HEK assay	Previous ERT (last dose days)	α-Gal A leucocyte Baseline	α-Gal A leucocyte Week 48	Urine GL-3 Baseline	Urine GL-3 Week 48	Kidney IC GL-3 Baseline	Kidney IC GL-3 Week 48
	50 mg	Yes	No	13.4	26	117.8	97.9	0.4	0.1
	50 mg	Yes	No	24.5	39.6	28.1	17.3	0.2	0.2
	150	Yes	No	25.1	40 [W36]	651.4	340.8	0.2	0.0

All Female	Dose mg QOD	Migalastat Amenable HEK assay	Previous ERT (last dose days)	α-Gal A leucocyte Baseline	α-Gal A leucocyte Week 48	Urine GL-3 Baseline	Urine GL-3 Week 48	Kidney IC GL-3 Baseline	Kidney IC GL-3 Week 48
	mg				BLQ [W48]				
	150 mg	Yes	No	6.39	16.1	502.2	284.6	0.3	0.2
	150 mg	No	Yes (38)	17.3	22.2	51.7	541.2	0.2	0.2 [W12]
	150 mg	No	Yes (69)	24.6	46.5	267.0	673.2	0.2	0.1
	250 mg	No	Yes (96)	3.25	4.83	408.7	267.7	0.1	0.0
	250 mg	Yes	No	14.7	29.2	295.5	42.4	0.2	0.0 [W12]
	250 mg	No	Yes (88)	13.1	7.58	169.7	97.2	0.1	0.1

Note: α-Gal A leucocyte activity = α-galactosidase A leucocyte activity (nmol 4-MU/hr/mg protein); Urine GL-3 = globotriaosylceramide (total urine [sum of 5 isoforms of GL-3 measured] pmol/nmol PC [phosphatidylcholine]); Kidney IC GL-3 = Kidney interstitial cells (IC) GL-3 (histological quantitative measurement by Barisoni method). Previous ERT - If yes, days since last dose provided in brackets. If no data available for EOS, then results for week of with last available data provided [W].

Comment: The sponsor stated that the normal reference range for α-Gal A enzyme activity has not been established in females. However, the sponsor commented that there is no biological reason for normal α-Gal A enzyme activity to be different between males and females. The mean ± SD for α-Gal A enzyme activity in healthy males was reported by the sponsor as 22 ± 5.7 nmol 4-MU/hr/mg protein, with a range from 14.1 to 31 nmol 4-MU/hr/mg protein. Based on the normal range for α-Gal A enzyme activity established in healthy males, all females in study *FAB-CL-204* had baseline levels that were lower than the upper limit for the normal reference range. Of the 9 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. Increases in leucocyte α-Gal A activity occurred irrespective of migalastat amenable *GLA* mutation status. Of the 5 subjects with migalastat amenable α-Gal A mutant forms, 4 subjects had an increase in α-Gal A activity at Week 48 compared to baseline. Of the 4 subjects with migalastat non-amenable α-Gal A mutant forms, 3 subjects had an increase in α-Gal A enzyme activity at Week 48 compared to baseline.

However, in females measurement of α-Gal A activity is unreliable due to mosaic expression of both mutant and wild type α-Gal A. Therefore, it is not possible to determine if the increased α-Gal A activity after treatment with migalastat HCl reflects the chaperoning of the wild type or the mutant enzyme. In the sponsor's response to Day 120 questions raised by the CHMP, in a tabulated summary of the key PD data by ERT status for female patients from *study FAB-CL-204* the sponsor

identified all results for baseline and end-of-study leucocyte α-Gal A activity as being 'N/A = not applicable'. The sponsor states in its response to the CHMP's Day 120 Question 80, that 'WBC α-Gal A activity results in heterozygous females cannot be used to interpret the effect of migalastat on the mutant form of α-Gal A in women with Fabry disease since migalastat increases wild-type enzyme activity as well as the activity of the mutant form'. The sponsor goes on to state that '[c]hanges in disease substrate are more reliable pharmacodynamic assessments in females and substrate reduction has been demonstrated in female patients with amenable mutations'.

The sponsor notes that, as assessed in a separate study, the mean ± SD urine GL-3 concentration in healthy females (n = 29) was 32.21 ± 10.8 pmol/nmol PC, ranging from 10.79 to 50.61 pmol/nmol PC. Based on these data, 8 of the 9 females in the study had baseline urine GL-3 concentrations greater than the upper value for the normal reference range. Of the 9 female subjects, 7 subjects had urine GL-3 concentrations that were lower at Week 48 compared to baseline. All 5 subjects with a migalastat amenable *GLA* mutation had urine GL-3 concentrations that were lower 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.

Of the 7 subjects in the study with paired data for the quantitative measurement of renal interstitial capillary GL-3 inclusions at Baseline and Week 48 assessed by the Barisoni method, 5 subjects had a decrease in the number of average inclusions per capillary and 2 had no change. Of the 5 subjects with a migalastat amenable GLA mutation, 4 subjects had a decrease in the average interstitial capillary GL-3 inclusions from baseline to their last available biopsy, and no change was seen for 1 subject. Of the 4 subjects with a migalastat non-amenable GLA mutations, 2 subjects had a decrease from baseline in GL-3 inclusions and 2 subjects had no change.

Study FAB-CL-205

Study FAB-CL-205 was a Phase II, multinational, multicentre, open-label, non-comparative, long-term extension study for male and female subjects with Fabry disease who had completed the treatment period of 1 of the 4 prior Phase II, PD studies. Subjects could enter this extension trial immediately upon completion of participation in their previous migalastat HCl trial, or at a later time point. Therefore, some subjects did not have continuous treatment with migalastat HCl between the original Phase II study and the follow-up long-term extension study.

The primary objective of the study was to evaluate the long-term safety and tolerability of migalastat HCl, the secondary objectives were to gain information about the PD and PK of migalastat HC, and the exploratory objective was to evaluate the effect of migalastat on disease related outcomes.

The secondary PD outcome measures were levels of α-Gal A activity in leukocyte and levels of GL-3 in plasma and urine. The exploratory PD outcome was change in functional renal parameters from baseline to EOS (serum creatinine, creatinine clearance, and eGFR).

During this study, subjects received the following oral doses of migalastat HCl: 150 QOD, 250 mg (3 days on/4 days off) and 500 mg 3 days on/4 days off. In the original protocol, patients were to be treated continuously with 150 mg QOD. However, following protocol amendment 2 and subsequent protocol amendments subjects were enrolled into a dose escalation period (DEP) consisting of 250 mg 3 days on/4 days off for 2 months followed by 500 mg QOD 3 days on/4 days off for further 12 months followed by 150 mg QD through to the EOS. During the DEP, PD parameters were assessed monthly on the 2nd day off the drug, and during the remainder of the study assessments were undertaken every 3 months.

The duration of treatment with the various regimens depended on the time of enrolment into the study. The overall median duration of exposure in the study was 4.14 years (range: 1.0, 4.7 years), which reflects 82.7 patient-years of treatment with migalastat HCl. The longest treatment duration occurred with the 150 mg QOD dose regimen (pre- and post-DEP protocol amendments) and accounted for 42.7 patient-years of treatment. The median duration of exposure for the 150 mg QOD dose regimen was 2.66 years compared to 0.15 and 1.41 years for the 250 mg (3 days on, 4 days off) dose regimen and the 500 mg (3 days on, 4 days off) dose regimen.

Twenty-three (23) subjects were enrolled in the study. Seventeen (17) subjects completed the study and 6 subjects prematurely discontinued. Of the 23 enrolled subjects, 14 (61%) subjects were male and 9 (39%) subjects were female. The median age at consent to participation in the study was 42 years (range: 19, 66 years). Sixteen (16) subjects (70%, 11 M/5F) had a migalastat amenable *GLA* mutation and 7 subjects (30%, 3M/4F) had a migalastat non-amenable *GLA* mutation.

Leukocyte α-Gal A activity (nmol/h/mg protein) – results

In the total population, the median leucocyte α-Gal A activity at baseline (n = 23) was 3.44 (range: 0.1, 25.1) and the median leucocyte α-Gal A activity at EOS (n = 20) was 15.03 (range: 0.1, 54.7). The median absolute change from baseline to EOS (n = 20) in α-Gal A activity was 9.68 (range: -0.1. 30.7).

In the female population with migalastat non-amenable *GLA* mutations, the median leucocyte α-Gal A activity at baseline (n = 4) was 15.28 (range: 3.3, 24.7) and the median leucocyte α-Gal A activity at EOS (n = 4) was 27.28 (range: 8.4, 41.7). The median absolute change from baseline to EOS (n = 4) in α-Gal A activity was 12.0 (range: 5.1, 17.1).

In the male population with migalastat non-amenable *GLA* mutations, the median leucocyte α-Gal A activity at baseline (n = 3) was 0.07 (range: 0.1, 0.1) and the median leucocyte α-Gal A activity at EOS (n = 2) was 0.44 (range: 0.4, 0.5). The median absolute change from baseline to EOS (n = 2) in α-Gal A activity was 0.38 (range: 0.4, 0.4).

In the female population with migalastat amenable mutations, the median leucocyte α-Gal A activity at baseline (n = 5) was 14.73 (range: 6.4, 25.1) and the median leucocyte α-Gal A activity at EOS (n = 4) was 36.5 (range: 19.8, 54.7). The median absolute change from baseline to EOS (n = 4) in α-Gal A activity was 22.17 (range: 13.5, 30.7).

In the male population with migalastat amenable *GLA* mutations, the median leucocyte α-Gal A activity at baseline (n = 11) was 0.91 (range: 0.1, 6.6) and the median leucocyte α-Gal A activity at EOS (n = 10) was 7.78 (range: 0.1, 26.0). The median absolute change from baseline to EOS (n = 10) in α-Gal A activity was 6.60 (range: -0.1, 20.7).

Leucocyte α-Gal A activity for subjects with migalastat amenable *GLA* mutations by dose and duration of exposure are summarised below. In subjects with migalastat amenable *GLA* mutations (n = 12), leucocyte α-Gal A activity generally increased on the 150 mg QOD dose. No consistent notable changes in leukocyte α-Gal A activity were observed when subjects switched from 150 mg QOD to higher, less frequent doses of 250 mg and 500 mg, 3 days on, 4 days off.

Table 37: FAB-CL-205 – Leucocyte α-Gal A activity (nmol/h/mg protein) in subjects with migalastat amenable *GLA* mutations (HEK assay).

Subject [a]	Baseline [b]	8 Weeks following last dose of 150 mg QOD	8 Weeks following last dose of 250 mg 3 don/4d off [d]	8 Weeks following escalation to 500 mg 3d on/4d off [e]	8 Weeks following last dose of 500 mg 3d on/4d off [f]
	5.23	13.38	15.44	18.75	21.31
	4.7	19.24	19.72	17.4	34.8

Subject [a]	Baseline [b]	8 Weeks following last dose of 150 mg QOD	8 Weeks following last dose of 250 mg 3 don/4d off [d]	8 Weeks following escalation to 500 mg 3d on/4d off [e]	8 Weeks following last dose of 500 mg 3d on/4d off [f]
	6.58	20.26	21.73	20.84	24.24
	0.98	3.96	6.03	12.62	0.06
	0.91	0.8	3.03	3.82	d/c
	0.23	0.58	0.97	2.18	0.35
	0.31	8.33	9.48	7.24	21.01
	3.44	9.48	9.51	3.71	3.33
	0.18	1.5	1.02	2.34	n/a
	6.39	11.93	13	13.06	18.57
	24.55	30.05	29.57	32.08	11.11
	14.73	18.52	19.09	17.08	33.07

a Subjects with amenable mutations. b Baseline value is from feeder study. c Subjects previously on 150 mg QOD (range approximately 8-120 weeks) (DEP 1 for most subjects). d Approximately 8 weeks after escalation to 250 mg (3 days on, 4 days off) (DEP 3 for most subjects). e Approximately 8 weeks after escalation to 500 mg (3 days on, 4 days off) (DEP 5 for most subjects). f Approximately 8 weeks after lasts 500 mg (3 days on, 4 days off) dose range (approximately 12-20 months) (V11 for most subjects).

Comment: 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. In females, there was a notable absolute increase in median α-Gal A activity in subjects with and without migalastat amenable GLA mutations following migalastat treatment. In the male population baseline median α-Gal A activity was low in all subjects, with a marked absolute increase in median α-Gal A activity from baseline to EOS being observed following treatment with migalastat in subjects with migalastat amenable GLA mutations. In male subjects with migalastat non-amenable GLA mutations, the increase in median α-Gal A activity from baseline to EOS was negligible following treatment with migalastat. In subjects with migalastat amenable GLA mutations, leukocyte α-Gal A activity generally increased on the 150 mg QOD dose. No notable change in leukocyte α-Gal A activity was observed when subjects switched from 150 mg QOD to higher, less frequent doses (250 and 500 mg 3 days on 4 days off).

Urine GL-3 (pmol CTH/nmol phosphatidylcholine) – results

In the total population, the median urine GL-3 at baseline (n = 23) was 336.21 (range: 28.1, 3875.9) and the median urine GL-3 at EOS (n = 16) was 837.16 (range: 41.9, 5755.1). The median absolute change from baseline to EOS (n = 16) in urine GL-3 was 460.58 (range: -361.7, 4266.4).

In the migalastat non-amenable *GLA* mutation group, the median urine GL-3 at baseline (n = 7) was 408.66 (range: 51.7, 3565.5) and the median urine GL-3 at EOS (n = 7) was 1006.18 (range: 367.5, 5755.1). The median absolute change from baseline to EOS (n = 7) in urine GL-3 was 739.20 (range: 192.2, 4266.4).

In the migalastat amenable *GLA* mutation group, the median urine GL-3 at baseline (n = 16) was 315.84 (range: 28.1, 3875.9) and the median urine GL-3 at EOS (n = 9) was 666.67 (range: 41.9, 3614.1). The median absolute change from baseline to EOS (n = 9) in urine GL-3 was 16.53 (range: -261.7, 3061.0).

In subjects with migalastat amenable *GLA* mutations (n = 12), urine GL3 generally decreased on the 150 mg QOD dose. When subjects switched from 150 mg QOD to higher, less frequent doses (250 and 500 mg 3 days on, 4 days off), no notable change in urine GL-3 was observed.

Table 38: FAB-CL-205 – Urine GL-3 levels (pmol CTH/nmol phosphatidylcholine) in subjects with migalastat amenable *GLA* mutations (HEK responders).

Subject[a]	Baseline[b]	8 Weeks following Last Dose of 150mg QOD[c]	8 Weeks Following Last Dose of 250mg (3 days on, 4 days off)[d]	8 Weeks Following Escalation to 500mg (3 days on, 4 days off)[e]	8 Weeks Following Last Dose of 500mg (3 days on, 4 days off)[f]
	66.5	45.3	58.2	63.7	76.7
	49.4	40.7	53.4	47.7	72
	64.1	34	41.5	35.4	50.7
	159	89	119.4	110.4	126
	851.9	1538.3	1786.4	2056.3	d/c
	457.7	449.5	893.4	769.9	863.3
	336.2	60	123.8	45.2	468.5
	170	177.9	98.8	153.6	279.1
	1159.7	1355.7	1111.5	1292.6	4362.9
	502.2	217.3	90.8	253.4	427.1
	28.1	30.7	15	9	40.5
	295.5	66.4	275	104.1	325

[a] Subjects with amenable mutations
[b] Baseline value is from feeder study
[c] Subjects previously on 150 mg QOD (range approximately 8-120 weeks) (DEP 1 for most subjects)
[d] Approximately 8 weeks after escalation to 250 mg (3 days on, 4 days off) (DEP 3 for most subjects)
[e] Approximately 8 weeks after escalation to 500 mg (3 days on, 4 days off) (DEP 5 for most subjects)
[f] Approximately 8 weeks after last 500mg (3 days on, 4 days off) dose (range approximately12-20-months) (V11 for most subjects)

Comment: The results suggest that the effect of migalastat on reducing urine GL3 levels was greater in subjects with migalastat amenable GLA mutations compared to subjects with migalastat non-amenable GLA mutations. In general, treatment with migalastat 150 mg QOD in subjects with migalastat amenable GLA mutations resulted in a reduction in urine GL-3 levels with no further changes being observed when subjects were switched to higher, less-frequent migalastat HCl doses of 250 mg 3 days on/4 days off and 500 mg 3 days on/4 days off.

GL-3 inclusions in kidney interstitial cells

At baseline, the median GL-3 inclusion per IC was 0.35 for the PD population, with the median number of inclusions being higher among subjects with amenable *GLA* mutations (0.66) than among subjects with non-amenable *GLA* mutations (0.32). For the 8 subjects with evaluable paired biopsy samples, a 53% median decline in IC GL-3 inclusions was observed from baseline to Visit 8 (0.35 → 0.14) and for 7 subjects with evaluable paired biopsy a 55% median decline in IC GL-3 inclusions was observed from baseline to Visit 12 (0.35 → 0.10). At Visit 8, the decline was consistent in the 5 subjects with amenable *GLA* mutations with a median decline of 78% and at Visit 12, the median decline of 27% was consistent in 4 subjects. Of the 3 subjects with non-amenable *GLA* mutations, a median increase in IC GL-3 inclusions of 114% was seen at Visit 8 (2 subjects showed an increase and 1 subject showed a decrease of 27%), while at Visit 12 a median decrease in IC GL-3 inclusions of 55% was seen (2 subjects showed a decreases of 75% and 55% and 1 subject showed an increase). No consistent trends were seen in GL-3 inclusions in other renal cells, percentage interstitial fibrosis and tubular atrophy, or in glomerular sclerosis.

Renal functional assessment

In the PD study population, mean and median baseline eGFR values were 101 and 96 mL/min/1.73 m^2 (range: 31, 138 mL/min/1.73 m^2), respectively, with 6 subjects having

baseline eGFR < 90mL/min/1.73 m^2. The mean and median annualised eGFR rates of change for the total population were -0.42 and 0.20 mL/min/1.73 m^2/year, respectively. In the 6 subjects who had eGFR < 90 mL/min/1.73m^2, the mean and median annualised eGFR rates of change were -0.44 and 0.24 mL/min/1.73 m^2/year, respectively. In the 3 subjects who had protein > 0.3 g/dL at baseline, the mean and median annualised eGFR rates of change were -0.80 and 0.20 mL/min/1.73 m^2/year, respectively. In summary, the mean and median annualised eGFR rate of change values were relatively stable, suggesting that renal function remained unchanged during the study. Urine creatinine clearance data were inconsistently reported by local laboratories.

Events and symptoms

All subjects had one or more events and symptoms at baseline considered by the investigators to be related to Fabry disease. The events and symptoms generally remained stable during the study.

5.2.2.2. Secondary pharmacodynamic effects

Study AT1001-010 – thorough QT/QTc study – four-way cross-over in healthy subjects

Study AT1001-010 was a randomised, double-blind, double-dummy, comparative, placebo and active controlled four-way crossover study investigating the effects of single, fasting doses of migalastat HCl at the proposed dose of 150 mg and a supra-therapeutic dose of 1250 mg on the QT/QTc interval in healthy subjects of both sexes.

The *primary objectives* were to evaluate the effects of single oral doses of migalastat HCl on ventricular repolarisation in healthy subjects compared to placebo at the proposed therapeutic dose of 150 mg and the supra-therapeutic dose of 1250 mg, and to evaluate the change from baseline of QTc interval corrected by QTcB, QTcF, and QTcI (subject-specific) at the Tmax using 12-lead electrocardiograms on the day of dosing. The *secondary objectives* were to determine if there was a PD relationship between the duration of the QTc intervals and the plasma concentration of migalastat, obtain additional PK information on migalastat HCl in healthy subjects when administered orally at the proposed therapeutic and supra-therapeutic dose, and provide additional safety information

The *four dosage groups* were: (A) Therapeutic - a single oral 150 mg dose of migalastat HCl solution and an oral moxifloxacin over-encapsulated placebo tablet; (B) Supra-therapeutic – a single oral 1250 mg dose of migalastat HCl solution and an oral moxifloxacin over-encapsulated placebo tablet; (C) Placebo – a single oral dose of migalastat placebo solution plus a moxifloxacin over- encapsulated placebo tablet; and (D) Moxifloxacin (positive control) - a single oral dose of migalastat placebo solution plus a moxifloxacin over- encapsulated 400 mg tablet.

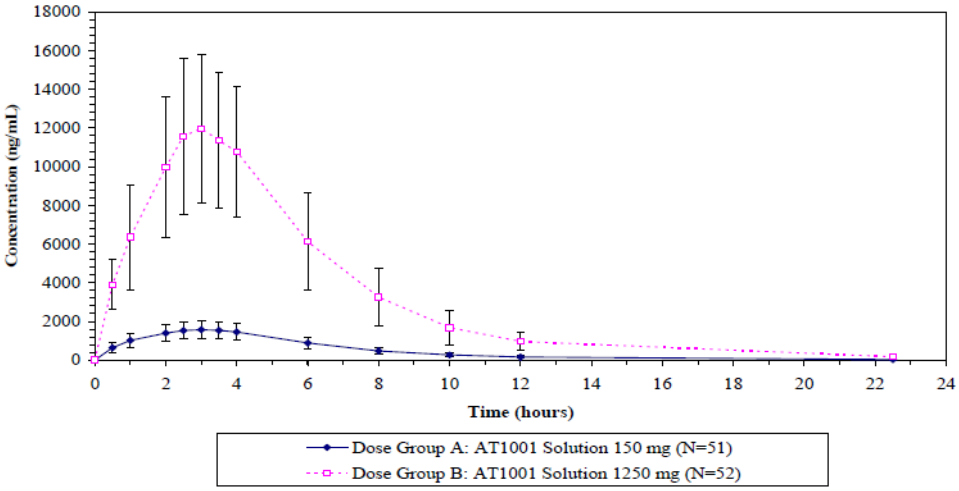
The *study population* included 52 healthy subjects (26 M, 26 F) with a mean (±SD) age of 29.2±11.3 years (range: 21, 54 years). Of the 52 subjects, 38 (73.2%) were White, 5 (9.6%) were Black or African American, 4 (7.7%) were Asian, and 1 (1.9%) was White and Black or African American. The mean (±SD) BMI was 24.6±3.2 kg/m^2 (range: 18.5, 39.9 kg/m^2). Of the 52 enrolled subjects, 51 completed the study and 1 discontinued.

Results – Pharmacokinetic

On the day of study drug administration of each cross-over arm, blood samples were taken for migalastat and moxifloxacin plasma levels pre-dose (0 hour) and then post-dose at 0.5, 1, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 22.5 hours. Plasma samples for moxifloxacin and placebo concentrations were not to be analysed unless the QT responses observed following these treatments differed from those expected. Only the PK parameters for migalastat were calculated, while moxifloxacin plasma concentrations were measured according to the protocol. The PK parameters for migalastat were calculated using standard non-compartmental methods (WinNonlin®, Version 5.0.1). No formal statistical analyses were planned. The limit of

quantification (LOQ) for migalastat was 5.88 ng/mL. The mean migalastat plasma concentration versus time profile for the two doses of migalastat HCl is summarised below.

Figure 7: AT1001-010 – Mean migalastat versus plasma concentration time profile, linear scale, following single-dose migalastat 150 mg and 1250 mg.



The PK parameters for migalastat for the two doses of migalastat HCl are summarised below. There were dose related increases in Cmax, AUC0-t, and AUCinf. These increases were less than dose proportional. The supra-therapeutic dose gave plasma exposure approximately 7.8 times higher than the administered therapeutic dose.

Table 39: AT1001-010 – Plasma PK parameters for migalastat, arithmetic mean ± SD

PK Parameter	Dose Group A (AT1001 Solution 150 mg) (Therapeutic) (N = 51)	Dose Group B (AT1001 Solution 1250 mg) (Supra-Therapeutic) (N = 52)
AUC_{0-t} (ng·hr/mL)	10654.26 (± 2612.25)	74189.57 (± 20096.95)
$AUC_{0-\infty}$ (ng·hr/mL)	10806.17 (± 2666.15)	75183.89 (± 20350.42)
C_{max} (ng/mL)	1700.22 (± 464.62)	13197.12 (± 3906.50)
T_{max} * (hr) x	3.00 (1.00 - 6.00)	3.00 (2.00 – 4.00)
λ_z (K_{el}) (1/hr)	0.1824 (± 0.0174)	0.1756 (± 0.0195)
T½ (hr)	3.84 (± 0.39)	4.00 (± 0.46)

Median and range are reported for Tmax.

Results – ECG

There were 52 subjects with baseline ECG data and any on-drug ECG results; 51 subjects completed the study and had data for placebo, migalastat 150 mg and moxifloxacin 400 mg and 52 subjects had data for migalastat HCl 1250 mg.

QTcI (individually corrected QT interval) – primary ECG parameter

The primary ECG parameter was the QTcI. The QTcI values were calculated by first running the following linear regression on all QT, RR pairs on study Day -1 before Period 1 to obtain the

slope (bi) for the subject specific correction formula: log(QT) = log (a) + b log(RR) where a is the log intercept and b is the slope of the line of fit of log QT versus log RR. The slope of the regression for each subject (bi) is derived from this formula. The resulting slope (bi) for the i-th subject was then used to calculate the individual correction for that subject as follows: QTcI = QT/RRbi

The primary ECG endpoint was the largest time-matched difference in change from the pre-dose baseline in QTcI between each migalastat dose level and placebo. The primary hypothesis was that the largest time-matched mean difference among all post-treatment ECG time points in change from the pre-dose baseline in QTcI between each migalastat dose and placebo (placebo-subtracted change) is equal to or greater than 10 ms. The null hypothesis was that the placebo subtracted change from baseline QTcI was ≥ 10 ms, and the alternative hypothesis was that the placebo-subtracted change from baseline QTcI was < 10 ms. The hypothesis was tested by placing the upper bound of a 1-sided 95% CI on the mean difference point-estimate between each migalastat dose and the corresponding time-matched placebo. If each of the upper bounds was less than 10 ms, the null hypothesis would be rejected in favour of the alternative hypothesis.

Mean changes in QTcI were analysed by a repeated measures mixed-effects linear model that included the effects of subject, study drug, ECG time-point, and study drug-by-ECG time point interaction. Under the assumption of a standard deviation of triplicate ECGs of 8 ms and a true increase in QTcI over placebo of 3 ms, a sample size of 44 subjects would provide 90% power to reject the null hypothesis. This sample size accounts for analyses of QTcI at each of 12 different post-dose time-points. To allow for as much as a 15% dropout rate, 52 subjects were enrolled.

The mean placebo-subtracted change from baseline and upper bound of the 1-sided 95% CI for the QTcI is summarised below, and mean changes from baseline in QTcI for each of the 4 treatment groups are provided below.

Table 40: AT1001-010 – QTcI placebo-subtracted mean change from baseline and upper bound (UB) of the 1-sided 95% CI.

Hours post-dose	AT1001 150 mg	UB	AT1001 1250 mg	UB
0.5	0.03	2.02	-1.11	0.88
1	-0.01	1.99	-1.56	0.43
2	-0.64	1.36	-2.14	-0.15
2.5	-0.84	1.15	-2.67	-0.69
3	-1.96	0.04	-2.83	-0.84
3.5	-1.90	0.09	-3.36	-1.37
4	-0.29	1.70	-1.60	0.39
6	-1.29	0.71	-1.28	0.71
8	-0.80	1.20	-0.17	1.82
10	-1.87	0.13	-1.63	0.37
12	0.06	2.06	0.08	2.06

Hours post-dose	AT1001 150 mg	UB	AT1001 1250 mg	UB
22.5	-2.32	-0.31	-0.88	1.12

Table 41: AT1001-010 – QTcI mean changes from baseline for each of the four treatment groups.

Hours post-dose	Placebo	AT1001 150	AT1001 1250 mg	Moxifloxacin 400 mg
0.5	-3.33	-3.30	-4.44	1.81
1.0	-1.55	-1.56	-3.11	7.12
2.0	-3.00	-3.64	-5.14	8.40
2.5	-1.27	-2.12	-3.95	9.79
3.0	-0.49	-2.45	-3.32	9.41
3.5	-0.24	-2.15	-3.61	9.64
4.0	-1.49	-1.79	-3.09	9.50
6.0	-5.96	-7.25	-7.24	1.46
8.0	-9.18	-9.98	-9.35	0.06
10.0	-4.34	-6.21	-5.96	0.51
12.0	-5.14	-5.08	-5.07	1.62
22.5	-1.86	-4.17	-2.73	1.82

The maximum increase in the QTcI response occurred at 12 hours post-dose for the 150 mg and 1250 mg doses of migalastat (0.06 ms and 0.08 ms, respectively). In both of the migalastat dose groups, the largest of the upper bounds of the 1-sided 95% CI of the placebo-subtracted change of QTcI were 2.06 ms at 12 hours. The results showed that the mean point-estimate at each post-dose time-point was < 5 ms, and that the upper bound of the 1-sided 95% CI was < 10 ms at each post-dose time-point.

Similar findings were observed for the QTcF changes as observed for the QTcI changes. The maximum increase of the placebo-subtracted QTcF response following migalastat 150 mg was 0.18 ms, which occurred at 1 hour post–dose and there were no placebo-subtracted QTcF increases at any time-point following migalastat 1250 mg. The largest of the upper bounds of the 1-sided 95% CI of the placebo-subtracted change of QTcF was 2.13 ms at 1-hour post-dose for migalastat 150 mg and 1.87 ms at 8 hours post-dose for migalastat 1250 mg. The results showed that the mean point-estimates at each post-dose time-point were < 5 ms, and that the upper bound of the 1-sided 95% CI was < 10 ms at each post-dose time-point.

Categorical changes in QTc > 450 ms

The number of subjects with post-dose QTcI > 450 ms was 2 (3.9%) for placebo, 3 (5.9%) for migalastat 150 mg, and 4 (7.7%) for migalastat 1250 mg. The number of subjects with post-dose QTcF > 450 ms was 2 (3.9%) for placebo, 2 (3.9%) for migalastat 150 mg, and 2 (3.8%) for migalastat 1250 mg. The time-matched data for QTcI and QTcF showed that no subjects had an increase from baseline of > 30 ms for either of the two parameters.

Morphological ECG changes

New ECG morphological changes occurring during the study and not present at baseline were bradycardia (2 subjects in the migalastat 150 mg group, no subjects in the three other groups), ectopic atrial rhythm (1 subject each in the placebo and the two migalastat groups, no subjects in the moxifloxacin group), sinus bradycardia (2 subjects in the migalastat 150 mg group, no subjects in the 3 other groups), T-wave flat (2 subjects in migalastat 1250 mg group, 1 subject each in the migalastat 150 mg and moxifloxacin groups, no subjects in the placebo group). The total number of subjects with new ECG morphologies not present at baseline were 1 (2.0%), 6 (11.7%), 3 (5.7%) and 1 (2.0%) for the placebo, migalastat 150 mg, migalastat 1250 mg and moxifloxacin 400 mg groups, respectively.

Sex and QT changes

The mean placebo-subtracted data showed that females had greater increases in QTcI values than males following both migalastat doses. However, the statistical test for the sex-by-treatment interaction was < 0.05 at each time-point, which indicates that the differences from placebo were comparable for males and female subjects. Inspection of the mean estimates for the placebo-subtracted increases from baseline in female subjects showed that the highest value following migalastat was 1.37 ms at 0.5 hours post-dose, and 0.26 ms at 6 hours post-dose following migalastat 1250 mg.

Concentration-QT relationship

The relationship between placebo-subtracted differences in changes from baseline in QTcI intervals and log migalastat plasma concentration was assessed. A repeated measures regression was run on these data, with an estimated linear slope of -0.521 (p = 0.168). To assess the linearity of this relationship, a squared term was added to the model, resulting in a p-value of 0.017. A cubic model was then used, resulting in a p-value for the cubic term of 0.290, therefore, the quadratic model was used, resulting in the following final model: $\Delta\Delta$QTcI = -0.698 + 4.360 conc – 0.826 conc$^{2.}$ The predicted line of fit showed no overall trends for change in QTcI with increasing concentration of migalastat. The estimated mean differences from placebo from the model, along with their 1-sided upper bound 95% CI for the lowest and highest observed concentrations, and the 20th, 40th, 60th, and 80th percentile concentrations were provided. The upper bound 95% CI for QTcI at each concentration was negative, indicating no relationship between migalastat plasma concentration and increase in QTcI.

Table 42: AT1001-010 – Estimated mean time matched difference from placebo in change from pre-dose baseline in QTcI at various migalastat concentrations.

Concentration (ng/mL)	Mean Difference (ms)	Upper 95% CI (ms)
10.2	-3.43	-1.25
437	-1.23	-0.38
1150	-1.38	-0.39
2020	-1.60	-0.52
7200	-2.46	-1.07
21,900	-3.63	-1.73

Sensitivity analysis

The sensitivity analysis confirmed that the positive control (moxifloxacin 400 mg) had adequate sensitivity to detect a change in the mean QTc interval of at least 5 ms. The lower bound of the 95% 1-sided CI of placebo-subtracted difference of QTcI after administration of moxifloxacin was 9.26 ms at the 2.0 hour time point. The placebo-subtracted mean point-estimate was > 10 ms at 2, 2.5 and 4 hours post-dose.

QT results in the Phase II clinical studies

Abnormal ECG findings reported in the literature in patients with Fabry disease include left ventricular hypertrophy, ST segment changes, and T-wave inversion, as well as arrhythmias, intermittent supra-ventricular tachycardia, and a short PR interval. Five Phase II studies of migalastat were conducted in male and female patients with Fabry disease, 2 of these studies [FAB-CL-203 and FAB-CL-204] reported ECG findings and the results are summarised below.

In *study FAB-CL-203*, 5 male subjects received single-dose migalastat 150 mg QOD for 24 weeks, with a 24 week optional extension. In this study, 1 subject had at least 1 post-baseline QTcB value > 450 ms (excluding subjects with abnormal QTc at baseline) and 1 subject had at least one post-baseline QTcB value increasing from baseline by > 60 ms.

In *study FAB-CL-204*, 4 female subjects received migalastat 150 mg, 3 female subjects received 250 mg QOD, and 2 female subjects received 50 mg QOD for 12 weeks, with a 36 week optional extension. In this study 3 female subjects had at least 1 post-baseline QTcB value > 450 ms (excluding subjects with abnormal QTc at baseline) and no female subjects had at least one post-baseline QTcB value increasing from baseline by > 60 ms.

None of the 4 subjects (1M, 3F) in *studies FAB-CL-203 and FAB-CL-204* with potentially clinical significant post-baseline QTcB values above 450 ms had an increase from baseline greater than 60 ms. Three (3) of the subjects were on 150 mg migalastat HCl QOD and 1 subject was on 250 mg migalastat HCl QOD.

Of the 3 female subjects, 2 had a QTcB above 450 ms at their screening visit (460 and 502 ms), although neither subject had a QTcB above 450 ms on the ECG recorded just before dosing on Day 1. Additionally, only 1 of these female subjects had a QTcB outside the range of 450 ms to 470 ms, which is within the normal range for females. The only longer QTcB (484 ms) occurred in the subject whose QTcB at screening was 502 ms.

The only male with a potentially clinically significant post-baseline QTcB had a QTcB on Day 56 of treatment of 452 ms 3 hours after dosing. His QTc interval was in the normal range for all other ECG tracings.

None of the QTcB abnormalities reported in the Phase II studies were deemed by investigators to be clinically significant or reported as adverse events.

5.3. Evaluator's conclusions on pharmacodynamics

5.3.1. 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 three 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 [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 [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.

5.3.2. Secondary pharmacodynamics

The 'thorough QT/QTc' study in healthy subjects [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.

6. Dosage selection for the pivotal studies

6.1. 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 [AR1001-102], 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 (18M/9F). 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 (i.e., 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.

6.2. Evaluator's conclusions on dose finding for the pivotal studies

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

7. Clinical efficacy

7.1. 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 III efficacy and safety studies, the submission also included the protocols from two, Phase III, open-label, long-term extension studies [AT1001-041; AT1001-042] 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 [FAB-CL-205, AT-1001-011, 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.

7.2. Pivotal or main efficacy studies

7.2.1. Study AT1001- 011: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Pharmacodynamics of AT1001 in Patients with Fabry Disease and AT1001-Responsive *GLA* Mutations

7.2.1.1. Study design, objectives, locations and dates

Objectives

· Stage 1 (randomised, placebo-controlled, double-blind, month 0 to month 6)

The *primary objective* of Stage 1 of the study was to compare the effect of migalastat versus placebo on kidney GL-3 as assessed by histological scoring of the number of inclusions in interstitial capillaries (ICs).

The *secondary objectives* of Stage 1 of the study were: (1) to compare the effect of migalastat versus placebo on urine GL-3 levels as measured by liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS); and (2) to compare the effect of migalastat versus placebo on renal function (measured glomerular filtration rate as assessed by plasma clearance of iohexol [$mGFR_{iohexol}$], estimated glomerular filtration rate [eGFR], 24-hour urine protein). The study also included a number of *tertiary objectives* and these are summarised.

· Stage 2 (open-label, migalastat treatment, month 6 to month 12)

There were a number of objectives for Stage 2 of the study and these are summarised.

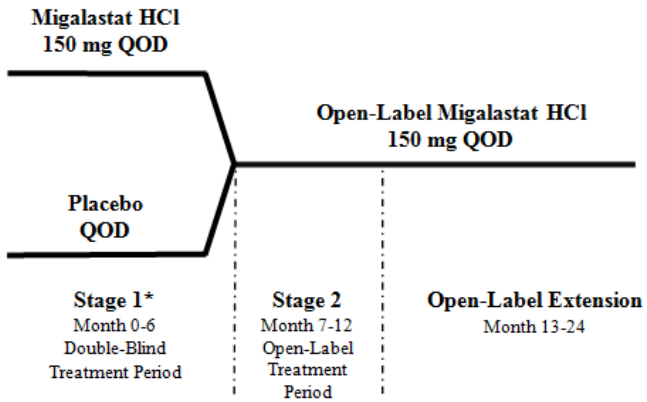
· Open-label extension phase (month 12 to month 24)

The protocol did not specify objectives for the open-label extension stage. However, the relevant SAP for the Stage 2 and open-label extension phase of study stated that the Stage 2 objectives were to be evaluated for the open-label extension phase.

Design

The study was a Phase III, double-blind, randomised, placebo-controlled efficacy and safety trial of 24 months duration in patients with Fabry disease and migalastat responsive (amenable) *GLA* mutations. An independent data safety monitoring board (DSMB) was chartered to monitor and evaluate the safety of all subjects in this study. The study consisted of 2 stages and an optional, open-label, extension phase. The study design is summarised schematically below.

Figure 8: Figure: AT1001-011 – Schematic of study design.



* 1:1 Randomization; stratified by gender

Stage 1 consisted of Screening (up to 2 months) and a 6-month, double-blind, randomised, placebo-controlled treatment period. Subjects who were naïve to ERT or had not received ERT for at least the 6 months before screening and who met all other eligibility criteria were

randomised 1:1 to migalastat (150 mg QOD) or matching placebo. The randomisation was stratified by sex. The schedule of assessments for Stage 1 is provided.

Stage 2 consisted of 6 months open-label treatment with migalastat 150 mg QOD. Subjects who received placebo during Stage 1 were switched to migalastat (placebo-migalastat group), and subjects who received migalastat during Stage 1 continued treatment with migalastat (migalastat-migalastat group). The schedule of assessments for Stage 2 is provided.

Subjects who completed both Stages 1 and 2 were eligible to participate in the 12-month, open-label extension phase. Subjects who withdrew from the study or who did not participate in the open-label extension phase underwent a follow-up visit 1 month after their last visit. Subjects who participated in the open-label extension phase continued to take 150 mg migalastat QOD for up to 12 months and underwent a follow-up visit 1 month after their last dose of study drug, unless the subject entered a separate open-label extension protocol [AT1001-041]. Subjects not entering the separate open-label extension protocol underwent a follow-up visit. The schedule of assessments for the open-label extension phase is provided.

Comment: Stage 1 provided 6 months of randomised, placebo-controlled, double-blind treatment. Stage 2 provided a further 6 months of open label-treatment with migalastat and the open-label extension phase provided a further 12 months of treatment with migalastat.

The target population for migalastat treatment is patients with Fabry disease who have migalastat amenable *GLA* mutations. *In Study AT1001-011*, male and female patients with amenable *GLA* mutations were identified by the *in vitro* Clinical Trial Human Embryonic Kidney [HEK] cell-based assay initially developed by the sponsor (Amicus Therapeutics).

The Clinical Trial HEK assay was designed to assess the subset of responsive mutant forms of α-Gal A that were most likely to respond to migalastat. An α-Gal A mutant form was categorised as responsive if the mutant form of the enzyme showed a relative increase in α-Gal A activity ≥ 1.20-fold above baseline and an absolute increase ≥ 3.0% of wild-type at a concentration of 10 μM migalastat. Mutant forms of the enzyme that met the criteria were defined as 'responsive' and mutant forms that did not meet the criteria were defined as 'non-responsive'.

The sponsor stated that the concentration of 10 μM for the assay was selected because this was the approximate migalastat Cmax value observed in subjects with Fabry disease following a single oral dose of 150 mg. Repeat dosing with migalastat 150 QOD in humans was associated with plasma Cmax values of 1500 to 2000 ng/mL (9 to 12 μM), a half-life of approximately 2.5 hours, and no observed accumulation of migalastat. A minimum threshold for the absolute increase in α-Gal A activity was specified based on scientific literature suggesting that increases of 1% to 5% of normal activity *in vivo* are expected to be clinically meaningful.

The sponsor stated that a minimum threshold for the relative increase in α-Gal A activity (≥ 1.20-fold above baseline) was specified in order to require mutant forms of the enzyme with relatively high baseline activity *in vitro* to demonstrate greater absolute increases than mutant forms of the enzyme with low or zero baseline activity. Based on the Phase II results, male subjects who expressed mutant forms of α-Gal A categorised as responsive by the Clinical Trial HEK assay were found to have a greater response to migalastat as measured by increases in α-Gal A activity in peripheral blood mononuclear cells (PBMCs). Male subjects that expressed mutant forms of α-Gal A categorised as nonresponsive by the Clinical Trial HEK assay showed very limited or no *in vivo* α-Gal A response in PBMCs. After applying pre-set criteria, the results of the Clinical Trial HEK assay were used to construct a pharmacogenetic reference table used as the inclusion criteria for the two Phase III studies [AT1001-010; AT1001-012].

Following completion of enrolment into *Study AT1001-011*, the Clinical Trial HEK assay was bioanalytically validated in a qualified third party laboratory in compliance with current regulatory guidance and relevant Good Laboratory Practice (GLP) regulations [Report CB-003026]. 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. Mutant forms of the enzyme that met the criteria (i.e., relative increase in α-Gal A activity ≥ 1.2-fold and absolute increase in α-Gal A activity ≥ 3% of WT after incubation with 10 μM migalastat) in the GLP HEK assay were categorised as amenable. Based on the GLP HEK assay, approximately 10% of mutations changed category from amenable to non-amenable, or vice versa. The efficacy analyses of the Phase III data focused on patients with amenable mutations.

The Stage 1 data which were initially evaluated using the Clinical Trial HEK assay were subsequently analysed *post-hoc* using the GLP HEK assay. The *post-hoc* analysis of the Stage 1 data took place after the study had been unblinded. The Stage 1 analyses in responsive subjects based on the Clinical Trial HEK assay were termed pre-specified, and the Stage 1 analyses in amenable subjects based on the GLP HEK assay were termed *post-hoc*. Both pre-specified and *post-hoc* results for Stage 1 data were included in the CSR *for Study AT1001-011*. The Stage 2 and open-label extension data were evaluated in subjects identified as having amenable α-Gal A mutant forms (i.e., positive GLA activity based on the GLP HEK assay) and the relevant analyses were termed pre-specified. Use of the GLP HEK assay changed the classification of 17 subjects who were enrolled in *Study AT1001-011* with responsive mutations based on the Clinical Trial HEK assay, to having non-amenable mutations based on the GLP HEK assay.

Location and dates

This study was conducted by 39 investigators at 36 study centres (including study centres that screened but did not randomise subjects) in the following 16 countries: Argentina, Australia, Belgium, Brazil, Canada, Denmark, Egypt, France, Germany, Italy, Netherlands, Poland, Spain, Turkey, the United Kingdom, and the United States. The study was undertaken from 23 October 2009 (first subject randomised) to 29 January 2014 (last subject completed). The study report was dated 14 January 2014. The sponsor was Amicus Therapeutics Inc. The study was stated to have been performed in compliance with GCP.

7.2.1.2. Inclusion and exclusion criteria

The study included male and female subjects aged 16 to 74 years, inclusive, with a confirmed diagnosis of Fabry disease. Subjects were required to be naive to ERT or not to have received ERT for at least 6 months before screening. Furthermore, subjects were required to have a migalastat responsive α-Gal A mutation identified by the Clinical Trial HEK assay. Urine GL-3 was required to be ≥ 4 x the upper limit of normal at screening. Subjects were ineligible for the study if they had undergone kidney transplantation, were currently on dialysis, or had an eGFR < 30 mL/min/1.73 m^2 (i.e., chronic kidney disease [CKD] stage 4 or 5).

The study also included criteria relating to discontinuation of women who became pregnant during the study, and for follow-up through to the outcome of pregnancy of these women and the female partners of male participants who became pregnant during the course of the study. The study also included standard criteria for removing subjects from the study or assessment, and specific criteria for discontinuing the study drug relating to the disease under investigation. The specific disease related criteria for the study drug being discontinued included confirmed 30% increase in serum creatinine from baseline, 25% decrease from baseline in cardiac ejection fraction as determined by ECHO, and cerebrovascular event with significant complications,

including stroke. All subjects who discontinued the study drug at any time during the study were encouraged to return for a follow-up visit or visits (depending on time of discontinuation).

7.2.1.3. Study treatments

Study drugs

During Stage 1, subjects took either 1 capsule of 150 mg migalastat or matching placebo orally QOD. During Stage 2 and the open-label extension phase, subjects took 1 capsule of 150 mg migalastat QOD. During Stage 1, subjects took either 1 capsule of 150 mg migalastat or matching placebo orally QOD. During Stage 2 and the open-label extension phase, subjects took 1 capsule of 150 mg migalastat QOD. Doses of the study drug were to be taken at approximately the same time of day. Subjects were required to fast for 2 hours before and 2 hours after taking each dose of migalastat. Subjects were to otherwise maintain normal food and fluid intake for the duration of the study.

Prior and concomitant therapy

Concomitant medications taken within 4 weeks prior to Screening or at any time throughout the study were recorded in the electronic case report form (eCRF), along with the reason for use, dates of administration, dosages, and frequency. Use of the following medications was prohibited as outlined below:

- Agalsidase beta: prohibited within 6 months of Screening and at any time during study participation.
- Agalsidase alfa: prohibited within 6 months of Screening and at any time during study participation.
- Miglitol: prohibited within 6 months of Screening and at any time during study participation.
- Miglustat; prohibited within 6 months of Screening and at any time during study participation.
- Other investigational/experimental therapy: prohibited within 30 days of Screening and at any time during study participation.

Treatment compliance

Dosing compliance was assessed at each clinic visit through subject interview and comparison of the amount of study drug that should have been taken since the last study visit to the amount of study drug returned.

7.2.1.4. Efficacy variables and outcomes

Stage 1 (pre-specified)

Primary efficacy endpoint

The *primary efficacy endpoint* in Stage 1 was the proportion of successes, which was defined as a ≥ 50% reduction from baseline to month 6 in the average number of globotriaosylceramide inclusions per kidney interstitial capillary (IC GL-3).

The average number of interstitial cell (IC) GL-3 inclusions was assessed by a quantitative histological method (Barisoni Lipid Inclusion Scoring System [BLISS]) undertaken by a Clinical Pathology Endpoints Committee (CPEC) according to the CPEC charter. The sponsor stated that the BLISS methodology for assessing IC GL-3 inclusions 'is rigorous, quantitative, and based on digital images of slides from biopsies'. The independent committee consisted of 3 renal pathologist blinded to treatment assignments, subject data, and biopsy sequence. Assessments were made using digital images. For each subject and visit, the first of three pathologists were to annotate 300 acceptable kidney interstitial capillaries in each biopsy and each of the other two

pathologists were to identify and count the number of GL-3 inclusions in each annotated capillary. The average number of GL-3 inclusions per capillary and percent changes were then calculated by an independent biostatistics group from a Clinical Research Organisation (CRO). No results were to be made available to the pathologists.

The change in the mean of the two pathologists' blinded and paired reading in the number of inclusions from the biopsies taken at each of the baseline and month 6 readings was used to analyse the primary study outcome. If the two pathologists reading of the baseline and month 6 slides scores did not agree on the change of either ≥ 50% or < 50% in the decrease of mean number of inclusions, the reading was subject to adjudication undertaken by the third pathologist. The paired reading of the baseline and month 6 slides from the adjudicator allowed the biostatistician to determine either a ≥ 50% or < 50% change in the mean number of inclusions. This resulted in declaration of an endpoint met or not met by concurrence with one of the two previously discordant pathologists.

The sponsor undertook an assessment of the intra-reader and inter-reader scoring reliabilities for IC GL-3 inclusions using Bland-Altman plots. For assessment of inter-reader reliability, the average kidney interstitial capillary GL-3 values for all biopsies (Baseline, Month 6, Month 12) assigned by each scoring pathologist across paired readings were compared between the two pathologists scoring the same biopsy. For assessment of intra-reader reliability, the kidney interstitial capillary GL-3 values for all biopsies (Baseline, Month 6, Month 12) assigned by each scoring pathologist were compared where the same pathologist scored the same biopsy in 2 different paired readings.

For intra-reader reliability of kidney IC GL-3 scoring, the Bland-Altman plots showed a mean difference of 0.0, indicating no systematic bias from the replicated reads within a reader. In addition, this plot showed that the majority of differences were within ±2 SD from the mean, stated by the sponsor to indicate lack of systematic variability. The interpretation from the Bland-Altman analysis of acceptable intra-rater reliability was supported by the correlation coefficients of the first and second reads within each individual reader, which ranged from r^2=0.93 to r^2=0.96 ($p<0.0001$ for each comparison).

For inter-reader reliability of kidney IC GL-3 scoring, the Bland-Altman plots provided a similar interpretation to that for intra-reader reliability. The mean difference was close to zero, and very few of the differences exceeded ±2 SD. The interpretation from the Bland-Altman analysis of acceptable inter-rater reliability was supported by the correlation between each set of readers, which ranged from r^2=0.92 to r^2=0.93 ($p<0.0001$ for each comparison).

Comment: The primary endpoint is considered to be clinically meaningful. The sponsor stated that '[i]t is generally understood that progressive accumulation of microvascular endothelial deposits of GL-3 lead to ischemia and infarction in the kidneys, contributing to kidney damage and impaired renal function. Given that Fabry disease is a chronic, slowly progressing disease, and that GL-3 accumulation appears to increase with age, a decrease in the number of inclusions per capillary by at least 50% over 6 months was considered likely to be associated with clinical benefit'. The sponsor's justification for the primary efficacy endpoint based on the number of IC GL-3 inclusions is considered to be satisfactory.

Secondary efficacy endpoints

- Urine globotriaosylceramide (GL-3) percent change in concentration from baseline to month 6. Urine samples collected or GL-3 determination were analysed by LC-MS/MS. The 24-hour samples were collected at screening, baseline, and months 6, 12, 18, and 24. First morning urine samples were collected at all other visits.
- Iohexol glomerular filtration rate ($GFR_{iohexol}$), change from baseline to month 6. This endpoint was calculated using standard methods to assess plasma clearance of iohexol using bolus dose IV administration and blood sampling from 2 to 4 hours post-infusion.

- Estimated glomerular filtration rate (eGFR), change from baseline to month 6. The eGFR was calculated using a revised Modification of Diet in Renal Disease (MDRD) equation ($eGFR_{MDRD}$) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ($eGFR_{CKD\text{-}EPI}$).
- 24-hour urine, protein, albumin and creatinine, change from baseline to month 6.
- IC GL-3 inclusions percent change from baseline to month 6.

Tertiary endpoints

- Echocardiography (ECHO), with tissue Doppler imaging where available, was used to assess cardiac function. The cardiac parameters included left ventricular mass index (LVMi), left ventricular mass (LVM), intra-ventricular septum thickness, left ventricular fractional shortening, left ventricular ejection fraction, and left ventricular posterior wall thickness. In addition, functional diastolic and systolic grades were calculated.
- The Short Form Health Survey with 36 Questions version 2 (SF-36 v2) was used by subjects to rate their health and capacity to perform activities of daily living in 8 domains including physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health. The health transition score was obtained by ranking on a scale of 0 to 4 the overall evolution under the treatment.
- The Brief Pain Inventory (BPI) short form was used by patients to collect data on pain severity ('worst,' 'least,' 'average,' and 'right now'). Scores were calculated for each response based on a 10-point scale.
- The Gastrointestinal Symptom Rating Scale (GSRS) was used to rate the 5 subscales of abdominal pain, reflux, diarrhoea, indigestion and constipation. The total number of individual items included in the 5 subscales was 15, and each item was rates on a 7-point Likert scale from no discomfort to very severe discomfort. The scores were calculated by taking the mean of the items completed within an individual subscale, with higher scores indicating greater severity of symptoms.
- White blood cell (WBC) α-Gal A activity was collected for male subjects only,
- Percent of renal ICs with zero percent inclusions.

7.2.1.5. Exploratory endpoints

Exploratory renal histological endpoints included – (a) qualitative assessment of GL-3 inclusions in renal cells (podocytes, endothelial cells, and mesangial cells); (b) interstitial fibrosis and tubular atrophy (IFTA); and (c) glomerular sclerosis. The exploratory renal histological endpoints were based on renal biopsies read by the same three independent pathologists who read the IC GL-3 data.

Stage 1 (post-hoc), Stage 2 (pre-specified), and open-label extension (pre-specified) efficacy endpoints

There was a significant difference in the assessment of efficacy between the Stage 1 (pre-specified) analysis and the Stage 1 (*post-hoc*) analysis. The Stage 1 (pre-specified) primary efficacy analysis based on categorical outcomes relating to percent change in the average number of IC GL-3 inclusions was not undertaken in Stage 1 (*post-hoc*) (i.e., ≥ 50% reduction from baseline to month 6 responder analysis not undertaken). Instead, the Stage 1 (*post-hoc*) analysis focussed on the quantitative change in the average number of IC GL-3 inclusions between baseline and month 6 expressed as a continuous rather than a categorical variable.

The sponsor identified several limitations of the pre-specified Stage 1 primary efficacy endpoint responder (categorical) analysis. It was noted that, because a number of subjects had low baseline values, small changes in IC GL-3 inclusions could result in large changes when viewed as a percent change from baseline to month 6. For example, a subject with an average baseline

level of 0.60 IC GL-3 inclusions and a follow-up level of 0.30 IC GL-3 inclusions (i.e., an absolute decrease of 0.3 IC GL-3 inclusions) would have a 50% decrease in the average number of inclusions from baseline to follow up. Furthermore, the Stage 1 data revealed an imbalance in the mean baseline level of IC GL-3 inclusions between the placebo and migalastat groups (about 50% higher in the migalastat group). Consequently, small decreases in IC GL-3 inclusions in subjects with low baseline IC GL-3 inclusions could meet the 50% reduction from baseline more easily than subjects with higher baseline IC GL-3 inclusions. As a result, the sponsor states that the responder analyses did not accurately reflect the effect of migalastat on IC GL-3 inclusions because the placebo group had a higher than expected 'response' rate.

The sponsor states that the change from baseline to follow up (i.e., quantitative difference) in IC GL-3 inclusions more accurately assesses the biological effect of migalastat on IC GL-3 inclusions than the responder analysis. The sponsor notes that this was reflected in the trend favouring migalastat seen in the Stage 1 secondary endpoint of percent change from baseline in IC GL-3 inclusions. The sponsor commented that, on this basis, the key analyses of IC GL-3 inclusions in the Stage 1 (*post-hoc*) analysis used the data as a continuous variable in an adjusted analysis of covariance (ANCOVA) and a mixed effects model for repeated measures (MMRM). The following efficacy endpoints based on the quantitative difference in IC GL-3 inclusions added to the analyses following unblinding of the Stage 1 data were the change from baseline in the average number of IC GL-inclusions on a continuous scale in Stage 1 (*post-hoc*) and Stage 2 (pre specified) and percent of capillaries with zero inclusions on a continuous scale.

The key objectives of the efficacy endpoint analyses for the Stage 2 and open-label extension analyses were: (1) determination of the IC GL-3 durability of response in Stage 2 as measured by mean change for subjects with amenable mutations who received migalastat in Stage 1; (2) determination of the mean change in IC GL-3 in Stage 2 for subjects with amenable mutations who received placebo in Stage 1; (3) assessment of whether renal function (eGFR) annualised rate of change is consistent with that in the literature; and (4) assessment of whether the changes in other exploratory kidney histology (podocyte, mesangial cell, glomerular endothelial cell GL-3) were directionally consistent with that for the IC-GL3 changes.

The study also included an exploratory efficacy endpoint analysis of plasma lyso-Gb_3 levels assessed in samples originally collected for the assessment of iohexol GFR at baseline, month 6, month 12 and month 24. The analysis was performed by independent laboratory personnel blinded to treatment, subject, visit and sample time-point. The endpoint for evaluation was the change in plasma lyso-Gb_3 from baseline to month 6 (mITT population), and from month 6 to month 12 (Stage 2 population).

7.2.1.6. Randomisation and blinding methods

Subjects who completed the screening assessments and met all of the inclusion criteria and none of the exclusion criteria were randomised and assigned to treatment using a central randomisation system. Subjects were randomised in a 1:1 ratio to either migalastat or placebo, with stratification by sex. A blocked randomisation scheme was used to provide an approximately balanced allocation to the 2 treatment groups during the study.

During the Stage 1 double-blind treatment period, all study drugs were identical in appearance and size. During the double-blind treatment period, subjects, investigators, and the sponsor were blinded to treatment assignments. The blind was not to be broken during the course of the study unless, in the opinion of the investigator, it was absolutely necessary to safely treat or continue to treat the subject. During Stage 2, the migalastat capsules were identical in appearance and size to the Stage 1 migalastat capsules. During Stage 2, subjects and investigators remained blinded to treatment assignments from Stage 1 until all biopsy samples had been scored and the Stage 2 database had been locked. All independent pathologists remained blinded to treatment group and visit while continuing to assess Stage 2 biopsies. A designated independent statistician remained blinded to Stage 1 treatment assignments and

was responsible for assessing biopsy scores and determining whether adjudication was required.

During the period following unblinding of the Stage 1 data, subject level results (tables, listings, and figures) were firewalled to ensure that treatment assignments were not provided externally, until such time all biopsy samples had been scored and the Stage 2 database had been locked. All datasets and any listings, summary tables, and figures with identifiable information were not available externally or available to any sponsor personnel whose primary job included interactions with clinical site personnel or site management.

After completion of the last Stage 2 visit, all corresponding data issues were resolved, and all biopsy samples were assessed by the pathologists prior to database lock. Summary tables, analyses, subject listings, and figures were generated. Then, subject-level data from Stage 1 were made available to firewalled functional areas, as needed, to interpret study results. During the optional open-label extension phase of the study, internal sponsor staff, subjects, and investigators could be informed of individual subjects' treatment assignments from Stage 1 as needed.

7.2.1.7. Analysis populations

Stage 1

- ITT population: Included all randomised subjects regardless of their participation in the study beyond randomisation. Subjects were analysed according to their original randomised treatment group. The ITT population included 34 subjects in the migalastat-migalastat group and 33 subjects in the placebo-migalastat group.
- Modified ITT (mITT) population: Included all randomised subjects who received at least 1 dose of study drug and underwent a renal biopsy at both baseline and month 6. Subjects were analysed according to their original randomised treatment group. The mITT population included 30 subjects in each of the two treatment groups. Four (4) subjects in the migalastat-migalastat group and 3 subjects in the placebo-migalastat group were excluded from the mITT population because they did not have both a baseline and month 6 kidney biopsy.
- PP populations: Included all randomised subjects who received at least 1 dose of study drug, had both baseline and month 6 kidney biopsies, and had no major protocol violations. Subjects were analysed according to the actual treatment received. The PP population included 30 subjects in each of the two treatment groups.
- Safety population: Included all randomised subjects who received at least one dose of study drug. Subjects were analysed according to treatment received. The safety population included 34 subjects in the migalastat-migalastat group and 33 subjects in the placebo-migalastat group.

Stage 2 and open-label extension analysis sets

- Stage 2 population: Included all randomised subject who completed Stage 1 and entered Stage 2. The Stage 2 population included 33 subjects in the migalastat-migalastat group and 30 subjects in the placebo-migalastat group.
- Open-label extension (OLE) population: Included all randomised subjects who completed Stage 2 and continued into the open-label extension phase. The OLE population included 29 subjects in the migalastat-migalastat group and 28 subjects in the placebo-migalastat group.

7.2.1.8. Sample size

To provide adequate power to test the primary outcome for the initial responder analysis, it was planned to randomise 30 subjects in each treatment group (total of 60 subjects). Power was calculated based on the following assumptions: (1) 1:1 randomisation; (2) null hypothesis (H0)

= percent success at month 6 is equal in the migalastat and placebo treatment groups; (3) alternate hypothesis (H1) = the percent success at month 6 is not equal for the two treatment groups; (4) a subject was considered a 'success' if the average number of IC GL-3 inclusions at month 6 had been reduced by at least 50% from the average number of inclusions at baseline (Fisher's exact test, 2-tailed Type I error rate of 5%, and a sample size of 30 subjects per group were used to calculate study powers for a set of assumptions regarding the percent success in the 2 groups); and (5) a sample size of 30 subjects per group was projected to detect a statistically significant difference between groups, including 10% who were expected to be missing the month 6 kidney biopsy and were counted as failures.

7.2.1.9. Statistical methods

Overview

The statistical methods used in this study were described in three separate Statistical Analysis Plans (SAPs): the Stage 1 Statistical Plan dated 17 September 2012; the *post-hoc* Stage 1, Stage 2, and Open-Label Extension Statistical Plan; and the Plasma Lyso-Gb_3 Exploratory Endpoint Statistical Analysis Plan.

The Stage 1 (pre-specified) analyses were based on the ITT population, which was the primary analysis population. The mITT and the PP populations were secondary populations used to support the ITT analysis. The primary endpoint was analysed using the ITT, mITT, and PP populations. The secondary and tertiary endpoints were analysed in the ITT population only. For the secondary endpoints based on continuous variables, homogeneity of variance and normality were assessed using a plot of the residuals versus the predicted values. If the assumptions of normality and homogeneity of variance were not supported by the data then a nonparametric analysis of variance model on the ranks of the change from baseline with treatment and sex as fixed effects was used. Significance tests (two-sided) were performed using α=0.05. P-values were reported for all statistical tests. All tests of interactions between treatment groups and other factors were conducted using a two-sided α=0.10.

The Stage 1 (*post-hoc*) analyses and selected analyses that combined Stage 1 and 2 data were based on the mITT population. The Stage 2 analyses were based on the Stage 2 population and the open-label extension analyses were based on the open-label extension population.

Primary efficacy analysis (pre-specified)

The primary efficacy pre-specified endpoint in Stage 1 was the proportion of successes defined as a ≥ 50% reduction from baseline to month 6 in the average number of IC GL-3 inclusions. The difference between the proportion of successes between the two treatment groups and its exact 95% CI was calculated. The p-value for the comparison between the two treatment groups was calculated using an exact Cochran-Mantel-Haenszel test stratified by sex.

Other statistical issues

- The secondary, tertiary, and exploratory Stage 1 (pre-specified) efficacy endpoints, the Stage 2 (pre-specified) efficacy endpoints and the open-label extension phase efficacy endpoints were analysed using various standard statistical methods. These methods are considered to be appropriate.
- Baseline was defined as the latest evaluation performed prior to or on the first dose day of study drug at the start of the study, including unscheduled and retest visits.
- Rules to impute missing data were described in the SAPs. For the analysis of the primary endpoint in the ITT population, subjects with missing month 6 kidney biopsies with a baseline measurement were considered to be treatment failures. Subjects with missing baseline measures were not included in the analysis. No imputation was done for the baseline values. The supportive analyses of the primary endpoint using the mITT and the PP populations did not include subjects missing the baseline or month 6 kidney biopsy result. A sensitivity analysis of the primary endpoint was specified to account for missing

data by using an imputed value based on the 95% CI for proportion of successes in the two groups.

- Stage 1 data were unblinded on 13 November 2012. There were no interim analyses of the study, except for interim safety analyses for the DMSB (8 meetings between 22 July 2011 and 3 December 2013).
- There were no statistical adjustments performed for multiple pairwise comparisons.
- No pooling of investigative study centres was performed. Study centres were not entered as covariates in the analyses models.

Changes in conduct of the study or planned analyses

The original protocol dated 10 June 2009 was amended 6 times, including 4 substantial amendments and 2 non-substantial amendments. Copies of the protocol and protocol amendments were provided. The amendments have been examined and are considered to be reasonable and not to have invalidated the study.

7.2.1.10. Participant flow

A total of 180 subjects consented to participate in the study. Subject disposition of the safety population is summarised below.

Table 43: AT1001-011 – Subject disposition.

		Treatment Group		
Parameter	Statistic	Migalastat-Migalastat	Placebo-Migalastat	Total
Number of Subjects in the Safety Population	N	34	33	67
Number of Subjects who Completed Month 6 (Safety Population)				
Yes	n (%)	34 (100)	30 (91)	64 (96)
No	n (%)	0	3 (9)	3 (4)
Number of Subjects in the Stage 2 Population	N	33	30	63
Number of Subjects who Completed Month 12 (Stage 2 Population)				
Yes	n (%)	31 (94)	29 (97)	60 (95)
No	n (%)	2 (6)	1 (3)	3 (5)
Number of Subjects in the Open-Label Extension Population	N	29	28	57
Number of Subjects who Completed Month 24 (Open-Label Extension Population)				
Yes	n (%)	27 (93)	27 (96)	54 (95)
No	n (%)	2 (7)	1 (4)	3 (5)

Note: Percentages are based on the number of subjects in the Safety Population, Stage 2 Population, or Open Label Extension phase.

In Stage 1, 67 subjects were randomised, including 34 to migalastat and 33 to placebo (ITT population). The majority of randomised subjects were from the USA (n = 20), Australia (n = 13), France (n = 6) and Italy (n = 5). Of the 67 subjects entering Stage 1, 34 (100%) in the migalastat group and 30 (91%) in the placebo group completed Stage 1. Of the 3 subjects in the placebo group who discontinued, 2 withdrew consent and 1 discontinued due to pregnancy. One (1) subject in the migalastat group withdrew consent after completing Month 6.

A total of 63 subjects completed Stage 1 and entered Stage 2, comprising 33 in the migalastat-migalastat group and 30 in the placebo-migalastat group (Stage 2 population). A total of 60 subjects completed Stage 2, comprising 31 (94%) in the migalastat-migalastat group and 29 (97%) in the placebo-migalastat group. Of the 2 subjects in the migalastat-migalastat group who

discontinued during Stage 2, 1 withdrew consent and 1 discontinued due to an SAE (amyotrophic lateral sclerosis). One (1) subject in the placebo-migalastat group discontinued during Stage 2 due to an SAE of anaplastic large cell lymphoma, which began while the subject was receiving placebo during Stage 1.

A total of 57 subjects completed Stage 2 and entered the open-label, comprising 29 in the migalastat-migalastat group and 28 in the placebo-migalastat group extension (Open-Label Extension Population). 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. Of the 2 subjects in the migalastat-migalastat group who discontinued during the open-label extension, 1 discontinued due to pregnancy, and 1 was lost to follow-up. One (1) subject in the placebo-migalastat group discontinued during the open-label extension (withdrew consent).

Study drug compliance was high (98% to 99%) and similar between treatment groups in all stages of the study. There were no notable differences between treatment groups in the reasons given for discontinuation during the study. No subjects met the mandatory stopping criteria (i.e., 30% increase in serum creatinine; 25% decrease in cardiac ejection fraction; or cerebrovascular event with complications). Two (2) subjects discontinued due to an AE (1 x anaplastic large cell lymphoma and 1 x amyotrophic lateral sclerosis). Both of these events were SAEs and were assessed by the investigator as unlikely to be related to study drug.

7.2.1.11. Major protocol violations/deviations

There were no major protocol violations during the study. During the study, 57% of subjects had a protocol deviation in study procedures criteria. The majority of deviations in study procedures criteria were due to specific procedures being missed at specified visits. A total of 54% of subjects had a protocol deviation in visit schedule criteria. The majority of deviations in visit schedule criteria were due to visits occurring outside the protocol-defined visit windows. Other common protocol deviations were in the categories of study drug compliance (48%) and laboratory assessment criteria (34%). Protocol deviations were not reported for the 2 subjects who became pregnant during the study. All subjects provided informed consent before their participation in the study. During Stage 1, the frequency of protocol deviations was similar between treatment groups with the exception of study procedures criteria, which occurred in a smaller percentage in the migalastat group (26%) compared to the placebo group (52%)

Comment: The protocol deviations documented during the study are considered not to have affected the assessments of safety or efficacy. No subjects were discontinued in Stage 1 for protocol violations or for non-compliance with the study drug. During Stage 1, compliance with the study drug was reported in 99% of subjects in the migalastat group and 98% of subjects in the placebo group, with no subjects in either treatment group being reported with < 80% compliance. The results for compliance in Stage 2 (open-label population) and the OLE population in the migalastat-migalastat and placebo-migalastat groups were similar to the results for compliance in the corresponding groups in Stage 1.

7.2.1.12. Baseline data

Demographics

The mean age of the total ITT population was 42 years (range: 16, 68 years), with the majority being female (64%), and 'White' (97%). The baseline demographic characteristics were well balanced between the two treatment groups. The baseline demographics of the ITT population are summarised below.

Table 44: AT1001-011 – Baseline demographics, ITT population.

Parameter		Migalastat-Migalastat (n = 34)	ERT-Migalastat (n = 33)	Total (n = 67)
Age	mean - ± SD	40.0 ± 13.29	44.5 ± 10.18	42.2 ± 11.99
	range	16, 68	24, 64	16, 68
Age ≤ 65 years	n (%)	33 (97%)	33 (100%)	66 (99%)
Age > 65 years	n (%)	1 (3%)	0	1 (1%)
Gender Male	n (%)	12 (35%)	12 (36%)	24 (36%)
Gender Female	n (%)	22 (65%)	21 (64%)	43 (64%)
American Indian or Alaska Native	n (%)	0	0	0
Asian	n (%)	0	0	0
Black or African American	n (%)	0	0	0
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
White	n (%)	32 (94%)	33 (100%)	65 (97%)
Other	n (%)	2 (6%)	0	2 (3%)

Baseline disease characteristics

The baseline disease characteristics of the two treatment groups in the safety population are summarised below.

Table 45: AT1001-011 – Baseline disease characteristics, safety population.

Parameter	Statistic	Migalastat Migalastat	Placebo-Migalastat	Total
Number of Subjects in the Safety Population	N	34	33	67
Number of Years Since Diagnosis of Fabry Disease	n	34	32	66

Parameter	Statistic	Migalastat Migalastat	Placebo-Migalastat	Total
	Mean	5.7	7.1	6.3
	SD	6.76	7.84	7.28
Proteinuria > 150 mg/24 h	n (%)	20 (59)	24 (73)	44 (66)
Proteinuria > 300 mg/24 h	n (%)	9 (26)	13 (39)	22 (
Proteinuria > 1000 mg/24 h	n (%)	3 (9)	3 (9)	6 (9)
Urine albumin:creatinine ratio (mg/mmol)	n	33	33	66
	Mean	18.83	26.71	22.77
	SD	36.404	47.259	42.044
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	n	34	33	67
	Mean	95.4	93.8	94.6
	SD	28.51	20.64	24.77
	Median	97.4	98.1	98.1
	Min, Max	41, 164	45, 127	41, 164
Use of ACEI/ARB/RI at Baseline	n (%)	6 (18)	13 (39)	19 (
Number of subjects who were previously on ERT	n (%)	5 (15)	12 (36)	17 (25)

The mean time since diagnosis was 6.3 years. A total of 25% of subjects had previously been treated with ERT. A total of 28% of subjects were receiving ACEIs, ARBs, or RIs at baseline. Most subjects (66%) had > 150 mg protein in their 24-hour urine, and 33% of subjects had > 300 mg protein in their 24-hour urine. A total of 13% of subjects had moderate renal impairment at baseline as assessed by $eGFR_{MDRD}$ (< 60 mL/min/1.73 m^2). There were no notable differences between treatment groups at baseline in the urine albumin:creatinine ratio, urine protein:creatinine ratio, $mGFR_{iohexol}$, $eGFR_{CKD-EPI}$, and $eGFR_{MDRD}$. In the total male population, baseline α A Gal activity was < 1% in 44%, and < 3% in 87%.

Prior and concomitant medications

Previous medications, defined as any medication taken within 30 days of the first administration of study drug, were similar between treatment groups in the safety population. The most commonly used previous medications (≥ 20% of subjects) were aspirin or acetylsalicylic acid (coded under both names: 21% and 7%, respectively), paracetamol or acetaminophen (coded under both names: 16% and 9%, respectively), and lidocaine (24%). A total of 36% of subjects in the safety population used NSAIDs during Stage 1, and concomitant NSAIDs use was similar between treatment groups.

Concomitant medications taken in Stage 1 were similar between the two groups in the safety population. The most commonly used concomitant medications (≥ 20% of subjects) were

paracetamol or acetaminophen (coded under both names: 24% versus 10%, respectively); aspirin or acetylsalicylic acid (coded under both names: 22% versus 9%, respectively); and lidocaine (24%). The concomitant medications used by a greater percentage of subjects (≥ 10% difference) in the migalastat group, compared to the placebo group, were ibuprofen (24% versus 12%, respectively) and plain multivitamins (18% versus 6%, respectively). A smaller percentage of subjects used ACEIs, ARBs, or RIs during Stage 1 in the migalastat group (24%), than in the placebo group (48%). A total of 7% of subjects in the safety population changed the dose or added a new ACEI, ARB, or RI during Stage 1, and the frequency was similar for the two groups. A greater percentage of subjects in the migalastat-migalastat group (33%) used NSAIDs during Stage 2, compared to the placebo-migalastat group (23%).

Concomitant medication use during Stage 2 was similar to use during Stage 1. A smaller percentage of subjects in the migalastat-migalastat group, compared to the placebo-migalastat group, used acetylsalicylic acid or aspirin (coded under both names: 18% and 6%, respectively, versus 7% and 30%, respectively) and vitamin D (0% versus 13%, respectively). A smaller percentage of subjects used ACEIs, ARBs, or RIs during Stage 2 in the migalastat-migalastat group (21%), compared to the placebo-migalastat group (50%). The concomitant ACEIs, ARBs, or RIs used during Stage 2 and the changes in their use were similar to Stage 1.

Concomitant medication use during the open-label extension was similar to concomitant medication use during Stages 1 and 2. A total of 40% of subjects used an ACEI, ARB, or RI during the open-label extension, and 19% of subjects changed the dose or added a new ACEI, ARB, or RI during the open-label extension. A total of 35% of subjects in the OLE population used NSAIDs during the open-label extension.

7.2.1.13. Results for the primary efficacy outcome

The pre-specified primary efficacy endpoint in Stage 1 was the percentage of subjects in the ITT population with a ≥ 50% reduction from baseline to month 6 in the average number of IC GL-3 inclusions. The response was greater in the migalastat group than in the placebo group (40.6% versus 28.1%, respectively), but the differenced was not statistically significant (p = 0.3; Cochrane-Mantel-Haenszel test stratified by sex). The results are summarised below in Table 47.

Table 46: AT1001-010 – Primary efficacy endpoint (Stage 1), responder analysis, Stage 1 ITT population.

IC GL-3 inclusions	Migalastat (n = 34)	Placebo (n = 33)	Difference	95% CI	p-value
Responder	13 (40.6%)	9 (28.1%)	12.5 %	-13.4, 37.3	0.2996
Non-Responder	19 (59.4%)	23 (71.9%)			

In males (ITT population), the responder rate was 41.7% (5/12) in the migalastat group and 33.3% (4/12) in the placebo group: difference 8.3% (95% CI: -34.4, 48.9). In females (ITT population), the responder rate was 40.0% (8/22) in the migalastat group and 25.0% (5/21) in the placebo group: difference 15.0% (95% CI -18.2, 45.9). The difference in the responder rate between the migalastat and placebo groups was not statistically significant in either male or female subjects.

In the mITT population, the responder rate was 43.3% (13/30) in the migalastat group and 30.0% (9/30) in the placebo group: difference 13.3% (95% CI: -13.5, 38.8); p = 0.2741. In the PP population, the results of the responder analysis were identical to the results of the responder analysis in the mITT population.

Comment: The pre-specified primary efficacy endpoint has not been met. The pre-specified response rate was higher in the migalastat group than in the placebo group, but the difference between the two treatment groups was not statistically significant.

7.2.1.14. Results for other efficacy outcomes

Results for Stage 1 pre-specified analyses

IC GL-3 inclusions percent change from baseline to month 6 (secondary endpoint)

The mean percent change from baseline to month 6 in the average number of IC GL-3 inclusions in the ITT population was -7.9% in the migalastat group and +13.0% in the placebo group. There was no statistically significant difference in the LS mean change from baseline between the two treatment groups (p = 0.0974). The results are summarised below in Table 48.

Table 47: AT1001-011 – Percent change in average number of IC GL-3 inclusions, Stage 1 ITT population.

Time-point	Statistic	Migalastat (n = 34)	Placebo (n = 33)
Baseline	n	30	30
	Mean ± SD	0.922 ± 1.6364	0.645 ± 0.230
	Median (max, min)	0.180 (0.02, 5.96)	0.230 (0.03, 2.77)
Baseline	n	30	30
Stage 1, Month 6	Mean ± SD	0.698 ± 1.524	0.707 ± 1.0317
	Median (max, min)	0.124 (0.00, 6.01)	0.236 (0.01, 4.32)
Change from baseline (%)	n	30	30
	Mean ± SD	-7.948 ± 105.2736 (%)	12.985 ± 90.5131 (%)
	Median (max, min)	- 40.81 (90.41, 433.82) (%)	-5.59 (-94.38, 285.08) (%)
Change from baseline (%) p = 0.0974			

Analysis - ANCOVA model based on ranked observations with covariate adjustment for the baseline value and factors for treatment group and the treatment by baseline interaction. The p-value was calculated for the LS mean difference between migalastat and placebo.

Comment: There was a reduction from baseline to month 6 in the average number of IC GL-3 inclusions in the migalastat group compared to an increase in the placebo group. However, the difference between the two treatment groups in favour of migalastat was not statistically significant.

Urine GL-3 percent change from baseline to month 6 (secondary endpoint)

The LS mean percent change in urine GL-3 (24-hour samples) from baseline to month 6 in the ITT population was 27.7% in the migalastat group and 20.21% in the placebo group, p = 0.7808.

$mGFR_{iohexol}$ change from baseline to month 6 (secondary endpoint)

The mean ± SD $mGFR_{iohexol}$ at baseline was 88.87 mL/min/1.73 m^2 in the migalastat group and 87.67 ± 23.064 mL/min/1.73 m^2 in the placebo group. During Stage 1, $mGFR_{iohexol}$ did not change notably from baseline to month 6 in either of the two treatment groups, and there was no notable difference between treatment groups. There were fewer $mGFR_{iohexol}$ measurements, compared with eGFR measurements, and more variability between subjects in $mGFR_{iohexol\ compared}$ with eGFR. The results suggest that the renal function, as assessed by $mGFR_{iohexol}$, was stable over the first 6 months of treatment in both the migalastat and placebo groups,

eGFR change from baseline to month 6 (secondary endpoint)

The mean ± SD $eGFR_{CKD\text{-}EPI}$ in the ITT population at baseline was 95.4 ± 28.51 mL/min/1.73 m^2 in the migalastat group and 93.8 ± 20.64 mL/min/1.73 m^2 in the placebo group. The mean ± SD $eGFR_{MDRD}$ in the ITT population at baseline was 89.8 ± 38.08 mL/min/1.73 m^2 in the migalastat group and 87.6 ± 23.19 mL/min/1.73 m^2 in the placebo group. During Stage 1, the $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ values did not change notably from baseline to month 6, and there were no notable differences between treatment groups. At month 6, no subjects had a ≥ 30% decrease from baseline in either parameter. The results suggest that the renal function, as assessed by eGFR, was stable over the first 6 months of treatment in both the migalastat and placebo groups.

24-hour urine protein, albumin, and creatinine (secondary endpoint)

24-hour urine protein and albumin levels increased from baseline to month 6 in subjects in the migalastat group (LS mean changes, 53.9 mg/24 h [vs 5.0 mg/24 h placebo] and 72.6 mg/24 h [vs -17.7 mg/24 h placebo], respectively). Creatinine levels remained stable during Stage 1 between baseline and month 6 in both the migalastat group (-0.013 mmol/24 h) and the placebo group (-0.433 mmol/24 h). There were no statistically significant differences between treatment groups in changes from baseline to month 6 for 24-hour urine protein, albumin, or creatinine. The results indicate that there was a trend towards increased 24-hour urine protein and albumin levels from baseline to month 6 in the migalastat group.

Tertiary efficacy endpoints

The LS mean change from baseline to month 6 in percent of capillaries with zero GL-3 inclusions in the ITT population was 7.3% in the migalastat group and 1.5% in the placebo group, with the LS mean difference between the two treatment groups being 6.0% (95% CI: 0.2, 11.7), p = 0.0418

During Stage 1, more subjects in the migalastat group compared to subjects in the placebo group in the ITT population had an improvement in the diarrhoea subscale of the GSRS from baseline to month 6 (38% versus 9%, respectively). There were no notable changes from baseline to month 6 in the other GSRS subscales in the two treatment groups.

There were no notable differences in the ITT population between the migalastat and placebo groups in changes from baseline to month 6 in ECHO parameters, the BPI short form assessment, or SF-36 v2 patient reported outcomes.

Although the Stage 1 SAP planned to analyse WBC α-Gal A activity for the full ITT population, only the results for male subjects were provided. There were no significant differences in WBC α-Gal A activity from baseline to month 6 in male subjects in the ITT population, with LS mean activity increasing by 0.981 nmol/h/mg in the migalastat group and decreasing by 0.380 nmol/h/mg in the placebo group, p = 0.0118.

Results for Stage 1 (post-hoc), Stage 2 (pre-specified) and Open-label extension (pre-specified) efficacy analyses

IC GL-3 change from baseline in average number of inclusions

In Stage 1, the *post-hoc* analysis (ITT) of the change from baseline to month 6 in subjects with an amenable α-Gal A mutation demonstrated a statistically significant reduction in the average

number of IC GL-3 inclusions in the migalastat group compared to the placebo group. The mean reduction in the average number of IC GL-3 inclusions was 0.250 in the migalastat group, while in the placebo group there was a mean increase in the average number of IC GL-3 inclusions of 0.071. The LS mean difference between the two treatment groups (migalastat minus placebo) in the average number of IC GL-3 inclusions was -0.3 in favour of migalastat, p = 0.0078. The results are summarised below.

Table 48: AT1001-011 – Change in average number of IC GL-3 inclusions in subjects with amenable mutations, ITT population.

Time-point	Statistic	Migalastat	Placebo
Baseline	n	25	20
	Mean ± SD	0.649 ± 1.2288	0.493 ± 0.5936
	Median (max, min)	0.218 (0.02, 5.69)	0.251(0.03, 2.41)
Stage 1, Month 6	n	26	20
	Mean ± SD	0.389 ± 0.7920	0.565 ± 0.9752
	Median (max, min)	0.134 (0.01, 3.92)	0.173 (0.01, 3.62)
Change from Baseline	n	25	20
	Mean ± SD	-0.250 ± 0.5126	0.071 ± 0.5627
	LS mean	-0.224	0.106
	Median (max, min)	-0.053 (-1.77, 0.41)	-0.057 (-0.83, 1.194)
Difference LS means migalastat minus placebo = -0.3 (95% CI: -0.6, -0.1); p = 0.0078			

Comment: The results of the Stage 1 *post-hoc* analysis showed a statistically significant reduction in the average number of IC GL-3 inclusions from baseline to month 6 in the migalastat group compared to the placebo group in subjects with amenable α-Gal A mutations. The percent reduction from baseline to month 6 in the mean number of IC GL-3 inclusions in subjects with amenable α-Gal A mutations in the migalastat group was 39% compared to 14% in the placebo group.

In Stage 2 (pre-specified analysis), for subjects with amenable α-Gal A mutations who switched to migalastat during Stage 2 (placebo-migalastat group), the average number of IC GL-3 inclusions statistically significantly decreased from month 6 to month 12 in the mITT population (difference in LS means [month 12 minus month 6] -0.320; p = 0.014). The results are summarised in below.

Table 49: AT1001-011 –Change in average number of IC GL-3 inclusions in the mITT population with amenable mutations.

Time-point	Statistic	Migalastat-Migalastat	Placebo-Migalastat
Baseline	n	25	20
	Mean ± SD	0.649 ± 1.2288	0.493 ± 0.5936
	Median (max, min)	0.218 (0.02, 5.69)	0.251(0.03, 2.41)
Stage 2, Month 12	n	22	17
	Mean ± SD	0.429 ± 0.8609	0.312 ± 0.6275
	Median (max, min)	0.147 (0.04, 3.77)	0.115 (0.03, 2.68)
Change from Baseline to	n	22	17
Month 12	Mean ± SD	-0.239 ± 0.4997	-0.243 ± 0.4038
	Median (max, min)	-0.084 (-1.92, 0.14)	-0.090 (-1.35, 0.30)
Difference LS means Month 12 compared with Month 6 for the placebo-migalastat group = -0.320 (95% CI: -0.5719, -0.-677), p = 0.014			

Comment: The results of the Stage 2 pre-specified analysis showed that the mean reduction in the average number of IC GL-3 inclusions from baseline at month 12 were similar in subjects with amenable α-Gal A mutations in the group maintained on migalastat (migalastat-migalastat) and in the group initially treated with placebo and switched to migalastat at month 6 (placebo-migalastat). In subjects with amenable α-Gal A mutations in the placebo-migalastat group, there was statistically significant reduction in the average number of IC GL-3 inclusions from month 6 (i.e., end of 6 months placebo treatment) to month 12 (i.e., end of 6 months treatment with migalastat after switching from placebo).

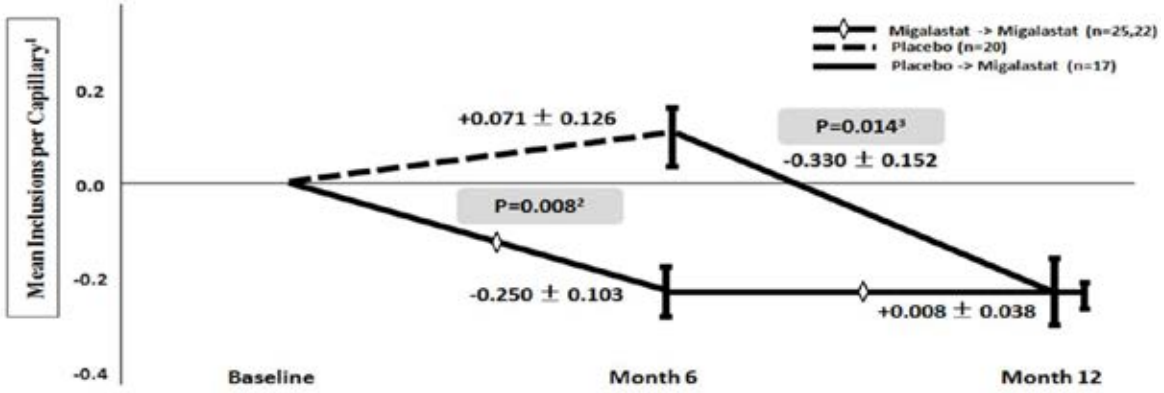
In Stage 2 (pre-specified analysis), for subjects with non-amenable α-Gal A mutations the difference in LS means for month 12 compared to Month 6 for the placebo-migalastat group (n = 9) was + 0.400 (95% CI: 0.0517, 0.7478), p = 0.025.

Comment: The results indicate that the average number of IC GL-3 inclusions increases from month 6 to month 12 in subjects with non-amenable α-Gal A mutations in the placebo-migalastat group. The results suggest that migalastat is ineffective in subjects with non-amenable α-Gal A mutations, based on change in average number of IC GL-3 inclusions.

The mean (± SEM) changes from baseline during Stage 1 (through to month 6) and Stage 2 (through to month 12) in subjects with amenable α-Gal A mutations in the migalastat-placebo and migalastat-migalastat groups are summarised below. The *post-hoc* analysis for Stage 1 demonstrated that 6 months treatment with migalastat was associated with a statistically significant greater mean (± SEM) reduction in the average number of IC GL-3 inclusions than placebo (-0.250 ± 0.103 versus +0.07 ± 0.126, respectively, p = 0.008). The pre-specified

analysis for Stage 2 demonstrated that in subjects switching from placebo to migalastat (placebo-migalastat group) a statistically significantly greater mean (± SEM) reduction from month 6 to 12 occurred than in subjects remaining on migalastat (migalastat-migalastat group) (-0.330 ± 0.152 versus +0.008 ± 0.038, respectively, p = 0.014). The reduction in the average number of IC GL-3 inclusions at month 6 (baseline through month 6) in the migalastat-migalastat group remained stable following a further 6 months of treatment (month 6 through month 12).

Figure 9: AT1001-001 – Change in IC GL-3 inclusions in Stage 1 and Stage 2 in subjects with amenable mutations; mITT population.



1. Data points (mean±SEM) are baseline-corrected data from mITT patients with amenable mutations (mITT-amenable population) and show the change in the mean number of GL-3 inclusions per IC. The change is from baseline for the migalastat-migalastat group; the change is from Month 6 for the placebo-migalastat group. 2. The statistical analysis of results at Month 6 used an ANCOVA model with covariate adjustment for baseline and factors for treatment group and treatment by baseline interaction. The p-value shown is for the LS mean difference between the migalastat-migalastat group and the placebo-migalastat group. 3. The analysis for the placebo-migalastat group of change from Month 6 to Month 12 used a mixed-models repeated measures analysis of the mITT-amenable population. Results are *post-hoc* at Month 6 and pre-specified at Month 12. Changes from baseline to Month 6 and from Month 6 to Month 12 are based on paired readings.

In the Stage 1 *post-hoc* analysis (ITT population) in subjects in the migalastat group the mean (± SD) change from baseline to month 6 in the average number of IC GL-3 inclusions was -0.250 ± 0.5126 in subjects with amenable α-Gal A mutations (n = 25) and +0.196 ± 0.3740 in subjects with non-amenable α-Gal A mutations (n = 5).

In the Stage 2 pre-specified analysis (Stage 2 population) in subjects in the placebo-migalastat group the mean (± SD) change from month 6 to month 12 in the average number of IC GL-3 inclusions was -0.330±0.6255 in subjects with amenable α-Gal A mutations (n = 17) and +0.394±0.8990 in subjects with non-amenable α-Gal A mutations (n = 9). The difference in LS means (amenable minus non-amenable) was -0.6 (95% CI: -1.0, -0.3), p = 0.0013.

Percent ICs with zero GL-3 inclusions

In the *post-hoc* MMR analysis in subjects with amenable mutations (mITT population, Stages 1 and 2 combined), there was a statistically significant greater percentage of ICs with zero GL-3 inclusions after 6 months of treatment with migalastat than with placebo. The analysis compared 6 months of active treatment with migalastat (i.e., month 6 for the migalastat-migalastat group, month 12 for the placebo-migalastat group) with 6 months of placebo treatment (month 6 for the placebo-migalastat group). The difference in LS means (migalastat minus placebo) was 5.6% in favour of migalastat (95% CI: 1.195, 10.106, p = 0.014). In this analysis, subjects with amenable α-Gal A mutations had high baseline percentages of IC with GL-3 inclusions in both the migalastat-migalastat and placebo-migalastat groups (81% versus 79%, respectively). The results are summarised below.

Table 50: AT1001-011 – Change in percent of ICs with zero GL-3 inclusions, MMR analysis in mITT population with amenable mutations.

Time-point	Statistic	Migalastat-Migalastat (n = 25)	Placebo-Migalastat (n = 20)
Baseline	n	25	20
	Mean ± SD	81.356 ± 21.070	78.686 ± 20.6234
	Median (max, min)	88.820 (13.06, 98.75)	86.830 (22.82, 97.80)
Stage 1, Month 6	n	25	20
Change from Baseline	Mean ± SD	4.286 ± 9.0344	1.502 ± 12.4819
	Median (max, min)	3.631 (-18,34, 24.68)	0.903 (-30.25, 39.64)
Stage 1, Month 12	n	22	17
Change from Baseline	Mean ± SD	3.458 ± 6.7663	9.916 ± 15.2644
	Median (max, min)	3.528 (-8.54, 24.97)	-14.28, 50.52
6 months treatment with migalastat compared with 6 months treatment with placebo: Difference in LS means (migalastat minus placebo = 5.651 (95% CI: 1.1951, 10.1064), p = 0.014.			

In the pre-specified Stage 2 MMR analysis, subjects with amenable α-Gal A mutations in the placebo-migalastat group had a statistically significant greater percentage of ICs with zero GL-3 inclusions at month 12 compared with month 6 (difference in LS means 8.1% [95% CI: 2.91, 13.37], p = 0.003). The analysis demonstrates the benefit of shifting from placebo to migalastat.

In the Stage 1 (*post-hoc*) analysis in subjects with amenable α-Gal A mutations, the percent of ICs with zero GL-3 inclusions at baseline was high in both the migalastat (n = 25) and placebo (n = 20) groups (81% versus 79%, respectively). The LS means for the change from baseline to month 6 in the percent of ICs with zero GL-3 inclusions were similar for the migalastat and the placebo groups (4.6% versus 1.5%, respectively), with LS mean difference being 3.1% (95% CI: -3.1, 9.3), p = 0.3206.

In the pre-specified Stage 2 analysis in subjects with amenable α-Gal A mutations, for the placebo-migalastat group in the Stage 2 Population, the LS mean change from month 6 to month 12 in the percent of ICs with zero GL-3 inclusions was statistically significantly greater in subjects with amenable mutations compared to subjects with non-amenable mutations (8.7% versus -3.3%, respectively, LS mean difference = 12.0% [95% CI: 3.3, 20.8], p = 0.0093.

GL-3 inclusions in other renal cells – podocytes, mesangial, and endothelial cells

A tertiary objective of the study was an exploratory assessment of GL-3 inclusions in podocytes, mesangial and endothelial cells. GL-3 inclusions in these renal cells were measured using a blinded qualitative methodology conducted by three independent renal pathologists. In brief, the pathologists assessed side–by-side digital images of baseline and post-baseline biopsies

(blinded to visit date), and categorised the biopsies as having more, less or equal GL-3 in the target cells. The results are summarised below.

Table 51: AT1001-011- Percentage of subjects with a qualitative increase or decrease in GL-3 inclusions in podocytes, mesangial, and endothelial cells, ITT population and Stage 2 population with amenable mutations.

		Placebo for 6 Months		Migalastat for 6 Months		Migalastat for 12 Months	
Parameter	Statistic	GL-3 Decrease	GL-3 Increase	GL-3 Decrease	GL-3 Increase	GL-3 Decrease	GL-3 Increase
Migalastat-Migalastat	N	N/A		28[a]		27[b]	
Cell Type		-		Month 6 Compared With Baseline		Month 12 Compared With Baseline	
Podocyte (Numerical)	%	-	-	16.0	16.0	21.7	0
Mesangial Cell	%	-	-	24.0	8.0	47.8	0
Endothelial Cell	%	-	-	24.0	4.0	26.1	0
Placebo-Migalastat	N	22[a]		20[b]		N/A	
Cell Type		Month 6 Compared With Baseline		Month 12 Compared With Month 6		-	
Podocyte (Numerical)	%	0	10.0	5.9	0	-	-
Mesangial Cell	%	35.0	25.0	35.3	5.9	-	-
Endothelial Cell	%	25.0	35.0	29.4	0	-	-

Notes: Percentages are based on the number of non-missing subjects in the respective population. Podocyte (numerical) assessment takes into account the number of podocytes with GL-3 inclusions and well as the density of GL-3 inclusions within those podocytes. a. ITT population with amenable mutations. b. Stage 2 Populations with amenable mutations.

In the Stage 1 *post-hoc* analysis in subjects with amenable α-Gal A mutations, podocyte GL-3 inclusions were: (1) lower at baseline compared to month 6 in 16% (n = 4) of subjects in the migalastat group and 0% (n = 0) of subjects in the placebo group; (2) equal to baseline at 6 months in 68% (n = 17) of subjects in the migalastat group and 90% (n = 18) of subjects in the placebo group; and (3) greater at 6 months than at baseline in 16% (n = 4) of subjects in the migalastat group and 10% (n = 2) of subjects in the placebo group. The distribution of less, equal, or more between treatment groups was not statistically significant (p = 0.4825, Mantel-Haenszel test). In all 5 subjects with non-amenable α-Gal A mutations treated with migalastat, podocyte GL-3 inclusions remained unchanged at month 6 from baseline. For endothelial cell and mesangial cell GL-3 inclusions, results in subjects with non-amenable α-Gal A mutations were similar to the results in subjects with amenable α-Gal A mutations

In the Stage 2 pre-specified analysis, all subjects in the placebo-migalastat group with non-amenable α-Gal A mutations and most subjects in the migalastat-migalastat group with non-amenable α-Gal A mutations had podocyte GL-3 inclusions at month 12 that were equal to month 6. A greater percentage of subjects in the placebo-migalastat group with non-amenable α-Gal A mutations had an increase in mesangial cell GL-3 inclusions at month 12 relative to month 6 compared to subjects with amenable α-Gal A mutations (22.2% versus 5.9%, respectively). A greater percentage of subjects in the placebo-migalastat group with non-amenable α-Gal A mutations had an increase in endothelial cell GL-3 from month 6 to month 12 compared to subjects with amenable α-Gal A mutations (22.2% versus 0%, respectively).

After 12 months treatment with migalastat, 22%, 26% and 48% of subjects with amenable α-Gal A mutations had a decrease in podocyte, endothelial and mesangial cell GL-3 inclusions, respectively. None of the subjects with amenable α-Gal A mutations had an increase in GL-3 inclusions in podocytes, endothelial or mesangial cells following 12 months treatment with migalastat.

The sponsor states that at the time of the study a reliable quantitative approach to the assessment of GL-3 in podocytes, mesangial and endothelial cells was not available. However,

the sponsor comments that a novel quantitative electron-microscopy based method has recently been developed to assess podocyte GL-3. The sponsor reports that pilot data in 5 male subjects from *Study AT1001-011* with amenable α-Gal A mutations using this methodology demonstrates a reduction in podocyte GL-3 in all 5 subjects.

eGFR

In the Stage 1 (*post-hoc*) analysis, in subjects with amenable α-Gal A mutations (ITT population) neither the $eGFR_{CKD-EPI}$ nor the $eGFR_{MDRD}$ changed notably from baseline to month 6 in either the migalastat or placebo groups. In addition, there were no notable differences between the two treatment groups. At month 6, no subjects had a ≥ 30% decrease from baseline in eGFR. The results are summarised below in Table 53.

Table 52: AT1001-011 – Stage 1 (*post-hoc*) change from baseline to month 6 and rate of change per year in eGFR parameters, ITT population including amenable subjects.

	eGFRCKD-EPI mL/min/1.73 m²		eGFRMDRD mL/min/1.73 m²	
Mean ± SD	Migalastat	Placebo	Migalastat	Placebo
Baseline	94.4 ± 26.98 [n = 28]	90.6 ± 17.13 [n = 22]	87.1 ± 30.25 [n = 28]	83.0 ± 18.78 [n = 22]
Month 6	95.3 ± 28.48 [n = 28]	91.4 ± 20.78 [n = 20]	89.3 ± 32.03 [n = 28]	83.4 ± 20.41 [n = 20]
Rate of change / year	0.3 ± 17.05 [n = 28]	2.0 ± 15.36 [n = 20]	4.60 ± 30.175 [n = 28]	1.88 ± 16.058 [n = 20]
			Difference in LSM (migalastat minus placebo) = 2.9 (95% CI: -12.6, 18.5), p = 0.7062	

In Stage 2 (pre-specified) analysis, $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ did not change notably from month 6 to month 12. In addition, there were no notable differences between the two treatment groups (placebo-migalastat, migalastat-migalastat) in the Stage 2 population. At month 12, no subjects had a ≥ 30% decrease from baseline in the eGFR.

Both $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ remained stable in subjects with amenable α-Gal A mutations throughout the study for up to 18 months of migalastat treatment (placebo-migalastat group) or 24 months of migalastat (migalastat-migalastat group). The mean annualised changes for the GFR parameters in subjects with amenable α-Gal A mutations treated with migalastat for 18 or 24 months are summarised below.

Table 53: AT1001-011 – Annualised change in GFR parameters in the open-label extension population with amenable mutations treated with migalastat for 18 or 24 months.

Annualized Change	Statistic	Total
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	n	41
	Mean (SEM)	-0.30 (0.663)
$eGFR_{MDRD}$ (mL/min/1.73 m^2)	n	41
	Mean (SEM)	0.79 (1.027)
$mGFR_{iohexol}$ (mL/min/1.73 m^2)	n	37
	Mean (SEM)	-1.51 (1.327)

The mean annualised change in the eGFR parameters were less favourable in male subjects than in female subjects with amenable α-Gal A mutations treated with migalastat for 18 or 24 months. In addition, the mean annualised change for both eGFR parameters demonstrated a greater decrease for subjects with amenable α-Gal A mutations with high baseline urine protein (> 1000 mg/24 h), compared to subjects with lower baseline urine protein levels. The results for $eGFR_{CKD-EPI}$ and $eGFR_{MDRD}$ at Month 24 by sex and baseline urine protein are summarised below.

Table 54: AT1001-001 – Annualised change in $eGFR_{CKD-EPI}$ at month 24 by sex and baseline urine protein, open-label extension population with amenable mutations.

		Sex		
Parameter	Statistic	Males	Females	Total
Annualized Change in $eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)				
Overall	n	14	27	41
	Mean (SEM)	-0.96 (1.013)	0.03 (0.865)	-0.30 (0.663)
Baseline Urine Protein < 100 mg/24 h	n	0	7	
	Mean (SEM)	-	0.22 (1.400)	
Baseline Urine Protein ≥ 100 mg/24 h and ≤ 1000 mg/24 h	n	12	18	
	Mean (SEM)	-0.03 (0.895)	0.16 (1.178)	
Baseline Urine Protein > 1000 mg/24 h	n	2	2	
	Mean (SEM)	-6.54 (2.049)	-1.78 (2.364)	

Note: The $eGFR_{CKD-EPI}$ is calculated as GFR = 141 x min(Scr/κ, 1)α x max(Scr/κ, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Table 55: 1AT1001-001 – Annualised change in $eGFR_{MDRD}$ at month 24 by sex and baseline urine protein, open-label extension population with amenable mutations.

Parameter	Statistic	Sex		Total
		Males	Females	
Annualized Change in $eGFR_{MDRD}$ ($mL/min/1.73\ m^2$)				
Overall	n	14	27	41
	Mean (SEM)	0.01 (1.403)	1.20 (1.392)	0.79 (1.027)
Baseline Urine Protein < 100 mg/24 h	n	0	7	
	Mean (SEM)	-	0.26 (1.385)	
Baseline Urine Protein ≥ 100 mg/24 h and ≤ 1000 mg/24 h	n	12	18	
	Mean (SEM)	0.99 (1.432)	1.84 (2.012)	
Baseline Urine Protein > 1000 mg/24 h	n	2	2	
	Mean (SEM)	-5.88 (1.750)	-1.25 (2.789)	

Note: The $eGFR_{MDRD}$ is calculated as GFR = 175 x (1/Serum Creatinine in $mg/dL^{1.154}$) x (1/Age in $years^{0.203}$) x (1.212 if Black) x (0.742 if Female).

The sponsor undertook a comparison of the annualised changes in GFR in migalastat treated subjects in *Study AT1001-011* with the natural history of renal disease in untreated patients in published studies. The sponsor stated that a comprehensive survey of published reports of renal function in untreated patients with Fabry disease revealed annual changes in eGFR ($mL/min/1.73m^2$) between -2.2 and -12.2. The annualised eGFR changes ($eGFR_{CKD-EPI}$, $eGFR_{MDRD}$) in migalastat treated patients ranged between -0.30 and +0.79 $mL/min/1.73m^2$. The results suggest that migalastat stabilises eGFR compared with eGFR reported in the natural history studies.

The sponsor undertook a statistical comparison of annualised changes in eGFR in migalastat-treated subjects from *Study AT1001-011* 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. A similar statistical analysis, stratified by gender and comparing the annualised changes in eGFR in Study AT*1001-011* with untreated patients from the published literature, also showed a statistically significant difference in the annualised rate of change in eGFR favouring migalastat. The three published studies selected for statistical comparison were chosen based on an observation period of at least 1 year, results presented separately by gender, results stratified by baseline proteinuria and GFR, and presented results included annualised rates of change in GFR. Two of the three studies reported $eGFR_{MDRD}$ and provided results by gender and baseline proteinuria, while the third study reported $eGFR_{CKD-EPI}$ and provided detailed results by gender only. The results for these analyses are summarised below.

Table 56: Annualised eGFR slopes stratified by gender and 24-hour urine protein, migalastat treated versus untreated patients.

Gender	24-h urine protein (g)	AT1001-011 Migalastat $eGFR_{MDRD}$	Schiffmann 2009 Untreated $eGFR_{MDRD}$	Schwarting 2006 Untreated $eGFR_{MDRD}$	AT1001-011 Migalastat $eGFR_{CKD-EPI}$	Wanner 2010 Untreated $eGFR_{CKD-EPI}$
Males	<0.1 (Low)	No patients	−1.6 (1.5) n=18, age=23, BL eGFR =138	-16.0 (N/A) n=1, age=30, BL eGFR =99		
	0.1-1.0 (Moderate)	+1.0 (1.4) n=12, age=45, BL eGFR=80	−3.3 (1.8) n=21, age=36, BL eGFR =85	-11.3 (8.3) n=3, age=37, BL eGFR =66	-0.96 (1.01) n=14, age=40, BL eGFR=93	−2.53 (0.21) n=121, age=33, BL eGFR=93
	>1.0 (High)	−5.9 (1.8) n=2, age=51, BL eGFR=65	−6.9 (1.5) n=22, age=39, BL eGFR =59	−8.0 (2.0) n=2, age=45, BL eGFR=56		
Females	<0.1 (Low)	+0.3 (1.4) n=7, age=42, BL eGFR=78	−0.6 (2.6) n=7, age=39, BL eGFR=92	−1.6 (1.5) n=3, age=42, BL eGFR=71		
	0.1-1.0 (Moderate)	+1.8 (2.0) n=18, age=44, BL eGFR=88	−2.2 (2.2) n=17, age=42, BL eGFR=90	-7.7 (3.3) n=9, age=52, BL eGFR=73	+0.03 (0.87) n=27, age=44, BL eGFR=96	-0.52 (0.68) n=341, age=39, BL eGFR=95
	>1.0 (High)	−1.3 (2.8) n=2, age=32, BL eGFR=103	−4.6 (2.3) n=5, age=47, BL eGFR=63	−2.5 (3.5) n=2, age=25, BL eGFR=59		

mGFRiohexol (measured iohexol GFR)

During Stage 1 (*post-hoc*), $mGFR_{iohexol}$ did not change notably in subjects (ITT population) with amenable α-Gal A mutations from baseline to month 6 in either the migalastat or placebo groups, and there were no notable differences between the two treatment groups. During Stage 2, $mGFR_{iohexol}$ did not change notably from month 6 to month 12 in the placebo-migalastat or migalastat-placebo groups, and there were no notable differences between the two treatment groups.

Overall, $mGFR_{iohexol}$ remained stable throughout the study for subjects with amenable α-Gal A mutations for up to 18 months treatment with migalastat (placebo-migalastat group) or 24 months treatment with migalastat (migalastat-migalastat group), with the mean annualised change being -1.51 mL/min/1.73 m^2. The mean annualised change for $mGFR_{iohexol}$ for subjects with amenable α-Gal A mutations was worse (i.e., greater decrease) in males compared to females (-2.98 versus -0.81 mL/min/1.73 m^2, respectively). The mean annualised change was worse (i.e., greater decrease) in subjects with high baseline urine protein (≥ 100 mg/24 h and ≤ 1000 mg/24 h), compared to subjects with lower baseline urine protein (< 100 mg/24 h). Only 1 male and 1 female subject had baseline urine protein > 1000 mg/24 h. The results for annualised change in $mGFR_{iohexol}$ the open-label extension population with amenable α-Gal A mutations at month 24 are summarised below.

Table 57: AT1001-011 - Annualised change in mGFRiohexol at month 24 by sex and baseline urine protein in the open-label extension population with amenable mutations.

Parameter	Statistic	Sex		Total
		Males	Females	
Annualized Change in $mGFR_{iohexol}$ ($mL/min/1.73\ m^2$)				
Overall	n	12	25	37
	Mean (SEM)	-2.98 (1.561)	-0.81 (1.819)	-1.51 (1.327)
Baseline Urine Protein < 100 mg/24 h	n	0	7	
	Mean (SEM)	-	3.53 (2.898)	
Baseline Urine Protein ≥ 100 mg/24 h and ≤ 1000 mg/24 h	n	11	17	
	Mean (SEM)	-3.25 (1.683)	-2.84 (2.278)	
Baseline Urine Protein > 1000 mg/24 h	n	1	1	
	Mean (SEM)	0.07 (-)	3.46 (-)	

Urine GL-3

There were no Stage 1 (*post-hoc*) analyses of urine GL-3 in subjects with amenable α-Gal A mutations in the ITT population. In the Stage 2 population with amenable α-Gal A mutations, there was a trend for a greater decrease in mean (± SD) urine GL-3 from baseline to month 6 in the migalastat group (-361 ± 878 ng/mg creatinine [n = 27]) compared to the placebo group (-147 ± 969 ng/mg creatinine [n = 20]). At the end of Stage 2, the mean (± SD) change from month 6 to month 12 was -469 ± 787 ng/mg creatinine in the placebo-migalastat group in subjects with amenable α-Gal A mutations. After 12 months of treatment, the mean (± SD) change from baseline to month 12 was -304 ± 693 ng/mg creatinine in the migalastat-migalastat group in subjects with amenable α-Gal A mutations. At the end of the open-label extension, the mean (± SD) change from baseline in the total open-label extension population with amenable α-Gal A mutations (n = 17) following 18 or 24 months treatment with migalastat was -166 ± 532 ng/mg creatinine.

24-hour urine protein, albumin, and creatinine

Most subjects in the total safety population (n = 67) had proteinuria at baseline, with 44 subjects (66%) having proteinuria > 150 mg/24 h, 22 subjects (33%) having proteinuria > 300 mg/ 24 h, and 6 subjects (9%) having proteinuria > 1000 mg/ 24 h. Of the 8 subjects (16.7%) with baseline proteinuria ≤ 100 mg/24 h, 6 had proteinuria ≤ 100 mg/24 h following treatment with migalastat for 18 to 24 months. Of the 28 patients (58.3%) with baseline proteinuria ≤ 300 mg/24 h, 23 had proteinuria ≤ 300 mg/24 h following treatment with migalastat for 18 to 24 months. Overall, the data suggest that treatment with migalastat for 18 to 24 months stabilises proteinuria (g/24h) in the majority of subjects with baseline levels ≤ 300 g/24 h, but does not appear to have a beneficial effect on subjects with higher levels of proteinuria.

In the Stage 1 (*post-hoc*) analysis in subjects with amenable α-Gal A mutations in the migalastat group the following changes in 24-hour urine concentrations of interest were observed: (1) the LS mean urine protein level increased by 69.3 mg/24 h from baseline to month 6 in the migalastat group (n = 28) and 9.6 mg/24 h in the placebo group (n = 20), p = 0.5234; (2) the LS mean urine albumin level increased by 90.2 mg/24 h from baseline to month 6 in the migalastat group (n = 28) and decreased by 24.0 mg/24 h in the placebo group (n = 20), p = 0.1325; and (3) the LS mean creatinine level increased by 0.082 mmol/24 h from baseline to month 6 in the migalastat group (n = 28) and decreased by 0.567 mg/24 h in the placebo group (n = 20), p = 0.3848.

In the open-label extension period (pre-specified) analysis in subjects with amenable α-Gal A mutations, there was a mean increase in 24-hour urine protein and albumin from baseline to month 24 in the migalastat-migalastat group (139.3 mg/24 h and 106.6 mg/24 h, respectively) and from month 6 to month 24 in the placebo-migalastat group (257.4 mg/24 h and 225.3 mg/24 h, respectively). Creatinine levels remained stable across the study.

GSRS

In the Stage 1 (*post-hoc*) analysis subjects with amenable α-Gal A mutations, the diarrhoea subscale of the GSRS improved from baseline to month 6 in the migalastat group (LS mean change, -0.3), but not in the placebo group (LS mean change, +0.2). The difference between LS mean change from baseline to month 6 between the two groups (0.5 units in favour of migalastat) was statistically significant ([95% CI: -1.0, -0.1], p = 0.0264). The sponsor refers to the published literature in a non Fabry disease population which indicates that the minimal clinically important difference (MCID) for the diarrhoea domain of the GSRS is ≥ 0.4 units. The sponsor comments that this MCID is likely to represent a clinically relevant improvement in the Fabry disease population. Based on the MCID, 69% of the migalastat-treated subjects experienced a clinically relevant change versus 11% of the placebo-treated subjects (p = 0.012).

In the Stage 1 (*post-hoc*) analysis, in subjects with amenable α-Gal A mutations and baseline symptoms of reflux, there was a statistically significant greater improvement during Stage 1 in the reflux domain in the migalastat group (LS mean, -0.6), compared to the placebo group (LS mean, +0.6); 95% CI of the LSM difference -2.4, -0.0, p = 0.0465. There were no notable changes from baseline to month 6 in the indigestion, constipation or abdominal pain domains. The results are summarised below in Table 59.

In the combined migalastat treatment group, at the end of the open-label extension there was an improvement from baseline to month 24 in subjects with amenable α-Gal A mutations with and without baseline symptoms of diarrhoea, reflux, and indigestion. There were no notable changes in the combined group in symptoms of reflux or abdominal pain.

Table 58: AT1001-001 – GSRS mean change from baseline in subscales during Stage 1 (*post-hoc*) in the ITT population and in the open-label extension population in amenable subjects.

Parameter	Statistic	Diarrhea		Reflux		Indigestion	
Stage 1		Migalastat	Placebo	Migalastat	Placebo	Migalastat	Placebo
	N	28	22	28	22	28	22
Mean Change From Baseline (Visit 1)							
All Subjects	n	28	19	28	19	28	19
	Mean	-0.3[a]	0.2	0.0	0.2	-0.1	-0.1
Subjects With Baseline Symptoms	n	17	10	10	6	23	18
	Mean	-0.6	0.2	-0.5[a]	0.3	-0.2	-0.1
Open-Label Extension		Combined group[b]		Combined group[b]		Combined group[b]	
	N	42		42		42	
Combined Change From Baseline (Visit 1)[b]							
All Subjects	n	40		40		40	
	Mean (CI)[c]	-0.5 (-0.908, -0.125)[d]		-0.2 (-0.492, 0.192)		-0.4 (-0.747, -0.040)[d]	
Subjects With Baseline Symptoms	n	24		15		36	
	Mean (CI)[c]	-1.0 (-1.519, -0.424)[d]		-0.6 (-1.480, 0.213)		-0.5 (-0.840, -0.063)[d]	

a. p-value < from ANCOVA, comparing the difference in LS means. The model includes treatment baseline and treatment by baseline interaction. b. Combined change for patients treated with migalastat for 18 or 24 months comprising migalastat-migalastat group (baseline to month 24) and placebo-migalastat group (month 6 to month 24). c. 95% CI is based on the mean. d. Statistically significantly different from baseline based on 95% CIs not overlapping with zero.

SF-36 v2

For subjects with abnormal baseline values and amenable α-Gal A mutations treated with migalastat for 18 or 24 months, improvements in SF-36 v2 scores from baseline to month 12 were observed for the vitality subscale (mean increase, 4.0) and the general health domain (mean increase, 4.5). No notable changes from baseline were observed in any other SF-36 v2 subscale or norm-based subscale scores or for the physical and mental components at any time-point.

BPI short form

In the Stage 1 (*post-hoc*) analysis, there were no notable differences in subjects with amenable α-Gal A mutations in change from baseline to month 6 between migalastat and placebo in pain scores assessed by the BPI. There were no notable changes from baseline to month 24 in subjects with amenable mutations treated with migalastat for 18 or 24 months.

ECHO

In the Stage 1 (*post-hoc*) analysis, no notable shifts at month 6 from baseline were observed in subjects with amenable α-Gal A mutations in either the migalastat or placebo groups in LVMi, LVM, fractional shortening, left ventricular ejection fraction, or left ventricular posterior wall thickness. All subjects with amenable α-Gal A mutations had normal fractional shortening at baseline and month 6, and more than 90% of subjects with amenable α-Gal A mutations in the migalastat and placebo groups had a normal LV ejection fractions at baseline and month 6.

In the Stage 2 (pre-specified) analysis, in subjects with amenable α-Gal A mutations no notable shifts from baseline in ECHO parameters were observed in either the migalastat-migalastat group or the placebo-migalastat group. At month 12, all subjects with amenable α-Gal A mutations had normal fractional shortening, and 97% of subjects with amenable α-Gal A mutations had a normal ejection fraction.

White Blood Cell (WBC) α-Gal A

In Stage 1 (*post-hoc*), in males with amenable α-Gal A mutations in the migalastat group (n = 9) in the ITT population, there was a median increase of 1.1 nmol/h/mg in WBC α-Gal A activity (n = 8) at month 1 from a median baseline activity of 0.240 nmol/h/mg (n = 8), and the median increase observed at month 1 was maintained through to month 6. No analysis of this parameter was undertaken in female subjects.

In Stage 2 (pre-specified), in males with amenable α-Gal A mutations in the placebo-migalastat group, there was a median increase of 2.7 nmol/h/mg from month 6 to month 7 after switching to migalastat (n = 9), and the median increase from month 6 observed in this group was maintained through to month 12 (2.2 nmol/h/mg [n = 9]). The median baseline and month 6 activity in the placebo-migalastat group (n = 9) was 0.4 nmol/h/mg.

In the open-label extension (pre-specified), in male subjects with amenable α-Gal A mutations (n = 12) there was a median increase (2.6 nmol/h/mg) from baseline to month 24 in patients treated with migalastat for 18 months (placebo-migalastat) or 24 months. (i.e., migalastat-migalastat).

Plasma Lyso-Gb_3

The sponsor states that plasma lyso-Gb_3 has become increasingly recognised as an important marker of disease severity in patients with Fabry disease. The sponsor comments that reductions in lyso-Gb_3 have been demonstrated to be associated with improved outcomes in Fabry disease. The sponsor notes that high plasma levels of lyso-Gb_3 have been associated with an increased risk of cerebrovascular disease in males with Fabry disease with LVH and in females with Fabry disease. Plasma lyso-Gb_3 levels were assessed in samples at baseline, month 6, month 12 and month 24.

In Stage 1 (*post-hoc*) analysis, for subjects in the ITT population with amenable α-Gal A mutations and available samples there was a statistically significant decrease from baseline to month 6 in the migalastat group compared to the placebo group. The results are summarised below in Table 60.

Table 59: AT1001-011 – Change from baseline to month 6 in plasma lyso-Gb_3 levels (nmol/L) in ITT population with amenable mutations.

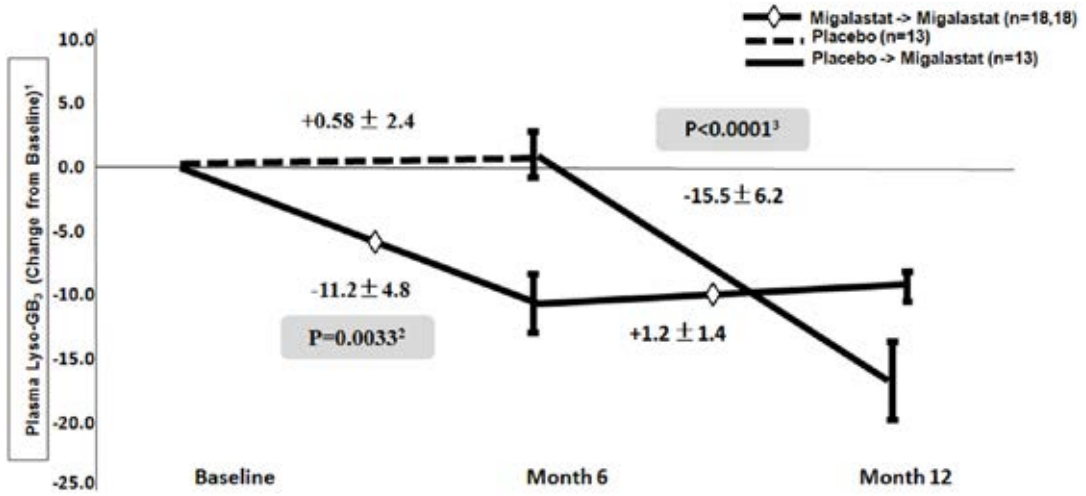
Time-point	Statistic	Migalastat	Placebo
Baseline	n	18	13
Lyso-Gb_3 (nmol/L)	Mean ± SD	47.27 ± 62.166	41.85 ± 39.144
	Median (max, min)	16.77 (1.2, 218.3)	23.27 (6.7, 113.3)
Stage 1 Change from	n	18	13
baseline at Month 6	Mean ± SD	-11.2 ± 20.196	0.58 ± 8.548
Lyso-Gb_3 (nmol/L)	LSM	-10.58	0.83
	Median (max, min)	-2.37 (-69.7, 1.8)	0.53 (-21.5, 16.3)
Difference LS mean (migalastat minus placebo) = -11.4 (95% CI: -18.7, -4.1); p = 0.0033			

The data were analysed using an ANCOVA model that included treatment as a factor with the baseline value as a covariate and a treatment by baseline interaction.

In the Stage 2 (pre-specified) analysis, in subjects in the placebo-migalastat group with amenable α-Gal A mutations and available samples the mean (± SD) plasma lyso-Gb_3 level decreased from month 6 to month 12 (mean change -15.5 nmol/L). There was a statistically significant greater decrease in plasma lyso-Gb_3 levels in the placebo-migalastat group during Stage 2 compared to Stage 1 (mean difference between change in Stage 2 and change in Stage 1, -16.1 nmol/L; $p < 0.0001$). During Stage 2, subjects in the migalastat-migalastat group with amenable α-Gal A mutations maintained the reduced levels of plasma lyso-Gb3 observed at the end of Stage 1.

The absolute change in plasma lyso-Gb_3 levels in subjects with amenable α-Gal A mutations are summarised below. The results demonstrated that the reduction in plasma lyso-Gb_3 concentration at month 6 compared to month 1 in the migalastat-migalastat group was maintained through month 12. In subjects in the placebo group, no reduction in plasma lyso-Gb3 levels was observed at month 6 compared with month 1, but a marked decrease at month 12 compared with month 6 was observed in these patients when switched to migalastat at month 6.

Figure 10: AT1001-011 – Absolute change in plasma lyso-Gb3 levels in patients with amenable mutations.

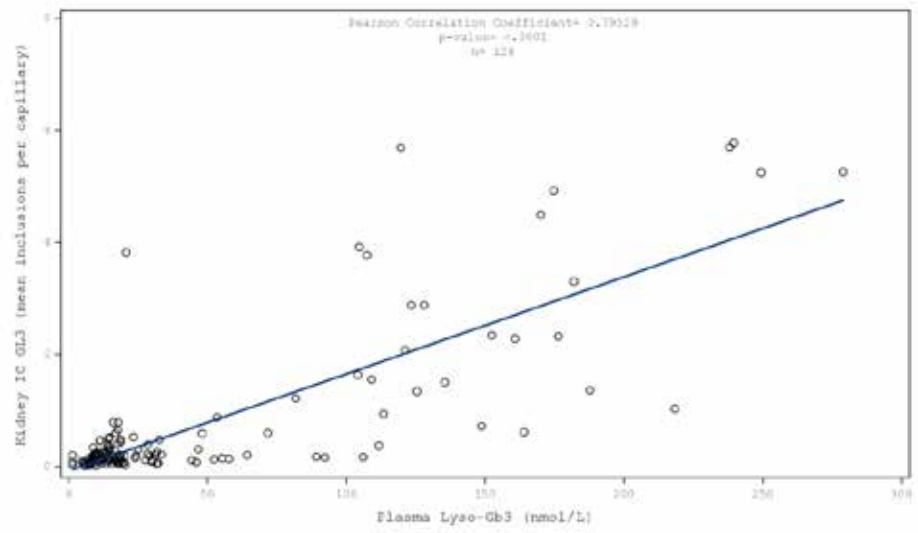


1. Data points are baseline corrected; represent mean ± SEM change from baseline to month 6 for patients with amenable mutations. 2. ANCOVA comparing baseline to month 6. 3. ANCOVA comparing change from Month 6 to Month 12 in patients switching from placebo to migalastat. The ANCOVA model included adjustment for baseline lyso-Gb_3 and factors for treatment group and treatment by baseline interactions. P-values correspond to least squares mean differences between migalastat and placebo.

During Stage 1 (*post-hoc*), there was an increase in plasma lyso-Gb_3 levels from baseline to month 6 for subjects with non-amenable α-Gal A mutations in the migalastat group (mean ± SD change = 15.48 ± 27.41 nmol/L; median change = 2.42 nmol/L), though not in the placebo group (mean ± SD change = -0.58 ± 5.73 nmol/L; median change = -0.37 nmol/L). However, the subject numbers were small (n = 6 and 7 in the migalastat and placebo groups, respectively) and inter-subject variability was high. During Stage 2, there was an increase in plasma lyso-Gb_3 levels in subjects in the placebo-migalastat group with non-amenable α-Gal A mutations (mean ± SD change from month 6 to month 12 = 4.94 ± 5.65 nmol/L; median change = 2.33 nmol/L), although the subject number was small (n = 7) and inter-subject variability high. There was also a trend for a greater increase in plasma lyso-Gb_3 levels for subjects with non-amenable α-Gal A mutations in the placebo-migalastat group during Stage 2, compared with Stage 1 (mean ± SD difference = 5.51 ± 7.11 nmol/L; median difference = 2.40 nmol/L). Stage 1 and 2 analyses in subjects with non-amenable α-Gal A mutations were exploratory, and no statistical analyses were undertaken.

In an exploratory analysis there was a statistically significant correlation between plasma lyso-Gb_3 levels and IC GL-3 inclusions in the ITT population (n = 128) with all treatment groups and time-points combined (Pearson correlation co-efficient = 0.795, < 0.0001). The results are summarised below.

Figure 11: AT1001-011 – Correlation between plasma lyso-Gb_3 level and the number of IC GL-3 inclusions, all treatment groups and time-points combined in the ITT population.



2.14 Composite clinical outcome

In subjects with amenable α-Gal A mutations, the sponsor undertook a *post-hoc* analysis of a composite clinical outcome in Stage 1 based on the methodology used in *Study AT1001-012*. The composite clinical outcome was 21% (6/28) in the migalastat group and 18% (4/22) in the placebo group, with all outcomes in both treatment groups being renal events (i.e., no cardiac or cerebrovascular events). The results are summarised below.

Table 60: Study AT1001-011 – Composite clinical outcome in subjects with amenable mutations in Stage 1 (i.e., 6 month-placebo controlled treatment period).

Parameter	Statistic	Migalastat (N=28)	Placebo (N=22)
Renal Event			
24-Hr Urine Proteina	n (%)	5 (18%)	4 (18%)
CKD-EPI eGFRb	n (%)	1 (4%)	0
Cardiac Event			
	n (%)	0	0
Cerebrovascular Event			
	n (%)	0	0

(a) An increase in 24-hour urine protein ≥ 33%, with the increased protein ≥ 300 mg/24 h relative to baseline. (b) Decrease in CKD-EPI eGFR ≥15 mL/min/1.73 m^2, with a decrease CKD-EPI eGFR <90 mL/min/1.73m^2 relative to baseline. | Notes: Cardiac event includes myocardial infarction; unstable cardiac angina, as defined by the ACC/AHA national practice guidelines; new symptomatic arrhythmia requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation; or congestive heart failure, NYHA Class III or IV. Cerebrovascular event includes stroke or transient ischemic attack. A subject may have appeared in more than 1 event category but was counted only once in the composite outcome.

Long-term efficacy data

The submission included long-term efficacy data for subjects with amenable α-Gal A mutations from *Study AT1001-011* who continued into *Study AT1001-041*. The disposition of these patients is summarised below.

Table 61: Disposition of subjects with amenable mutations continuing from *Study AT1001-011* to *Study AT1001-041*

Parameter	Number Patients (%)[1]	
	Randomised to Migalastat	Randomised to Placebo
Randomised	34	33
Amenable mutations[2]	28 (82.4)	22 (66.7)
Entered AT1001-041	19 (67.9)	16 (72.7)
Ongoing in AT1001-041	16 (57.1)	16 (72.7)
Total treatment duration		
≥ 6 months	28 (100)	18 (81.8)
≥ 12 months	25 (89.3)	18 (81.8)
≥ 18 months[3]	22 (78.6)	18 (81.8)
≥ 24 months	21 (75.0)	15 (68.2)
≥ 30 months	17 (60.7)	14 (63.6)
≥ 36 months	14 (50.0)	11 (50.0)
≥ 42 months	11 (39.3)	4 (18.2)
≥ 48 months	4 (14.3)	1 (4.5)
≥ 54 months	0	1 (4.5)
≥ 60 months	0	0

1. Percentages are based on the number of subjects with amenable mutations. 2. Based on GLP HEK assay. 3. To account for visit windows, Month 18 data represents data from subjects treated for at least 17 months.

In *Study AT1001-011*, after 18 or 24 months of migalastat treatment the mean annualised rate of change in $eGFR_{CKD-EPI}$ (± SEM) was -0.30 ± 0.66 mL/min/1.73 m^2/year. In the subjects who continued into the long-term extension *Study AT1001-041*, the annualised $eGFR_{CKD-EPI}$ remained stable over an average of 36 months of treatment (range: 18, 54 months), with the rate of change being -0.81 (95% CI: -2.00, 0.37) mL/min/1.73 m^2/year. In updated data from *Study AT1001-041*through to March 2015, $eGFR_{CKD-EPI}$ remained stable over an average of 38 months (range: 18, 55 months), with rate of change being -0.77 (95% CI: -1.94, 0.39) mL/min/1.73 m^2/year. The sponsor comments that the rate of change in GFR over an average of 38 months compares favourably to the decline in GFR in untreated Fabry disease patients reported in the literature (i.e., -2.2 to -12.2 mL/min/1.73 m^2/year), and is comparable to the annual rate of change in GFR in healthy adults (-1 mL/min/1.73 m^2/year).

In *Study AT1001-011*, after 18 or 24 months of migalastat treatment the mean changes from baseline in the LVMi were -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 the long-term *extension Study AT1001-041*, the mean changes from baseline in the LVMi after 30 to 36 months treatment with migalastat were -17.0 g/m^2 (95% CI: -26.2, -7.9) in all patients (n = 15) and -30.0 g/m^2 (95% CI: -57.9, -2.2) in patients with LVH at baseline (n = 4). In updated data from *Study AT1001-041* through to March 2015, mean changes in LVMi from baseline after 42 to 48 months of migalastat treatment were - 12.2 g/m^2 (95% CI: -28.1, 3.6) (n = 12) in all patients and -35.1g/m^2 (95% CI: -86.8, 16.6) (n = 3) in patients with LVH at baseline. The results indicate that reductions from baseline in the LVMi can be maintained with migalastat administered for 42 to 48 months in subjects with both normal cardiac function and LVH at baseline.

7.2.2. Study AT1001-012: A Randomized, Open-Label Study to Compare the Efficacy and Safety of AT1001 and Enzyme Replacement Therapy (ERT) in Patients With Fabry Disease and AT1001-Responsive *GLA* Mutations, Who Were Previously Treated With ERT.

7.2.2.1. Study design, objectives, locations and dates.

Objectives

The objective of this study was to compare the efficacy and safety of migalastat to that of Enzyme Replacement Therapy (ERT) in subjects with Fabry disease who were currently receiving ERT and who had migalastat-responsive *GLA* mutations

Design

This was a Phase III, multi-national, multi-centre, randomised, open-label, active-controlled clinical trial to evaluate the efficacy and safety of migalastat HCl (150 mg QOD) compared to ERT over 18 months of randomised treatment in male and female subjects with Fabry disease who had been receiving treatment with ERT and who had migalastat-responsive *GLA* mutations.

The study included 2 treatment periods. Period 1 was an 18-month treatment period in which subjects previously treated with ERT for at least 12 months and with migalastat-responsive *GLA* mutations were randomised 1.5:1 to switch to treatment with migalastat (150 mg QOD) or to continue treatment with ERT. Randomisation was stratified by sex and proteinuria (< 100 mg/24 h; ≥ 100 mg/24 h). 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 (150 mg QOD) and patients randomised to migalastat for Period 1 continued on migalastat (150 mg, QOD). Following completion of the OLE period (Month 30), subjects were invited to continue to receive migalastat via a separate protocol, early access, or other program depending on local regulations.

The Schedule of Assessments is summarised. The Screening Period (Visit 1) could have lasted for up to approximately 2 months. On the day of treatment initiation (Visit 2), the enrolment criteria were confirmed and the subject was randomised to ERT or migalastat. During the Treatment Period there were seven scheduled visits (Visit 3 through Visit 9), which corresponded with the end of Months 1, 3, 6, 9, 12, 15, and 18. There were four visits during the Optional Extension Period (Visit 10, 11, 12, and 13), which corresponded with the end of Months 19, 21, 24, and 30, and one Follow-Up visit (Visit 14) within 1 month after the last treatment visit (Visit 9 or 13).

An independent Data Safety Monitoring Board (DSMB) was chartered to monitor and evaluate the safety of all subjects in the study by periodically reviewing the safety data, evaluating risk/benefit where possible, identifying any clinically relevant trends, and assessing whether it was safe for the study to continue.

Comment: This was an open-label, active-controlled study. Therefore, the study is subject to the well-known biases associated with clinical trials that are not double-blinded. However, the two primary endpoints were objective endpoints (i.e., annualised rates of change for $GFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$). The use of objective endpoints to measure efficacy are considered to mitigate the bias associated with the open-label comparison of the two treatment groups. The active-control treatment in this study was ERT, which is an approved therapy in Australia for the treatment of patients with Fabry disease. The evaluation of the efficacy of migalastat in subjects who were switched from previous therapy with ERT compared with subjects who were maintained on ERT is considered to be clinically relevant. If migalastat is approved, then switching from ERT to migalastat will be a treatment option for patients with Fabry disease. It is noted that previous treatment with ERT could have been with either agalsidase α or β, which increased the number of subjects eligible for enrolment.

In this study, assessment of migalastat responsiveness of α-Gal A mutations during enrolment for all subjects was determined by the Clinical Trial HEK assay. However, a third party GLP HEK assay was validated after enrolment of all subjects in the study. Therefore, the α-Gal A mutation status all subjects in the study was re-assessed using the GLP HEK assay. This re-assessment took place prior to the database lock for the 18-month randomised treatment period. Consequently, all analyses in the study were undertaken on subjects categorised as amenable or non-amenable based on the GLP HEK assay. The GLP HEK assay changed the classification of 4 subjects (2 in each treatment group) from migalastat responsive α-Gal A mutations based on the Clinical Trial HEK assay to migalastat non-amenable α-Gal A mutations based on the GLP HEK assay.

Location and dates

The coordinating investigator was located at the Royal Melbourne Hospital, Melbourne, Victoria, Australia. The study was undertaken at 25 study centres in 10 countries (Australia, Austria, Belgium, Brazil, Denmark, France, Italy, Japan, the UK, and the USA). The first subject was enrolled on 8 September 2011 and the last subject completed the study on 28 May 2015. Two separate CSRs were included in the submission (18-month [dated 9 March 2015] and 30-month [dated 31 March 2016]).

7.2.2.2. Inclusion and exclusion criteria

The study included male and female subjects with Fabry disease aged between 16 and 74 years, inclusive, at screening. Subjects were required to have a confirmed *GLA* mutation shown to be responsive to migalastat by the Clinical Trial HEK assay or a confirmed *GLA* mutation that was not testable using this assay. Subjects were also required to have initiated treatment with ERT at least 12 months before starting study treatment. Subjects were also required to have a GFR ≥ 30 mL/min/1.73 m^2. The exclusion criteria included subjects with clinically significant conditions associated with Fabry disease (including cardiac, renal or cerebrovascular disease), and/or other clinical conditions that would preclude participation in the study. Patients who required treatment with miglitol or miglustat were excluded from the study. The inclusion and exclusion criteria for this study are summarised. The protocol included pre-specified criteria for withdrawing subjects from the study. These have been examined and are considered to be acceptable.

7.2.2.3. Study treatments

Study drugs

During Period 1 (18-month randomised treatment period), subjects in the migalastat group took migalastat (150 mg capsule) orally QOD at approximately the same time each day, and inactive reminder capsules on alternate days. Subjects were required to fast 2 hours before and 2 hours after taking each dose of migalastat, and to otherwise maintain normal food and fluid intake for the duration of the study.

The active control during the 18-month randomised treatment period was ERT (agalsidase α or agalsidase β, referred to interchangeably as agalsidase). Throughout the screening period and the 18-month randomised treatment period, commercially available agalsidase for IV infusions was prescribed by the subject's treating physician and was administered in accordance with the approved prescribing information. All subjects were to continue ERT during the screening period, and were to be given at least 80% of their currently labelled dose and regimen. Subjects randomised to the ERT group were to continue to receive at least 80% of their currently labelled dose and regimen during the 18-month randomised treatment period.

During Period 2 (OLE period), subjects who received migalastat during the 18-month randomised treatment period continued to receive migalastat (migalastat-migalastat group), while subjects who had received ERT switched to treatment with migalastat (ERT-migalastat

group). During the OLE period, all subjects took 1 migalastat (150 mg) capsule orally QOD at approximately the same time each day and inactive reminder capsules on alternating days.

Comment: There were no data in the CSR indicating whether the agalsidase formulations were the same in each of the centres contributing subjects to the study. In addition, there were no data in the submission defining the relationship between the agalsidase formulations used in the study and the Australian approved products. The sponsor is requested to comment on these matters (see Questions). In *Study AT1001-012*, subjects taking migalastat 150 mg QOD took an inactive reminder capsule on alternating days. No inactive capsules on alternating days were taken in *Study AT1001-011* by subjects taking migalastat 150 mg QOD. This is not considered to be a significant clinical issue.

Prior and concomitant therapy

Concomitant medications taken within 1 month prior to screening or at any time throughout the study were recorded in the eCRF, along with the reason for use, dates of administration, dosages, and frequency. Subjects taking ACEIs or ARBs must have been on a stable dose for at least 1 month before Visit 1.

Use of the following concomitant medications was prohibited while on study: (1) any investigational/experimental therapy; (2) miglitol; and (3) miglustat. If any prohibited medications were taken, or if the investigator determined that the subject required treatment with a prohibited medication, then the subject was prematurely discontinued from the study and the study assessments performed at the last relevant treatment visit.

The study permitted enrolment of subjects with eGFR ≥ 30 mL/min/1.73 m^2. In subjects with chronic kidney disease, inhibitors of the renin-angiotensin system (RAS) as well as other drugs that could affect renal perfusion might have reduced the GFR and confounded the primary efficacy parameters. Therefore, the sponsor requested that investigators give due consideration before initiating treatment with, or making dosing changes during the treatment period to, drugs that inhibited the RAS or could modify renal perfusion.

Treatment compliance

Dosing compliance was assessed at each clinic visit. Subjects who were not 100% compliant (at least 4 consecutive active capsules) when they arrived for their study visit were asked to return within 7 to 10 days to draw an additional blood sample for measurement of α-Gal A activity.

7.2.2.4. Efficacy variables and outcomes

Primary efficacy endpoint

The study had two co-primary efficacy endpoints, which were the annualised rates of change in the $mGFR_{iohexol}$ and the $eGFR_{CKD\text{-}EPI}$ from Baseline through Month 18.

Comment: These two co-primary efficacy endpoints are considered to be clinically meaningful. Progressive renal disease resulting in ESRD is associated with untreated Fabry disease. The sponsor states that '[a]lthough measured GFR (mGFR) using urinary or plasma clearance of exogenous filtration markers [e.g., iohexol] has been thought of as the gold standard for determining renal function in an individual subject at a given time, there are various reasons that mGFR methodology may be associated with higher variability in a clinical study setting. For example, day to day variability in mGFR is affected by protein intake, exercise, and diurnal variation. Sources of variability in measurement include inconsistent timing of blood draws for plasma iohexol determinations. Assessment of eGFR has been established as a reliable measure to monitor the progression of chronic kidney disease in clinical study settings'. The sponsor's rationale for selection of the two co-primary efficacy endpoints is considered to be acceptable.

Secondary efficacy endpoints

The secondary efficacy endpoints were:

- Change from baseline in the $mGFR_{iohexol}$ and change from baseline in $eGFR_{MDRD}$.
- Change from baseline and annualised rate of change in the $eGFR_{MDRD}$.
- Change from baseline in 24-hour urine protein and 24-hour urine albumin:creatinine ratio.
- Composite clinical outcome of proportion of subjects with renal, cardiac, cerebrovascular event or death. The following events contributed to the composite clinical outcome: (1) renal events (decrease in $eGFR_{CKD-EP}$I ≥ 15 mL/min/1.73 m^2 with the decreased eGFR < 90 mL/min/1.73 m^2 relative to baseline; increase in 24-hour urine protein ≥ 33%, with the increased protein ≥ 300 mg relative to baseline); (2) cardiac events (myocardial infarction; unstable cardiac angina, as defined by the American College of Cardiology/American Heart Association national practice guidelines; new symptomatic arrhythmia requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation); (3) cerebrovascular events (stroke; transient ischaemic attack); and (4) death.
- Change from baseline in ECHO parameters LVMi and LVEF.
- Change from baseline in plasma lyso-Gb_3 levels.
- Change from baseline in WBC α-Gal A Activity
- Change from baseline in BPI short form.
- Change from baseline in SF-36 v2 subscales.

Comment: The secondary efficacy parameters are considered to be clinically meaningful. In contrast to *Study AT1001-011*, *Study AT1001-012* did not include histological assessment of IC GL-3 based on renal biopsy.

Tertiary efficacy endpoints

Change from baseline in ECHO additional parameters of left ventricular mass (LVM), intra-ventricular septum wall thickness, left ventricular fractional shortening, left ventricular posterior wall thickness, functional diastolic grade, and functional systolic grade.

7.2.2.5. Randomisation and blinding methods

After study eligibility was confirmed at Visit 2, subjects were randomised using an Interactive Voice Response System (IVRS) in a 1.5:1 ratio to either stop ERT treatment and start treatment with migalastat or to continue treatment with ERT. Randomisation was stratified by sex and proteinuria (< 100 mg/24 h; ≥ 100 mg/24 h). The study was open-label. Therefore, no blinding procedures were undertaken.

7.2.2.6. Analysis populations

The Intent-to-Treat (ITT) Population included all randomised subjects regardless of participation in the study beyond randomisation.

The modified ITT (mITT) Population included all randomised subjects with α-Gal A mutations amenable to migalastat in the GLP HEK assay who received at least 1 dose of study drug, and had both a baseline and a post-baseline efficacy measure of $mGFR_{iohexol}$ and a post-baseline measure of $eGFR_{CKD-EPI}$. The co-primary primary efficacy endpoint analysis was performed in the mITT population.

The Safety Population included all subjects in the ITT population who received at least 1 dose of study drug during the 18-month randomised treatment period. Subjects were classified according to the treatment received.

The OLE Population included all subjects who completed the 18-month randomised treatment period and took at least 1 dose of migalastat during the 12-month optional OLE period. The OLE Population was used for all 30-month analyses, and subjects were classified in the migalastat-migalastat and ERT-migalastat groups according to the treatment received.

The analysis populations by treatment group are summarised below.

Table 62: Study AT1001-012 – analysis populations by treatment group.

		Randomized Treatment Groups			Extension Period Treatment Groups		
Parameter	Statistic	Migalastat	ERT	Total	Migalastat Migalastat	ERT Migalastat	Total
Number of Subjects Enrolled (Signed Informed Consent)	N	-	-	68	-	-	-
Number of Randomized Subjects	N	36	24	60	-	-	-
Number of Randomized Amenable Subjects	n (%)	34 (94)	22 (92)	56 (93)	-	-	-
Number of Subjects in the ITT Population	n (%)	36 (100)	24 (100)	60 (100)	33 (92)	15 (63)	48 (80)
Number of Subjects in the OLE Population	n (%)	-	-	-	33 (92)	15 (63)	48 (80)
Number of Amenable Subjects in the OLE Population	n (%)	-	-	-	31 (86)	15 (63)	46 (77)

7.2.2.7. Sample size

The sample size for the 18-month randomised treatment period was calculated based on the co-primary endpoint of $mGFR_{iohexol}$ and the measure of comparability between the migalastat and ERT treatment groups specified in Version 1.0 of the clinical study protocol (i.e., overlap of the 95% CIs for the annualised change from baseline in $mGFR_{iohexol}$ for the two treatment groups). In the 18-month randomised treatment period, the planned enrolment was approximately 50 subjects (approximately 30 subjects in the migalastat group and 20 subjects in the ERT group). The annual decline of $mGFR_{iohexol}$ in the ERT group was expected to be between 2 and 4 mL/min/1.73 m^2 with a standard deviation of approximately 7.5 to 8.5 mL/min/1.73 m^2. If the expected mean annual decline of $mGFR_{iohexol}$ in the migalastat group ranged from 3 to 7.5 mL/min/1.73 m^2, and the above assumptions were correct, then a sample size of 50 subjects would allow for a substantial overlap of the 95% CIs for the mean change from baseline in $mGFR_{iohexol}$ for the 2 treatment groups.

7.2.2.8. Statistical methods

Month 0 to Month 18 (randomised, active-controlled treatment period)

The sponsor stated that, since Fabry disease is a very rare disease and the number of patients who could be enrolled in a trial was limited, a traditional non-inferiority analysis based on the 95% CI of the difference between the two treatment groups was not feasible, as the available sample size would not have proved adequate for this type of analysis. Therefore, based on interactions with the Scientific Advice Working Party of the EMA, pre-specified criteria were developed to enable a descriptive comparison of the GFR results for migalastat and ERT.

The annualised rates of change in $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$ from baseline through month 18 were analysed using an analysis of covariance (ANCOVA) model with the following factors and covariates: treatment group, sex, age, baseline GFR ($mGFR_{iohexol}$ or $eGFR_{CKD\text{-}EPI}$) and baseline 24-hour urine protein. Descriptive statistics for the annualised rate of change from Baseline to Month 18 were generated for each treatment group from the ANCOVA model, including least squares (LS) means and 95% CIs.

The measure of comparability in the annualised rate of change in $mGFR_{iohexol}$ and $eGFR_{CKD\text{-}EPI}$ between migalastat and ERT was assessed in 2 ways:

- The percent of the width of the migalastat 95% CI that was at or above the lower bound of the ERT 95% CI was calculated. If this percent was > 50%, the conclusion would be that migalastat was comparable to ERT.

- The LS mean annualised rate of change in GFR for the migalastat group and ERT group was compared. If the migalastat LS mean annualised change in GFR was no lower than 2.2 mL/min/1.73 m^2/year below the ERT mean annualised rate of change in GFR, the conclusion would be that migalastat was comparable to ERT. This difference of 2.2 mL/min/1.73 m^2/year was based on the smallest expected rate of decline in eGFR for subjects treated with agalsidase alfa for 18 months from the literature, and was supported by other studies of ERT in the literature.

Comment: No statistical inference testing was undertaken, therefore, no hypothesis testing was performed. All analyses were performed with descriptive statistics and consequently, no adjustments were required for multiplicity of testing. Where appropriate, 2-sided 95% CIs were provided for summary purposes. No missing data were imputed. The preferable method of statistical analysis would have been to use inferential methods testing non-inferiority between the two randomised, double-blind, treatment groups. However, based on sample size considerations arising from the rarity of Fabry disease the EMA accepted non-inferential, descriptive analysis to compare the two unblinded treatment groups. This is considered to be acceptable.

Month 30 analyses

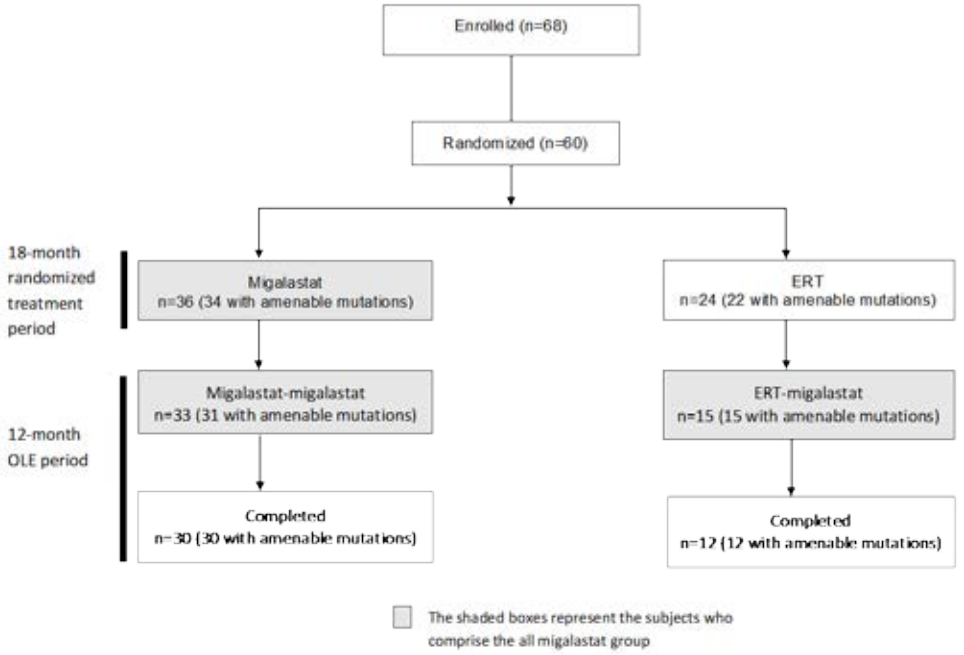
The primary analyses of efficacy in the 30-month analyses were performed on the open-label extension (OLE) population in the migalastat-migalastat and ERT-migalastat groups with amenable *GLA* mutations. The OLE Population consisted of 33 subjects in the migalastat-migalastat group and 15 subjects in the ERT-migalastat group. Two (2) subjects in the migalastat-migalastat group and no subjects in the ERT-migalastat group had non-amenable *GLA* mutations in the OLE population. Supportive analyses were performed on the mITT population with the all migalastat group.

7.2.2.9. Participant flow

Overall

A total of 68 subjects were enrolled in the study, and 60 subjects were randomised (36 to the migalastat group, and 24 to the ERT group). A total of 52 subjects completed the 18-month randomised treatment period, 38 in the migalastat group and 14 in the ERT group. Of the 52 subjects who completed the 18-month randomised treatment period, 48 were treated in the 12-month OLE period (OLE Population). Of the 48 subjects in the OLE population, 46 had amenable *GLA* mutations (31 in the migalastat-migalastat group and 15 in the ERT-migalastat group). The disposition of subjects in the study is summarised below.

Figure 12: AT1001-012 – Subject disposition.



Month 0 to month 18 – (randomised, active-controlled treatment period)

The subject disposition at the end of the month 0 to month 18 randomised, active-controlled, treatment period based on subjects in the safety population is summarised below. All subjects who failed to complete the 18 month treatment period did so because they withdrew consent.

Table 63: AT1001-012 – Subject disposition at the end of 18 months randomised, active-controlled treatment based on the safety population, percentages based on subjects in the safety population.

Parameter – number of subjects	Migalastat	ERT	Total
Randomised population	36	24	60
Safety population	36	21	57
Subjects completing 18 months of treatment			
Yes	34 (94%)	18 (86%)	52 (91%)
No	2 (6%)	3 (14%)	5 (9%)
Reason for discontinuing per CRF			
Adverse events	0	0	0
Physician decision	0	0	0
Lost to follow-up	0	0	0

Parameter – number of subjects	Migalastat	ERT	Total
Non-compliance with study drug	0	0	0
Pregnancy	0	0	0
Protocol violation	0	0	0
Lack of efficacy	0	0	0
Withdrawal by subject	2 (6%)	3 (14%)	5 (9%)
Study terminated by the sponsor	0	0	0
Death	0	0	0

Disposition through to end of month 30

The subject disposition of the OLE population in subjects with amenable *GLA* mutations is summarised below.

Table 64: AT1001-012 – Subject disposition at the end of the study in the OLE population in subjects with amenable mutations.

Parameter – number of subjects	Migalastat	ERT	Total
Subjects in the OLE population	31	15	46
Subjects completing 12 months OLE treatment			
Yes	30 (97%)	12 (80%)	42 (91%)
No	1 (3%)	3 (20%)	4 (9%)
Reason for discontinuing per CRF			
Adverse events	0	0	0
Physician decision	0	1	1
Lost to follow-up	0	1	1
Non-compliance with study drug	0	0	0
Pregnancy	1	0	1
Protocol violation	0	0	0

Parameter – number of subjects	Migalastat	ERT	Total
Lack of efficacy	0	0	0
Withdrawal by subject	0	1	1
Study terminated by the sponsor	0	0	0
Death	0	0	0

Of the 52 subjects who completed the 18 month randomised, active-controlled treatment period, 48 were treated in the 12-month OLE period (OLE Population), and 46 of these 48 subjects had amenable *GLA* mutations (31 in the migalastat-migalastat group and 15 in the ERT-migalastat group). Of the 46 subjects with amenable mutations, 42 (91%) completed the 12 month OLE period (30 [97%] in the migalastat-migalastat group and 12 [80%] in the ERT-migalastat group).

7.2.2.10. Major protocol deviations

In the 18 month, randomised, active-controlled treatment period there were 8 subjects with protocol violations (2 in the migalastat group, 6 in the ERT group). All protocol violations consisted of a change in the use of ACEIs, ARBs, or RIs during the 18-month treatment period. During the 18-month treatment period, 39 subjects had a protocol deviation in study procedures criteria, the majority of which were due to specific procedures being missed at visits. A total of 35 subjects had a protocol deviation in visit schedule criteria, the majority being due to visits occurring outside the protocol-defined visit windows. Other common protocol deviations were in the categories of study drug compliance (23 subjects), laboratory assessment criteria (18 subjects), and informed consent (16 subjects). All subjects provided informed consent before their participation in the study.

During the OLE period, 41 subjects (85%) had a protocol deviation in study drug compliance. These deviations were mainly due to subjects missing a dose or not taking inactive reminder capsules. Other common protocol deviations were in the categories of study procedures (40 subjects), mainly due to missed procedures such as assessments of respiratory rate, telephone contacts, and MRIs; visit schedule criteria (36 subjects), mainly due to visits outside of a visit window; informed consent (32 subjects); and laboratory assessment criteria deviations (28 subjects), mainly due to lost or unstable specimens. All subjects provided informed consent before their participation in the OLE study.

Comment: The protocol deviations documented during the study are considered not to have affected the assessment of safety or efficacy. In both the 18-month, randomised, active-controlled treatment period and the 12-month OLE period, there were a number of subjects with protocol deviations relating to missing a dose of the study drug. However, these events did not translate into subjects being discontinued due to non-compliance with study drug treatment. In both the 18-month treatment period and the 12-month OLE period, no subjects with amenable *GLA* mutations were discontinued due to non-compliance with the study drug and no subjects were discontinued due to a protocol violation. In the 18-month treatment period, study drug compliance in the safety population was high in both the migalastat group (99%) and the ERT group (97%). Similarly, in the 12-month OLE period study drug compliance in the OLE population was high in both the ERT-migalastat group (98%) and the migalastat-migalastat group (99%).

7.2.2.11. Baseline demographics

In the 18-month, randomised, active-controlled treatment period the demographic characteristics were comparable between the two treatment groups in the ITT population. The demographic characteristics in the ITT and OLE populations are summarised below.

Table 65: AT1001-012 – Demographic characteristics of the ITT population in the 18-month randomised, active-controlled treatment period.

Parameter		Migalastat (n = 36)	ERT (n = 24)	Total (n = 60)
Age	mean ± SD	50.5 ± 13.76	44.9 ± 14.47	48.2 ± 14.20
	range	18, 70	18, 72	18, 72
Age ≤ 65 years	n (%)	33 (92)	22 (92)	55 (92)
Age > 65 years	n (%)	3 (8)	2 (8)	5 (8)
Gender Male	n (%)	16 (44)	10 (42)	26 (43)
Gender Female	n (%)	20 (56)	14 (58)	34 (57)
Race – American Indian or Alaska Native	n (%)	0	0	0
Race – Asian	n (%)	5 (14)	2 (8)	7 (12)
Race – Black or African American	n (%)	1 (3)	0	1 (2)
Race – Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
White	n (%)	29 (81)	22 (92)	51 (85)
Multiple	n (%)	1 (3)	0	1 (2)
Other	n (%)	0	0	0

Table 66: AT1001-012 – Demographic characteristics of the OLE population.

Parameter		Migalastat-Migalastat (n = 33)	ERT-Migalastat (n = 15)	Total (n = 48)
Age	mean ± SD	50.3 ± 14.37	45.3 ± 15.69	48.7 ± 14.80
	range	18, 70	18, 70	18, 70
Age ≤ 65 years	n (%)	30 (91)	14 (93)	44 (92)
Age > 65 years	n (%)	3 (9)	1 (7)	4 (8)

Parameter		Migalastat-Migalastat (n = 33)	ERT-Migalastat (n = 15)	Total (n = 48)
Gender Male	n (%)	16 (48)	5 (33)	21 (44)
Gender Female	n (%)	17 (52)	10 (67)	27 (56)
Race – American Indian or Alaska Native	n (%)	0	0	0
Race – Asian	n (%)	5 (15)	1 (7)	6 (13)
Race – Black or African American	n (%)	1 (3)	0	1 (2)
Race – Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
White	n (%)	26 (79)	14 (93)	40 (83)
Multiple	n (%)	1 (3)	0	1 (2)
Other	n (%)	0	0	0

7.2.2.12. Baseline disease characteristic

The baseline disease characteristics in the safety population in the randomised, active-controlled 18-month treatment period are summarised below. The mean time since diagnosis was 11.4 years. Most subjects (65%) were receiving agalsidase alfa at baseline, and 33% of subjects were receiving agalsidase beta. For one subject, ERT at baseline was not collected.

In the total population, the mean $eGFR_{CKD\text{-}EPI}$ was 91.9 mL/min/1.73 m^2, and 48% of subjects had baseline levels < 90 mL/min/1.73 m^2. The mean $mGFR_{iohexol}$ was 82.8 mL/min/1.73 m^2, and 66% of subjects had baseline levels < 90 mL/min/1.73 m^2. In the total safety population, 58% of subjects had baseline 24-hour urine protein levels ≥ 100 mg/24 h (58% in the migalastat group; 57% in the ERT group).

Table 67: AT1001-012 – Randomised, active-controlled, 18-month treatment period, safety population.

Parameter	Statistic	Treatment Group		Total
		Migalastat	ERT	
Number of Subjects in the Safety Population	N	36	21	57
Sex				
Male	n (%)	16 (44)	9 (43)	25 (44)
Female	n (%)	20 (56)	12 (57)	32 (56)
Age (years)	Median	54.0	48.0	53.0
	Min, Max	18, 70	18, 72	18, 72
Number of Years Since Diagnosis of Fabry Disease	Mean (SD)	10.2 (11.76)	13.4 (12.47)	11.4 (12.02)
24-Hour Urine Protein at Baseline (mg/24 h)	Mean	267.0	360.0	301.2
	SD	411.15	693.27	528.54
	Median	129.0	108.0	128.0
	Min, Max	0, 2282	0, 3154	0, 3154
$mGFR_{iohexol}$ (mL/min/1.73 m^2)	Mean	82.37	83.58	82.81
	SD	18.105	23.938	20.245
	Median	81.30	85.10	81.40
	Min, Max	51.7, 124.0	33.0, 132.2	33.0, 132.2
$eGFR_{CKD-EPI}$ (mL/min/1.73 m^2)	Mean	89.583	95.783	91.867
	SD	22.1982	19.2021	21.1841
	Median	85.914	96.840	89.932
	Min, Max	51.33, 145.12	44.83, 129.52	44.83, 145.12
ERT at Baseline				
Agalsidase beta	n (%)	11 (31)	8 (38)	19 (33)
Agalsidase alfa	n (%)	24 (67)	13 (62)	37 (65)
Use of ACEIs/ARB/RIs at Baseline	n (%)	16 (44)	11 (52)	27 (47)
Amenable subjects (GLP HEK assay)	n (%)	34 (94)	19 (90)	53 (93)

Baseline disease characteristics for the OLE population were comparable between the migalastat-migalastat and ERT-migalastat treatment groups (i.e., baseline is disease characteristics at the beginning of the 18-month randomised treatment period). Overall, the mean time since diagnosis was 12.7 years. Most subjects (67%) were receiving agalsidase alfa at baseline, and 31% of subjects were receiving agalsidase beta. For one subject, ERT at baseline was not collected. A total of 46% of subjects were receiving ACEIs, ARBs, or RIs at baseline. Approximately half of subjects (56%) had ≥ 100 mg protein in their 24-hour urine. The mean $eGFR_{CKD-EPI}$ was 92.3 mL/min/1.73 m^2, and the mean $mGFR_{iohexol}$ was 82.3 mL/min/1.73 m^2. There were no notable differences between treatment groups at baseline in the urine albumin:creatinine ratio, urine protein:creatinine ratio, $mGFR_{iohexol}$, $eGFR_{CKD-EPI}$, or $eGFR_{MDRD}$. The baseline disease characteristics for the OLE population are summarised below in Table 69. The baseline characteristics of the subjects in the OLE were similar to those in the safety population.

Table 68: AT1001-012 – Baseline characteristics in the OLE population.

Parameter	Statistic	Treatment Group: Migalastat-Migalastat	Treatment Group: ERT-Migalastat	Total
Number of Subjects in the OLE Population	N	33	15	48
Sex				
Male	n (%)	16 (48)	5 (33)	21 (44)
Female	n (%)	17 (52)	10 (67)	27 (56)
Age (years)	Median	54.0	48.0	52.5
	Min, Max	18, 70	18, 70	18, 70
Number of Years Since Diagnosis of Fabry Disease	Mean (SD)	10.6 (12.16)	16.1 (13.62)	12.3 (12.74)
24-Hour Urine Protein at Baseline (mg/24 h)	Mean	276.1	372.6	306.3
	SD	427.23	800.51	563.20
	Median	128.0	108.0	123.5
	Min, Max	0, 2282	0, 3154	0, 3154
$mGFR_{iohexol}$ (mL/min/1.73 m)	Mean	82.84	81.18	82.32
	SD	18.800	25.908	21.004
	Median	81.40	74.30	81.30
	Min, Max	51.7, 124.0	33.0, 132.2	33.0, 132.2
$eGFR_{CKD-EPI}$ (mL/min/1.73 m)	Mean	90.589	96.045	92.294
	SD	22.8936	20.9965	22.2417
	Median	88.129	96.840	92.110
	Min, Max	51.33, 145.12	44.83, 129.52	44.83, 145.12
ERT at Baseline				
Agalsidase beta	n (%)	10 (30)	5 (33)	15 (31)
Agalsidase alfa	n (%)	22 (67)	10 (67)	32 (67)
Use of ACEIs/ARB/RIs at Baseline	n (%)	15 (45)	7 (47)	22 (46)
Amenable subjects (GLP HEK assay)	n (%)	31 (94)	15 (100)	46 (96)

7.2.2.13. Medical history and concurrent illness

In the safety population, the medical history was comparable between migalastat and ERT treatment groups. The most commonly involved system organ classes (≥ 50% of subjects) in the safety population were nervous system disorders (81%), cardiac disorders (63%), gastrointestinal disorders (63%), renal and urinary disorders (60%), skin and subcutaneous tissue disorders (56%), ear and labyrinth disorders (54%), musculoskeletal and connective tissue disorders (54%), and metabolism and nutrition disorders (51%). The most common medical history preferred terms (≥ 30% of subjects) in the total safety population were paraesthesia (39%), hypertension (33%), proteinuria (32%), angiokeratoma (32%), and left ventricular hypertrophy (30%). The medical history in the OLE was qualitatively and quantitatively similar to that in the overall safety population.

7.2.2.14. Prior and concomitant medications

In the OLE population, previous medications were reported in all subjects in both the migalastat-migalastat and ERT-migalastat treatment groups. Previous medications reported in ≥ 20% of subjects in either of the two treatment groups (migalastat-migalastat versus ERT-migalastat) were Replagal (36% versus 60%), aspirin (30% versus 13%), paracetamol (24% versus 33%), Fabrazyme (21% versus 27%), and ibuprofen (21% versus 27%).

Concomitant medication during the study (0 to 30 months) was comparable between the migalastat-migalastat and ERT-migalastat treatment groups. Concomitant medication use during the OLE period was comparable between the migalastat-migalastat and ERT-migalastat treatment groups in the OLE population. The most common concomitant medications overall (≥ 25% of subjects) during the OLE period were paracetamol/acetaminophen (50%), aspirin/acetylsalicylic acid (35%), and ibuprofen (27%). The most common concomitant medications used by ≥ 10% of subjects in either of the two treatment groups (migalastat-

migalastat versus ERT-migalastat) were paracetamol/acetaminophen (42% versus 66%), aspirin/acetylsalicylic acid (39% versus 27%), ibuprofen (21% versus 40%), lisinopril (18% versus 13%), simvastatin (15% versus 0%), amoxicillin (12% versus 7%), and vitamin D (12% versus 13%).

The use of concomitant ACEIs, ARBs, and RIs was comparable between treatment groups in the OLE population (53% in the ERT-migalastat group and 52% in the migalastat-migalastat group) and during the OLE period (53% in the ERT-migalastat group and 52% in the migalastat-migalastat group). Overall, 52% of subjects used at least one ACEI, ARB, or RI during the OLE period. No subject in the migalastat-migalastat group started taking a new ACEI, ARB, or RI during the OLE period, whereas 20% of subjects in the ERT-migalastat group started a new ACEI, ARB, or RI. The new ACEIs, ARBs, or RIs started by the ERT-migalastat group during the OLE period were losartan (13%) and losartan potassium (7%).

7.2.2.15. Efficacy results for the randomised, active-controlled 18-month treatment period

Results for the two co-primary efficacy endpoints

The results for the two co-primary efficacy endpoints for the randomised, active-controlled, 18-month treatment period in the mITT population is summarised below. The results showed that the two treatments were comparable, as the two pre-specified comparability criteria were met.

Table 69: AT1001-012 - Annualised eGFR parameters from baseline to month-18, ANCOVA analysis in the mITT population.

ANCOVA	Migalastat (mean [1], ±SEM); [95% CI] N=34	ERT (mean, ±SEM) [95% CI] N=18	Differences in means	Overlap of 95% CIs
$eGFR_{CKD-EPI}$	-0.40 (0.93) [-2.27, 1.48]	-1.03 (1.29) [-3.64, 1.58]	+0.63	100%
$mGFR_{iohexol}$	-4.35 (1.64) [-7.65, -1.06]	-3.24 (2.27) [-7.81, 1.33]	-1.11	100%

1. LS means and CI based on the analysis of covariance (ANCOVA) models that includes the treatment groups, baseline eGFR parameter, sex, age, and baseline 24-hour urine protein stratification factor.

The results for the $eGFR_{CKD-EPI}$ and the $GFR_{iohexol}$ for the 18-month treatment period are summarised below.

Table 70: AT1001-012 - $eGFR_{CKD-EPI}$ annualised rate of change, ANCOVA analysis in the mITT population.

Parameter	Statistic	Treatment Group: Migalastat	Treatment Group: ERT
Number of Subjects in the mITT Population	N	34	18
Annualized Rate of Change in $eGFR_{CKD-EPI}$ ($mL/min/1.73\ m^2$) Baseline - 18 Months	LSMean[a]	-0.397	-1.031
	SE(LSMean)	0.9315	1.2943
	95% CI[a]	(-2.272, 1.478)	(-3.636, 1.575)
	Median	-1.289	-0.874
	Mean	-0.627	-1.493
	SD	4.3001	7.4257
	Min, Max	-6.97, 15.82	-15.58, 15.09

a. LS means and CI based on the analysis of covariance (ANCOVA) models that include the treatment groups, baseline $eGFR_{CKD-EPI}$, sex, age, and baseline 24-hour urine protein stratification factor.

Table 71: AT1001-012 - $GFR_{iohexol}$ annualised rate of change, ANCOVA analysis in the mITT population.

Parameter	Statistic	Treatment Group	
		Migalastat	ERT
Number of Subjects in the mITT Population	N	34	18
Annualized Rate of Change in $mGFR_{iohexol}$ ($mL/min/1.73\ m^2$) Baseline - 18 Months	LSMean[a]	-4.354	-3.238
	SE(LSMean)	1.6381	2.2712
	95% CI[a]	(-7.651, -1.056)	(-7.809, 1.334)
	Median	-3.233	-3.569
	Mean	-4.472	-2.135
	SD	9.4187	9.1922
	Min, Max	-28.77, 9.45	-11.62, 21.68

a. LS means and CI based on the analysis of covariance (ANCOVA) models that include the treatment groups, baseline $GFR_{iohexol}$, sex, age, and baseline 24-hour urine protein stratification factor.

In *post-hoc* analyses, the sponsor evaluated the annualised rates of change on $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ in subjects with more severe baseline renal impairment (GFR for the two parameters < 90 $mL/min/1.73\ m^2$ and baseline 24-hour urine protein ≥ 100 mg), and in subjects with multi-organ disease or classic phenotype. The results are summarised below.

Table 72: AT1001-012 – Post-hoc analysis of annualised rate of change from baseline to month 18 in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ in all subjects and subjects with more severe baseline renal impairment (GFR < 90 $mL/min/1.73\ m^2$ and 24-hour urine protein ≥ 100 mg), mITT.

Parameter: Mean (SD, n)	All Patients (LS Mean)		Patient with baseline GFR<90 $mL/min/1.73m^2$		Patients with baseline 24-hr urine protein≥100mg	
	Migalastat	ERT	Migalastat	ERT	Migalastat	ERT
$eGFR_{CKD\text{-}EPI}$ annualised CFB	-0.4 (4.3, n=34)	-1.0 (7.4, n=18)	-0.2 (5.3, n=20)	-1.7 (10.5, n=7)	-2.2 (2.8, n=19)	-2.7 (8.3, n=12)
$mGFR_{iohexol}$ annualised CFB	-4.4 (9.4, n=34)	-3.2 (9.2, n=18)	-2.6 (7.6, n=24)	-2.7 (9.2, n=12)	-2.8 (8.6, n=19)	-1.2 (11.0, n=12)

Table 73: AT1001-012 – Post-hoc analysis of annualised rate of change from baseline to month 18 in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ in all subjects, subjects with multi-organ disease at baseline and subjects with mutations associated with classic phenotype, mITT.

	All Patients LS Mean (SD, n)		Patients with multi-organ disease at baseline Mean (SD, n)		Patients with mutations associated with classic phenotype Mean (SD, n)	
	Migalastat	ERT	Migalastat	ERT	Migalastat	ERT
$eGFR_{CKD\text{-}EPI}$ annualised CFB	-0.4 (4.3, n=34)	-1.0 (7.4, n=18)	-0.6 (4.6, n=29)	-1.5 (7.7, n=17)	-0.8 (2.3, n=12)	-2.7 (10.5, n=7)
$mGFR_{iohexol}$ annualised CFB	-4.4 (9.4, n=34)	-3.2 (9.2, n=18)	-4.2 (9.0, n=29)	-2.0 (9.5, n=17)	-2.4 (10.4, n=12)	-1.9 (11.6, n=7)

Comment: Overall, it is considered that the totality of the data have satisfactorily established the comparability of migalastat and ERT in patients with Fabry disease previously treated with ERT, based on the annualised rates of change in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ from baseline to month 18. The two pre-specified criteria established that treatment with migalastat was comparable to treatment with ERT. The LS mean annualised rates of change for the two co-primary GFR efficacy endpoints for migalastat were less than 2.2 $mL/min/1.73\ m^2$ below the corresponding annualised rates of change for ERT, and the 95% CIs for the annualised rates of change for the two GFR endpoints were completely (100%) above the lower bound of the corresponding 95% CIs for ERT.

The sponsor undertook a *post-hoc* sensitivity analysis to calculate the 90% and 95% CIs of the difference in annualised rates of change in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ between migalastat and ERT. Based on this analysis, the lower bounds of the difference in the annualised rates of change for the mean $eGFR_{CKD\text{-}EPI}$ were -2.03 for the 90% CI and -2.57 mL/min/1.73 m^2 for the 95% CI. For $eGFR_{CKD\text{-}EPI}$, the lower bound 95% CI for the difference in the annualised rates of change between the two treatment groups (2.57 mL/min/1.73 m^2/year) was greater than the minimal pre-specified difference between the migalastat and the ERT group (i.e., 2.2 mL/min/1.73 m^2/year). However, a difference of 2.57 mL/min/1.73 m^2/year between the two treatment groups is unlikely to be clinically meaningful.

For $mGFR_{iohexol}$, the lower bounds of the difference in the annualised rates of change between the two treatment groups (migalastat minus ERT) were -5.81 ml/min/m^2 for the 90% CI and -6.74 mL/min/1.73 m^2, reflecting the higher variability of $mGFR_{iohexol}$ compared with $eGFR_{CKD\text{-}EPI}$. The sponsor undertook a blinded review of the $mGFR_{iohexol}$ which identified six $mGFR_{iohexol}$ values as potential outliers. When these values were excluded from the *post-hoc* sensitivity analysis, the lower bounds for the 90% and 95% CIs of the difference for $mGFR_{iohexol}$ were -1.02 and -1.79, respectively.

The *post-hoc* analyses in subjects with baseline renal impairment demonstrated that the annualised rates of change for $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ were comparable in the migalastat and ERT groups. The *post-hoc* analyses in subjects with multi-organ disease at baseline and in subjects with *GLA* mutations associated with classic Fabry disease phenotype demonstrated that the annualised rates of change for $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ were comparable in the migalastat and ERT groups.

Results for the secondary efficacy endpoints

- ***GFR (mL/min/m²)***: The changes from baseline to month 18 in the GFR endpoints were based on the LS means using an ANCOVA model (mITT population). For $eGFR_{CKD\text{-}EPI}$, the LS mean change from baseline was comparable in the migalastat group and the ERT group (-3.2 versus -4.3, respectively). For $mGFR_{iohexol}$, the LS mean change from baseline was greater in the migalastat group than in the ERT group (-6.5 versus -3.2, respectively). For $eGFR_{MDRD}$, the LS mean change from baseline was comparable in the migalastat group and the ERT group (-4.8 versus -4.6, respectively).
- ***Annualised rate of change for $eGFR_{MDRD}$ (mL/min/m²)***: Based on the ANCOVA analysis (mITT population), the annualised LS mean rate of change in $eGFR_{MDRD}$ was comparable in the migalastat group and the ERT group (-1.51 versus -1.53, respectively). The 95% CI for the annualised LS mean change for migalastat (95% CI: -3.428, 0.401) was enclosed entirely with the 95% CI for the annualised LS mean change for ERT (95% CI: -4.195, 1.131).
- ***Urine 24 hour endpoints***: At baseline (mITT population), the mean (±SD) 24-hour urine protein 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) change from baseline to month 18 was lower in the migalastat group than in the ERT group (49.2 ± 199.53 mg/day 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 compared to the ERT group (5.8 ± 19.66 mg/mmol and 14.3 ± 40.20 mg/mmol, respectively).
- ***Composite clinical outcome***: The percentage of subjects in the mITT population who had a composite clinical outcome during the 18-month treatment period was 29% in the migalastat group and 44% in the ERT group. In both treatment groups, the majority of clinical outcomes were renal (24% in the migalastat group; 33% in the ERT group) followed by cardiac (6% in the migalastat group; 17% in the ERT group). Only 1 cerebrovascular event occurred (transient ischaemic attack in the ERT group). No subjects died during the

18-month treatment period. No subjects in the migalastat group had events in 2 or more different categories. Two (2) subjects in the ERT group had events in 2 or more different categories, with both subjects having events in the cardiac and renal categories. The results for the composite clinical outcome at month-18 are summarised below.

Table 74: AT1001-012 – Composite clinical outcome, mITT population.

Parameter	Migalastat (n = 34)	ERT (n = 18)
Renal Event in the First 18 Months of Study	8 (24%)	6 (33%)
Cardiac Event in the First 18 Months of Study	2 (6%)	3 (17%)
Cerebrovascular Event in the First 18 Months of Study	0	1 (6%)
Death in the First 18 Months of Study	0	0
Composite clinical outcome	10 (29%) [95% CI: 14.1, 44.7]	8 (44%) [95% CI: 21.5, 67.4]

- ***LVMi:*** The mean (± SD) baseline LVMi (mITT population), as measured by ECHO, was 95.3 ± 22.75 g/m^2 in the migalastat group and 92.9 ± 25.67 g/m^2 in the ERT group. At baseline, 34% of patients had LVH (LVMi > 95 g/m^2 for females; LVMi > 115 g/m^2 for males). The LVMi decreased from baseline to month 18 in the migalastat group (mean change, -6.6 g/m^2; [95% CI: -11.0, -2.1]), and decreased by a notably smaller amount in the ERT group (mean change, -2.0 g/m^2; [95% CI: -11.0, 7.0]). 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 [95% CI: -17.03, -1.80]; females, -4.5 g/m^2 [95% CI: -10.301, 1.244]). The ANCOVA analysis of subjects with abnormal LVMi at baseline (i.e., LVH) 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 favour of migalastat, [95% CI: -28.864, 8.015]; p = 0.2416). The mean change in LVMi from baseline to month 18 in subjects in the migalastat group (n = 13) with baseline LVH was -8.4 (95% CI: -15.7, 2.6) and 4.5 (95% CI: -10.7, 18.4) in subjects in the ERT group (n = 5).
- ***LVEF:*** The median baseline LVEF (mITT population), as measured by ECHO, was 64.6% in the migalastat group and 61.1% in the ERT group. The median change from baseline to month 18 was comparable in the migalastat group and the ERT group (-1.540% versus 0.210%, respectively). The change from baseline was also comparable at all earlier visits. One subject in each treatment group had an abnormal LVEF at baseline. At month 18, all subjects had a normal LVEF with the exception of 1 subject in the migalastat group (who was also abnormal at baseline), and 3 subjects in the ERT group (1 of whom was abnormal at baseline).
- ***Plasma lyso-Gb$_3$***: Levels of plasma lyso-Gb$_3$ remained low and stable in subjects with amenable *GLA* mutations during the 18-month treatment period, and there were no notable differences between the two treatment groups at any visit. In the 2 male subjects with non-amenable *GLA* mutations in the migalastat group, plasma lyso-Gb$_3$ levels increased notably from baseline to month 18. As expected in the 2 subjects with non-amenable *GLA* mutations in the ERT group (1 male and 1 female), the plasma lyso-Gb$_3$ levels remained low and stable from baseline through month 18.
- ***WBC α-Gal A Activity***: There was an increase in WBC α-Gal A activity in males in the migalastat group from baseline to month 18 in the mITT population. The median change from baseline for the migalastat group was 6.6 nmol/h/mg (median baseline and month 18

levels were 1.8 and 8.5 nmol/h/mg, respectively). There was no change from baseline in the ERT group (mean change, -0.4 nmol/h/mg with median baseline and month 18 levels being 0.30 and 0.47 nmol/h/mg, respectively). The results are consistent with the mechanism of action of migalastat. The assessment of WBC α-Gal A activity in females is not relevant because females are mosaic (i.e., express both mutant and wild type α-Gal A).

- ***Patient reported outcomes SF-36 v2 and BPI:*** There were no notable changes from baseline to month 18 in either SF-36 v2 or BPI scores in either of the migalastat or ERT group, and no notable differences between the two treatment groups.
- ***Subgroup analyses eGFR$_{CKD-EPI}$:*** The subgroup analyses for the annualised rate of change in eGFR$_{CKD-EPI}$ in the mITT population are summarised. The subgroup analyses showed: (1) a greater decrease from baseline to month 18 in the migalastat group in males compared to females; (2) a decrease from baseline to month 18 in subjects in the migalastat group with high baseline 24-hour urine protein levels compared to an increase in subjects in the migalastat group with low baseline 24-hour urine protein levels; (3) a smaller increase from baseline to month 18 in males in the migalastat group with low baseline 24-hour protein compared to females; and (4) a greater decrease from baseline in males in the migalastat group with high baseline 24-hour urine levels compared to females.
- ***Subgroup analyses mGFR$_{iohexol}$:*** The subgroup analyses for the annualised rate of change in mGFR$_{iohexol}$ in the mITT population are summarised. The subgroup analyses showed: (1) a smaller decrease from baseline to month 18 in the migalastat group in males compared to females; (2) a smaller decrease from baseline to month 18 in subjects with high 24-hour urine protein levels compared to subjects with low 24-hour urine levels; and (3) a smaller decrease from baseline to month 18 in females with high or low 24-hour urine levels compared to males.

7.2.2.16. Efficacy results for entire study period (0-30 months)

- In the migalastat-migalastat group (n = 31), the mean annualised rate of change from baseline to month 30 in eGFR$_{CKD-EPI}$ was -1.7 mL/min/1.73 m^2 (95% CI, -2.7, -0.8).
- In the migalastat-migalastat group (n = 31), the mean annualised rate of change from baseline to month 30 in mGFR$_{iohexhol}$ was -2.7 mL/min/1.73 m^2 (95% CI, -4.8, -0.7).
- In the migalastat-migalastat group (n = 31), the mean annualised rate of change from baseline to month 30 in eGFR$_{MDRD}$ was -2.3 mL/min/1.73 m^2 (95% CI, -4.0, -0.6).
- In the migalastat-migalastat group, the mean (± SD) change from baseline to month 30 in 24-hour urine protein level was +70.2 mg/day (95% CI: -32.4, 172.7). At Month 30, the mean 24-hour urine albumin:creatinine ratio was 19.0 mg/mmol in the migalastat-migalastat group and 38.5 mg/mmol in the ERT-migalastat group. The mean change from baseline to month 30 in the albumin:creatinine ratio was 4.7 mg/mmol in the migalastat-migalastat group. For the ERT-migalastat group, the mean change from baseline to month 18 in the albumin:creatinine ratio while the subjects were receiving ERT was 11.6 mg/mmol and the mean change from Month 18 to Month 30 was 7.5 mg/mmol.
- The percentage of subjects in the migalastat-migalastat group who had a composite clinical outcome at month 30 was 32% (10/31), consisting primarily of renal events (29% [9/31]). There was only one cardiac event through to month 30 in the migalastat-migalastat group, and no cerebrovascular events or deaths.
- The LVMi (ECHO) decreased from baseline to month 30 in all subjects (n = 28) (mean change, -3.8 g/m^2; [95% CI: -8.9, 1.3]) and in subjects with LVH at baseline (n = 10) (mean change, -10.0 g/m^2; [95% CI, -16.6, -3.3]).

- In the migalastat-migalastat group (n = 31), the mean (± SEM) baseline plasma lyso-Gb_3 level was 9.2 ± 1.97 nmol/L, and the mean (± SEM) change from baseline to month 18 was +1.7 ± 1.03 nmol/L and from baseline to month 30 was 3.6 ± 2.50 nmol/L.
- There was an increase in WBC α-Gal A activity in males in the migalastat-migalastat group from baseline to month 30, with the mean ± SD increase from baseline to month 30 being 4.0 ± 3.80 nmol/h/mg. The mean (± SD) baseline (n = 14), month 18 (n = 14), and month 30 (n = 14) WBC α-Gal A activities in males in the migalastat group were 2.9 ± 3.38, 8.3 ± 7.33, and 6.9 ± 6.68 nmol/h/mg, respectively.
- Scores on the BPI short form remained stable throughout the study in both treatment groups. No notable difference was noted between treatment groups or study periods at any time point.
- For the SF-36 v2, the scores on all tested parameters remained stable over the duration of the study. No notable difference was noted between treatment groups or study periods at any time point.
- The GFR results were consistent across subgroups of age, sex, and baseline severity.

7.2.2.17. Effect of ERT type on efficacy outcomes

The sponsor undertook a *post-hoc* analysis on the effect of ERT type (Replagal or Fabrazyme) on GFR, LVMi and plasma lyso-Gb_3 levels in the mITT population with amenable *GLA* mutations. The effect of ERT type on the annualised rates of change in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ from baseline to month 18 are summarised below.

Table 75: AT1001-012 – Annualised rates of change in $eGFR_{CKD\text{-}EPI}$ by baseline ERT, mITT population.

	Treatment Group			
	Migalastat		ERT	
Annualized Rate of Change in $eGFR_{CKD\text{-}EPI}$	Replagal (N=22)	Fabrazyme (N=11)	Replagal (N=11)	Fabrazyme (N=7)
n	22	11	11	7
Mean (SD)	-0.418 (4.7600)	-1.001 (3.6283)	-4.414 (6.7009)	3.096 (6.4181)
Median	-1.289	-1.475	-6.854	1.557
Min, Max	-6.41, 15.82	-6.97, 5.59	-15.58, 6.21	-4.49, 15.09

Table 76: AT1001-012 – Annualised rates of change in $mGFR_{iohexol}$ by baseline ERT, mITT population.

	Treatment Group			
	Migalastat		ERT	
Annualized Rate of Change in Iohexol mGFR	Replagal (N=22)	Fabrazyme (N=11)	Replagal (N=11)	Fabrazyme (N=7)
n	22	11	11	7
Mean (SD)	-6.819 (10.0245)	0.386 (6.5813)	-1.798 (9.3566)	-2.664 (9.6415)
Median	-4.259	0.547	-1.734	-6.424
Min, Max	-28.77, 9.30	-12.00, 9.45	-11.62, 21.68	-11.53, 17.60

Comment: The results for GFR showed no consistent effects of ERT type on the annualised rates of change in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$. Subject numbers in each treatment group were small and inter-subject variability in the mean annualised rate of change in the GFR parameters was high within each treatment group. The results

for changes in the LVMi showed that reductions from baseline to month 18 occurred in all subjects and subjects with LVH at baseline treated with migalastat irrespective of prior treatment with Replagal or Fabrazyme. However, the mean and median reductions from baseline to month 18 in LVMi were greater in all subjects and subjects with baseline LVH switched from Fabrazyme to migalastat than from Replagal to migalastat. The results for plasma lyso-Gb_3 levels from baseline thorough to month 18 have been examined in male and female subjects, and showed that levels in subjects randomised to migalastat remained constant over 18 months irrespective of whether they were switched from Replagal or Fabrazyme.

7.3. Analyses performed across trials: pooled and meta analyses

The submission included no meta-analyses. However, the submission included limited pooled analyses from *studies AT1001-011 and AT1001-012* for selected efficacy endpoints comparing pooled data for migalastat from the two studies from baseline through to month 18 with data for ERT from *Study AT1001-012*. The results from these pooled analyses comparing migalastat to ERT were consistent with the results from the pivotal study comparing migalastat to ERT.

7.4. 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 [AT1001-011; 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 III 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 77: 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]	Neuropathic pain [a]	Renal involvement [d]	Gastro-intestinal [a]
Study AT1001-012 (n = 57)							
Males	21/24 (88%)	13/24 (54%)	16/24 (67%)	18/24 (75%)	14/24 (58%)	18/22 (75%)	14/22 (64%)

Gender	≥ 2 organ systems	Angio-keratoma or corneal whorling [a]	Cardiac involvement [b]	CNS involvement [c]	Neuropathic pain [a]	Renal involvement [d]	Gastro-intestinal [a]
Females	29/33 (88%)	16/33 (48%)	25/33 (75%)	12/33 (36%)	22/33 (67%)	25/33 (76%)	22/31 (71%)
Study AT1001-012 (n = 50)							
Males	18/18 (100%)	12/18 (67%)	15/18 (83%)	11/18 (61%)	13/18 (72%)	18/18 (100%)	10/18 (56%)
Females	29/32 (91%)	13/32 (41%)	11/32 (35%)	16/32 (50%)	25/32 (78%)	27/32 (84%)	18/32 (56%)

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 m2, 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 waiting 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 78: 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, Dvorakova et al. 2005)	I403S	Classic (Shimotori, Maruyama et al. 2008)
Y216C	Classic (Filoni, Caciotti et al. 2010)	P409T	Unknown
I253S	Unknown		

Table 79: 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	Classic (Shabbeer, Yasuda et al. 2006)*
G144V	Classic (Eng 1994)	D313Y	Both (Eng 1993; Froissart, Guffon 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.

7.4.1. 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. 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 (0-6 months), including 34 in the migalastat group and 33 in the placebo group. A total of 63 subjects entered Stage 2 (6-12 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 (i.e., 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.

7.4.2. 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 (i.e., 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 (0-18 month), single-group extension (18-30 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 (i.e., 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 (i.e., $eGFR_{CKD\text{-}EPI}$, $eGFR_{MDRD}$ 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 to30 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.

8. Clinical safety

8.1. Studies providing safety data

The submission did not include an integrated safety summary for migalastat due to differences in subject characteristics (i.e., 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.

8.2. 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 III studies are summarised.

8.3. Pivotal Phase III studies – safety data

8.3.1. Extent of exposure

8.3.1.1. Study AT1001-011

Overall, a total of 66 subjects in the safety population had a mean (±SD) duration of study drug exposure of 22.1 ± 5.95 months (range 1.2, 34.6 months). The mean (±SD) duration of exposure was similar in the migalastat-migalastat group (n = 34) and in the placebo-migalastat group (n = 32), with the respective exposures being 21.7 ± 5.28 months (range: 5.7, 25.6 months) and 22.6 ± 6.63 months (range: 1.2, 34.6 months).

In Stage 1, the mean (±SD) duration of exposure was similar in the migalastat group (n = 34) and the placebo group (n = 32), with the respective exposures being 5.9 ± 0.21 months (range: 5.3, 6.3 months) and 6.11 ± 1.5 months (range: 1.2, 11.0 months).

In Stage 2, the mean (±SD) duration of exposure was similar in the migalastat-migalastat group (n = 33) and the placebo-migalastat group (n = 30), with the respective exposures being 5.8 ± 0.56 months (range: 3.2, 6.5 months) and 5.8 ± 1.03 months (range: 1.1, 7.5 months).

In the OLE population, the mean (±SD) duration of exposure was similar in the migalastat-migalastat group (n = 29) and the placebo-migalastat group (n = 28), with the respective exposures being 11.8 ± 1.88 months (range: 2.4, 13.6 months) and 12.5 ± 2.20 months (range: 10.1, 22.6 months).

8.3.1.2. Study AT1001-012

The safety of migalastat in *Study AT1001-012* has been evaluated based on the data provided in the 18-month CSR safety population consisting of subjects randomised to migalastat (n = 36) or ERT (n = 21) and treated for 18 months, and on the data provided in the 30-month CSR for 51 subjects treated with migalastat at any time during the 30 month study (i.e., 36 subjects who were initially randomised to migalastat and continued the medication throughout the study, and 15 subjects who were initially randomised to ERT and then switched to migalastat after month 18).

For the 18-month data, the safety population included 57 subjects (36 randomised to migalastat, 21 randomised to ERT). The mean duration of exposure in the two treatment groups was 45 days longer in the migalastat group than in the ERT group (522 and 477 days, respectively). The exposure is summarised below.

Table 80: AT1001-012 – Exposure, 18-month randomised treatment period, safety population.

		Treatment Group		
Parameter	Statistic	Migalastat	ERT	Total
Number of Subjects in the Safety Population	N	36	21	57
Extent of Exposure (days)				
Randomized Treatment Period[a]	n	32	21	53
	Mean	522.19	476.67	504.15
	SD	91.048	106.531	99.056
	Median	540.00	524.00	535.00
	Min, Max	106.0, 574.0	155.0, 540.0	106.0, 574.0

The mean duration of exposure in all subjects treated with migalastat (n = 51) over the whole 30 months of the study was 756 days. Of the 51 subjects treated with migalastat, 45 were exposed for > 12 months. The overall exposure to migalastat during the study in the safety population is summarised below.

Table 81: AT1001-012 – Exposure to migalastat during the whole study period, safety population.

		Treatment Group	
Parameter	Statistic	All Migalastat	All Migalastat With Amenable Mutations
Number of Subjects in the Safety Population	N	51	49
Extent of Exposure (days)			
Randomized Treatment Period (0-18 Months)[a]	n	36	34
	Mean	521.67	520.00
	SD	84.962	87.198
	Median	539.00	539.00
	Min, Max	106.0, 573.0	106.0, 573.0
OLE Period (18-30 Months)[b]	n	48	46
	Mean	411.42	424.87
	SD	125.806	108.118
	Median	401.50	434.50
	Min, Max	7.0, 565.0	33.0, 565.0
Whole Study Period (0-30 Months)[c]	n	51	49
	Mean	755.94	760.18
	SD	287.952	292.502
	Median	896.00	897.00
	Min, Max	33.0, 1106.0	33.0, 1106.0
Duration of Exposure Across Whole Study Period (Categorical)			
≤ 3 Months	n (%)	1 (2)	1 (2)
> 3 - ≤ 6 Months	n (%)	1 (2)	1 (2)
> 6 - ≤ 12 Months	n (%)	4 (8)	4 (8)
> 12 - ≤ 18 Months	n (%)	11 (22)	11 (22)
> 18 - ≤ 24 Months	n (%)	2 (4)	1 (2)
> 24 - ≤ 30 Months	n (%)	18 (35)	17 (35)
> 30 Months	n (%)	14 (27)	14 (29)

8.3.2. Adverse events

8.3.2.1. Overview

Study AT1001-011

Treatment-emergent AEs were defined as AEs that started or worsened after the first dose of study drug. Stage 1 TEAEs were any AEs that started between the first dose of Stage 1 and the first dose of Stage 2 (or last Stage 1 administration for subjects that discontinued during Stage 1). Stage 2 TEAEs were any AEs that started between the first dose of Stage 2 and the first dose of the open-label extension (or the last Stage 2 administration for subjects that discontinued during Stage 2), and open-label extension TEAEs were any AEs that started after the first dose of the open-label extension through to 30 days after the last treatment visit.

The high-level overview of TEAEs in Stage 1, Stage 2 and the OLE are summarised below. AEs were coded using MedDRA dictionary (Version 15.0). Related TEAEs included AEs that were assessed by investigators as being definitely, probably of possibly related to the study drug.

Table 82: AT1001-011 – High-level overview of treatment-emergent adverse events

	Stage 1		Stage 2		OLE	
Parameter	**Migalastat**	**Placebo**	**Mig-Mig**	**Pbo-Mig**	**Mig-Mig**	**Pbo-Mig**
Subjects in safety population	34	33	33	30	29	28
Number of TEAEs	204	142	132	108	99	143

	Stage 1		Stage 2		OLE	
Parameter	**Migalastat**	**Placebo**	**Mig-Mig**	**Pbo-Mig**	**Mig-Mig**	**Pbo-Mig**
TEAEs, subjects n (%)	31 (91%)	30 (91%)	26 (79%)	24 (80%)	24 (83%)	24 (86%)
Treatment-related TEAEs, subjects n (%)	15 (44%)	9 (27%)	4 (12%)	8 (27%)	5 (17%)	7 (25%)
Severe TEAEs, subjects n (%)	3 (9%)	2 (6%)	4 (12%)	2 (7%)	3 (10%)	4 (14%)
Treatment-emergent SAEs, subjects n (%)	2 (6%)	4 (12%)	3 (9%)	2 (7%)	5 (17%)	11 (19%)
Discontinued TEAEs, subjects n (%)	0	1 (3%)	1 (3%)	1 (2%)	0	0
AEs leading to death, subjects n (%)	0	0	0	0	0	0

Comment: In Stage 1 (0-6 months), a similar proportion of subjects in the migalastat and placebo groups experienced TEAEs, but the absolute number of TEAEs was notably greater in the migalastat group than in the placebo group. Treatment-related TEAEs were reported more frequently in subjects in the migalastat group compared to the placebo group. The absolute number of severe TEAEs and treatment-emergent SAES was small in both treatment groups. One subject discontinued due to a TEAE in the placebo group, and no AEs leading to death were reported in either treatment group. In Stage 2 and the OLE, the AE profiles were similar in the migalastat-migalastat and placebo-migalastat treatment groups.

Study AT1001-012

The high-level overview of TEAEs in the 0-18 month randomised treatment period (migalastat versus ERT) and the 0-30 month treatment period for the all migalastat group is summarised below.

Table 83: AT1001-012 – High-level overview of treatment-emergent adverse events.

	Month 0 to 18		Month 0-30
Parameter	**Migalastat**	**ERT**	**All migalastat**
Subjects in safety population	36	21	51
Number of TEAEs	308	166	598
TEAEs, subjects n (%)	34 (94%)	20 (95%)	50 (98%)
Treatment-related TEAEs, subjects n (%)	13 (39%)	3 (14%)	19 (37%)

	Month 0 to 18		Month 0-30
Parameter	**Migalastat**	**ERT**	**All migalastat**
Severe TEAEs, subjects n (%)	3 (8%)	2 (10%)	9 (18%)
Treatment-emergent SAEs, subjects n (%)	7 (19%)	7 (33%)	16 (31%)
Discontinued TEAEs, subjects n (%)	0	0	0
AEs leading to death, subjects n (%)	0	0	0

Comment: The 18-month comparator data showed that most patients in both treatment groups experienced at least one TEAE, and that treatment-related TEAEs were reported more frequently in the migalastat group than in the ERT group. Treatment-emergent SAEs were reported more frequently in the ERT group than in the migalastat group, while discontinuations and deaths due to TEAEs were reported in neither of the two treatment groups.

8.3.2.2. Most frequently reported TEAEs – System Organ Class (SOC)

Study AT1001-011

In Stage 1, the most frequently reported primary SOCs occurring in ≥ 20% of subjects in the migalastat group (vs the placebo group) were: infections and infestations (56% versus 39%); nervous system disorders (50% versus 33%); general disorders and administration site conditions (41% versus 30%); gastrointestinal disorders (38% versus 39%); respiratory, thoracic, and mediastinal disorders (29% versus 12%); investigations (26% versus 21%); injury, poisoning and procedural complications (21% versus 18%); and musculoskeletal and connective tissue disorders (21% versus 21%). The primary SOCs that occurred in ≥ 10% more subjects in the migalastat group than in the placebo group were: infections and infestations (56% versus 39%); nervous system disorders (50% versus 33%); general disorders and administration site conditions (41% versus 30%); and respiratory, thoracic, and mediastinal disorders (29% versus 21%).

In Stage 2, the most frequently reported primary SOCs occurring in ≥ 20% of subjects in the total open-label population (n = 63) were: infections and infestations (35%); nervous system disorders (30%); injury, poisoning and procedural complications (27%); musculoskeletal and connective tissue disorders (25%); and gastrointestinal disorders (22%).

In the OLE period, the most frequently reported SOC occurring in ≥ 20% of subjects in the total open-label extension population (n = 57) were: infections and infestations (47%); musculoskeletal and connective tissue disorders (30%); nervous system disorders (26%); renal and urinary disorders (25%); and gastrointestinal disorders (21%).

Comment: Primary SOCs reported in ≥ 20% of subjects treated with migalastat in Stage 1, Stage 2 and the OLE were: infections and infestations; nervous system disorders; gastrointestinal disorders; and musculoskeletal and connective tissue disorders. In general, the subject incidence of the most frequently occurring primary SOCs decreased over the duration of the study. Of note, ≥ 20% of subjects had renal and urinary disorders in the OLE period but not in Stages 1 and 2.

Study AT1001-012

In the 18-month treatment period, the most frequently reported primary SOCs occurring in ≥ 20% of subjects in the migalastat group (vs the placebo group) were: infections and infestations (67% versus 76%); gastrointestinal disorders (58% versus 48%); musculoskeletal and connective tissue disorders (47% versus 29%); nervous system disorders (39% versus 38%); general disorders and administrative site conditions (36% versus 33%); investigations (28% versus 14%); respiratory, thoracic and mediastinal disorders (22% versus 38%); and skin and subcutaneous tissue disorders (22% versus 19%).

In the 18-month treatment period, the primary SOCs with a higher frequency (≥ 10% difference) in subjects in the migalastat group compared to subjects in the ERT group were: gastrointestinal disorders (58% versus 48%,); musculoskeletal and connective tissue disorders (47% versus 29%); investigations (28% versus 14%); and hepatobiliary disorders (11% versus 0%). The primary SOCs with a lower frequency (≥ 10% difference) in subjects in the migalastat group compared to the ERT group were: respiratory, thoracic, and mediastinal disorders (22% versus 38%); injury, poisoning, and procedural complications (17% versus 33%); and reproductive system and breast disorders (0% vs14%).

In the safety population (0-30 months), the primary SOCs reported with a frequency of ≥ 20% in subjects in the all migalastat group (n = 51) were: infections and infestations (84%); gastrointestinal disorders (67%); nervous system disorders (55%); musculoskeletal and connective tissue disorders (53%); general disorders and administration site conditions (47%); investigations (31%); respiratory, thoracic and mediastinal disorders (27%); injury poisoning and procedural complications (24%); cardiac disorders (22%); psychiatric disorders (22%), skin and subcutaneous tissue disorders (22%).

8.3.2.3. Most frequently reported TEAEs – preferred term

AT1001-011

In Stage 1, TEAEs reported in ≥ 10% of subjects in the migalastat group (vs placebo) were headache (35% versus 21%), nasopharyngitis (18% versus 6%), fatigue (12% versus 12%), pyrexia (12% versus 3%), nausea (12% versus 6%), and paraesthesia (12% versus 12%). TEAEs reported in ≥ 5% of subjects in the migalastat group and in ≥ 5% more subjects than in the placebo group were headache (35% versus 21%), nasopharyngitis (18% versus 6%), pyrexia (12% versus 3%), nausea (12% versus 6%), cough (9% versus 0%), epistaxis (9% versus 3%), haematuria (9% versus 3%), diarrhoea (9% versus 3%), back pain (9% versus 0%), cystitis (6% versus 0%) urinary tract infection (6% versus 0%), atrial fibrillation (6% versus 0%), abdominal pain upper (6% versus 0%), post procedural complication (6% versus 0%), torticollis (6% versus 0%), and hypoaesthesia (6% versus 0%). TEAEs reported in ≥ 5% of subjects in the migalastat group are summarised.

In Stage 2 (open-label population), there were 240 TEAEs reported in 63 patients in the total population. TEAEs were reported in 50 (79%) subjects in the total group, including 26 (79%) in the migalastat-migalastat group and 24 (80%) in the placebo-migalastat group. TEAEs reported in ≥ 5% of subjects in the total group were headache (14%), procedural pain (11%), nasopharyngitis (8%), upper respiratory tract infection (8%), diarrhoea (8%), paraesthesia (6%), arthralgia (6%), abdominal pain (5%), tachycardia (5%), vertigo (5%), urinary tract infection (5%), incorrect dose administered (5%), neck pain (5%), depression (5%), oropharyngeal pain (5%), and hypertension (5%). The only TEAE with a higher frequency (≥ 10% difference) in subjects in the placebo-migalastat group, compared to the migalastat-migalastat group, was tachycardia (0% versus 10%). No TEAEs had a higher frequency (≥ 10% difference) in subjects in the migalastat-migalastat group, compared to the placebo-migalastat group.

In the OLE, there were 242 TEAEs reported in 57 patients in the total OLE population. TEAEs were reported in 48 (84%) of subjects in the total group. TEAEs reported in ≥ 5% of subjects in

the total group were proteinuria (16%), headache (11%), bronchitis (11%), urinary tract infection (9%), arthralgia (9%), fatigue (7%), depression (7%), nasopharyngitis (5%), upper respiratory tract infection (5%), back pain (5%), microalbuminuria (5%), constipation (5%), nausea (5%), vomiting (5%), atrial fibrillation (5%), palpitations (5%), vitamin D deficiency (5%), and paraesthesia (5%).

Study AT1001-012

In the 18-month treatment period, the most frequently reported TEAEs occurring in ≥ 20% of subjects in migalastat group compared to the ERT group, respectively: were nasopharyngitis (33% versus 33%); and headache (25% versus 24%). Of the TEAEs reported in ≥ 10% of subjects in either treatment group, TEAEs reported in ≥ 5% more subjects in the migalastat group compared to the placebo group, respectively, were: upper respiratory tract infection (11% versus 5%) and urinary tract infection (11% versus 5%). Of the TEAEs reported in ≥ 10% of subjects in either treatment group, TEAEs reported in ≥ 5% more subjects in the ERT group compared to the migalastat group were: influenza (19% versus 14%); cough (24% versus 8%); 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%). TEAEs reported in ≥ 10% of subjects in either treatment group are summarised below in Table 85.

Table 84: AT1001-012 – TEAEs reported in ≥ 10% of subjects in either treatment group, safety population.

		Treatment Group	
Preferred Term	Statistic	Migalastat	ERT
Number of Subjects in the Safety Population	N	36	21
Number of TEAEs	n	308	166
Number of Subjects with TEAEs	n (%)	34 (94)	20 (95)
Nasopharyngitis	n (%)	12 (33)	7 (33)
Headache	n (%)	9 (25)	5 (24)
Dizziness	n (%)	6 (17)	2 (10)
Influenza	n (%)	5 (14)	4 (19)
Abdominal Pain	n (%)	5 (14)	2 (10)
Diarrhoea	n (%)	5 (14)	2 (10)
Nausea	n (%)	5 (14)	2 (10)
Back Pain	n (%)	4 (11)	3 (14)
Upper Respiratory Tract Infection	n (%)	4 (11)	1 (5)
Urinary Tract Infection	n (%)	4 (11)	1 (5)
Cough	n (%)	3 (8)	5 (24)
Vomiting	n (%)	3 (8)	3 (14)
Sinusitis	n (%)	3 (8)	3 (14)
Arthralgia	n (%)	3 (8)	2 (10)
Bronchitis	n (%)	2 (6)	3 (14)
Oedema Peripheral	n (%)	2 (6)	2 (10)
Vertigo	n (%)	1 (3)	2 (10)
Dry Mouth	n (%)	1 (3)	2 (10)
Gastritis	n (%)	1 (3)	2 (10)
Pain In Extremity	n (%)	1 (3)	2 (10)
Dyspnoea	n (%)	1 (3)	2 (10)
Procedural Pain	n (%)	0	2 (10)

In the safety population (0-30 months), the most frequently reported TEAEs occurring in ≥ 20% of subjects in all migalastat group (n = 51) were: nasopharyngitis (41%); headache (31%); influenza (24%); and diarrhoea (22%). TEAEs reported in ≥ 10% of subjects in the all migalastat group are summarised below.

Table 85: AT1001-012 – TEAEs reported in ≥ 10% of subjects in the all migalastat group, safety population.

Parameter	Statistic	Treatment Group All Migalastat During 0-30 Months
Number of Subjects in the Safety Population	N	51
Number of TEAEs	n	598
Number of Subjects With TEAEs	n (%)	50 (98)
Nasopharyngitis	n (%)	21 (41)
Headache	n (%)	16 (31)
Influenza	n (%)	12 (24)
Diarrhoea	n (%)	11 (22)
Cough	n (%)	8 (16)
Dizziness	n (%)	8 (16)
Nausea	n (%)	8 (16)
Vomiting	n (%)	8 (16)
Abdominal Pain	n (%)	7 (14)
Blood Creatine Phosphokinase Increased	n (%)	7 (14)
Arthralgia	n (%)	6 (12)
Myalgia	n (%)	6 (12)
Pyrexia	n (%)	6 (12)
Urinary Tract Infection	n (%)	6 (12)
Back Pain	n (%)	5 (10)
Bronchitis	n (%)	5 (10)
Insomnia	n (%)	5 (10)
Pain	n (%)	5 (10)
Palpitations	n (%)	5 (10)
Tinnitus	n (%)	5 (10)
Upper Respiratory Tract Infection	n (%)	5 (10)

8.3.2.4. Treatment-related TEAEs

Study AT1001-011

In Stage 1, a higher percentage of subjects in the migalastat group experienced TEAEs considered by the investigator to be related to the study drug in the migalastat group than in the placebo group (44%, 15/34 versus 27%, 9/33). The most frequently reported primary SOCs (≥ 10% of subjects) considered related to the study drug in the migalastat group were gastrointestinal disorders (18%) and nervous system disorders (12%). Treatment-related primary SOCs with a higher frequency (≥ 5% difference) in subjects in the migalastat group compared to the placebo group were gastrointestinal disorders (18% versus 12%), investigations (9% versus 0%) and musculoskeletal and connective tissue disorders (9% versus 3%).

In Stage 1, treatment-related TEAEs reported in ≥ 5% of subjects in the migalastat group 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 epistaxis (6% versus 3%). Treatment-related TEAEs reported in ≥ 5% more subjects in the migalastat group compared to the placebo group were nausea (6% versus 0%), diarrhoea (6% versus 0%), weight increased (6% versus 0%), torticollis (6% versus 0%), and paraesthesia (6% versus 0%).

In Stage 2, treatment-related TEAEs were reported in 27% (8/34) of subjects in the placebo-migalastat group and 12% (4/33) of subjects in the migalastat-migalastat group. No primary SOC for treatment-related TEAEs was reported in ≥ 10% of subjects. The only treatment-related primary SOC with ≥ 5% more subjects in the placebo-migalastat group compared to the migalastat-migalastat group was gastrointestinal disorders (10% versus 3%). The only treatment-related primary SOC with ≥ 5% more subjects in the migalastat-migalastat group compared to the placebo-migalastat group was general disorders and administrative site conditions (6% versus 0%).

In Stage 2, treatment-related TEAEs reported in ≥ 5% of subjects in the total population were headache (5%, 3/63) and incorrect dose administered (5%, 3/63). Headache was the only treatment-related TEAE reported in ≥ 5% more subjects in the placebo-migalastat group than in the migalastat-migalastat group (10% versus 0%). No treatment-related TEAEs were reported in ≥ 5% more subjects in the migalastat-migalastat group than in the placebo-migalastat group.

In the OLE, treatment-related TEAEs were reported in 21% (12/57) of subjects in the total group. No treatment-related TEAEs (SOC or preferred term) were reported in ≥ 5% of subjects in the total group.

Study AT1001-012

In the 18-month 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 ≥ 2 subjects in the migalastat group compared to the ERT group were: headache (6, 17% versus 0%); diarrhoea (3, 8% versus 0%); abdominal pain (2, 6% versus 0%); nausea (2, 6% versus 0%); dyspepsia (2, 6% versus 0%); blood creatinine phosphokinase increased (2, 6% versus 0%); and dizziness (2, 6% versus 0%);

In the safety population (0-30 months), treatment-related TEAEs were reported in 37% (19/51) of subjects in the all migalastat group. Treatment-related TEAEs reported in ≥ 2 patients were: diarrhoea (12, 24%); headache (7, 14%); nausea (4, 8%); dizziness (3, 6%); blood creatinine phosphokinase increased (3, 6%); vomiting (2, 4%); dyspepsia (2, 4%); muscle spasms (2, 4%); pain in extremity (2, 4%); and paraesthesia (2, 4%).

8.3.2.5. Death and SAEs

Study AT1001-011

There were no deaths in *Study AT1001-011*.

There were 26 treatment-emergent SAEs reported in 19 (28%) of the 67 subjects in the overall safety population. Two (2) of the treatment-emergent events were considered to be possibly related to treatment (fatigue and paraesthesia).

In Stage 1, there were 2 treatment-emergent SAEs in 2 (6%) subjects in the migalastat group (n = 34) and 4 treatment-emergent SAEs in 4 (12%) subjects in the placebo group (n = 33). 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, and anaplastic large cell lymphoma.

In Stage 2 (Stage 2 population), there were 5 treatment emergent SAEs in 3 (9%) subjects in the migalastat-migalastat group and 3 treatment-emergent SAEs in 2 (7%) subjects in the placebo-migalastat group. In the migalastat-migalastat group, 1 subject experienced ventricular tachycardia (unrelated to the study drug), 1 subject experienced bulimia nervosa (unrelated to the study drug) and 1 subject experienced 3 events consisting of amyotrophic lateral sclerosis (unrelated to the study drug), cerebral haemorrhage (unrelated to the study drug) and pulmonary embolism (unrelated to the study drug). In the placebo-migalastat group, 1 subject experienced a bone cyst (unrelated to the study drug) and 1 subject experienced 2 events unrelated to the study drug consisting of pulmonary embolism and deep vein thrombosis.

In the OLE (OLE population), there were 5 treatment-emergent SAEs in 5 (17%) subjects in the migalastat-migalastat group and 7 treatment-emergent SAEs in 6 (21%) of subjects in the placebo-migalastat group. The 5 treatment-emergent events in the 5 subjects in the migalastat-migalastat group were 1 each for palpitations, constipation, malaise, transient ischaemic attack, and pneumothorax. The 7 treatment-emergent SAEs in the 6 patients in the placebo-migalastat group were 1 each for lower abdominal pain, fatigue, non-cardiac chest pain, helicobacter gastritis, multiple fractures, paraesthesia, and syncope.

Study AT1001-012

There were no deaths in *Study AT1001-012.*

In the 18-month treatment period, treatment-emergent SAEs were reported less frequently in subjects in the migalastat group than in the ERT group (19% [7/36] versus 33% [7/21]). All 24 treatment-emergent SAEs reported in the two treatment-groups (9, migalastat; 14, ERT) were considered by investigators to be unrelated to treatment.

In the 18-month treatment period, the 9 treatment-emergent SAEs reported in the 7 subjects in the migalastat group were: pneumonia in 1 subject; morbid obesity in 1 subject; chest pain in 1 subject; symptomatic sustained VT during exercise and chest pain in 1 subject; chest pain in 1 subject; phaeochromocytoma and shoulder fracture in 1 subject; and bile duct stone in 1 subject. The most frequently reported treatment-emergent SAE in the migalastat group was chest pain (reported in 3 subjects).

In the 18-month treatment period, the 15 treatment-emergent SAEs reported in the 7 subjects in the ERT group were: hernial eventration x 2 events in 1 subject; transient ischaemic attack and abdominal pain in 1 subject; device malfunction (lap band) in 1 subject; asthenia, altered mental status unknown aetiology, bilateral blurred vision unknown aetiology, and left facial numbness in 1 subject; vertigo in 1 subject; deterioration of chronic heart failure x 4 events in 1 subject; and dyspnoea in 1 subject. The most frequently reported treatment-emergent SAEs in the ERT group were deterioration of chronic heart failure (4 events in 1 subject) and hernia eventration (2 events in 1 subject).

In the safety population (0-30 months), a total of 16 (31%) subjects in the all migalastat group experienced 20 treatment-emergent TEAS at any time after the first dose of migalastat. The 20 treatment-emergent SAEs in the 16 subjects in the all migalastat group were: 3 events of chest pain; 2 events of obesity; and 1 event each for ventricular tachycardia, hernial eventration, bile duct stone, endocarditis, perineal abscess, pneumonia, phaeochromocytoma, upper limb fracture, embolic stroke, transient ischaemic attack, suicidal ideation, proteinuria, atelectasis, dyspnoea, and haemoptysis. Of the 20 treatment-emergent SAEs, proteinuria was the only event considered to be treatment-related. However, the sponsor comments that proteinuria is a common clinical manifestation of Fabry disease and the event occurred during pregnancy. The patient was discontinued due to pregnancy.

8.3.2.6. Discontinuations due to AEs

Study AT1001-011

Only 2 subjects discontinued the study drug due to TEAEs, and both were SAEs assessed by investigators as being unrelated to the study drug. No subjects met the mandatory stopping criteria (i.e., 30% increase in serum creatinine; 25% decrease cardiac ejection fraction; or cerebrovascular event with sequelae). The 2 TEAEs resulting in discontinuation were anaplastic large cell lymphoma and amyotrophic lateral sclerosis. Anaplastic large cell lymphoma was reported in 1 subject in the placebo-migalastat group (began in Stage 1 [placebo] discontinued in Stage 2 [placebo-migalastat]). Amyotrophic lateral sclerosis was reported in 1 subject in the migalastat-migalastat group in Stage 2.

Study AT1001-012

No subjects discontinued migalastat due to TEAEs.

8.4. Safety issues with the potential for major regulatory impact

8.4.1. Liver function and liver toxicity

8.4.1.1. AT1001-011

- In Stages 1 and 2, there were no hepatobiliary disorders (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 (1x 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 ALT, AST, alkaline phosphatase or bilirubin in any of the treatment groups during the study. The criteria for potentially clinically significant laboratory abnormalities are summarised.

8.4.1.2. 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 (0-30 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 (i.e., 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 (i.e., ALT, AST, Alkaline Phosphatase). The criteria for potentially clinically significant laboratory abnormalities are summarised.

8.4.2. Renal function and renal toxicity

8.4.2.1. 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 (x3) 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 (x4), dysuria (x2), and 1 each for costovertebral tenderness, nephrolithiasis, and urinary retention. In the placebo-migalastat group, the TEAEs were proteinuria (x5) and micoalbuminuria (x3). 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.

8.4.2.2. 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 (x1) and renal impairment (x1) in the migalastat group and hypertonic bladder (x1) and microalbuminuria (x1) 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 (0-30 months), renal and urinary disorders (SOC) were reported in 6% (n = 12) subjects in the all migalastat group. The TEAEs were proteinuria (x2), renal impairment (x2), nephrolithiasis (x1), and strangury (x1). 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.

8.4.3. Other clinical chemistry

8.4.3.1. 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.

8.4.3.2. 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.

8.4.4. Haematology and haematological toxicity

8.4.4.1. 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).

8.4.4.2. 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 x1). 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 (0-30 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.

8.4.5. Electrocardiograph findings and cardiovascular safety

8.4.5.1. 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 (x2) 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 (x3). 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 (x3), palpitations (x2) and cyanosis (x1). In the placebo-migalastat group, the TEAEs were sinus bradycardia (x2) 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 (i.e., 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.

8.4.5.2. 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 (x2), bradycardia (x1), cyanosis (x1), ventricular extrasystoles (x1) and ventricular tachycardia (x1). In the 3 subjects in the ERT group, the TEAEs were palpitations (x1), arrhythmia (x1), chronic cardiac failure (x1). There were two serious TEAEs (1x ventricular tachycardia in the migalastat group; 1 x chronic cardiac failure in the ERT group).
- In the safety population (0-30 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 (x1) and atrial fibrillation (x1). 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).

8.4.6. Vital signs and clinical examination findings

8.4.6.1. 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.

8.4.6.2. 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.

8.4.7. Immunogenicity and immunological events

8.4.7.1. 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 (1x drug hypersensitivity) and 1 (3%) subject in the migalastat-placebo group (1x 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.

8.4.7.2. 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 (0-30 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.

8.4.8. Serious skin reactions

8.4.8.1. 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).

8.4.9. 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 (x1), actinic keratosis (x1), alopecia (x1), hyperkeratosis (x1), pruritus (x1), skin discolouration (x1) and skin lesion (x1). In the 4 subjects in the ERT group, the TEAEs were night sweats (x1), psoriasis (x1), acne (x1) and blister (x1).
- In the safety-population (0-30 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 (x1), alopecia (x1), hyperkeratosis (x1), pigmentation disorder (x1), pruritus (x1), psoriasis (x1), skin discolouration (x1), skin lesion (x1), skin striae (x1), skin ulcer (x1) and stasis dermatitis (x1).

8.5. Other safety issues

8.5.1. Safety in special populations

8.5.1.1. Sex

Study AT1001-011

In Stage 1, the percentage of subjects who experienced a TEAE was similar in males and female subjects in both treatment groups for each sex: i.e., males - 100% (12/12) migalastat and 100% (12/12) placebo; females - 86% (19/22) migalastat and 86% (18/21) placebo. The most frequently reported TEAEs (≥ 10%) in males in the migalastat group were headache (33%), pyrexia (25%), vertigo (17%), haematuria (17%), and cough (17%). The most frequently reported TEAEs (≥ 10%) in females in the migalastat group were headache (36%), nasopharyngitis (23%), fatigue (18%), paraesthesia (18%), nausea (14%), back pain (14%), insomnia (14%), and epistaxis (14%).

In Stage 2, in the total population the overall frequency of TEAEs was similar in males and females (78% [18/23] versus 80% [n = 32/40], respectively). The most frequently reported TEAE (≥ 10%) in males was procedural pain (17%). The most frequently reported TEAEs (≥ 10%) in females were headache (18%) and diarrhoea (13%).

In the OLE, the percentage of subjects in the total population who experienced a TEAE was 68% (13/19) in males and 92% (35/38) in females. The most frequently reported TEAEs (≥ 10%) in males were proteinuria (16%), microalbuminuria (11%), constipation (11%), diarrhoea (11%), fatigue (11%), peripheral oedema (11%), and headache (11%). The most frequently reported TEAEs (≥ 10%) among females were proteinuria (16%), bronchitis (16%), urinary tract infection (13%), arthralgia (13%), and headache (11%).

2. Study AT1001-012

In the 18-month treatment period, the percentage of subjects with TEAEs in the migalastat group was greater in females than in males (100% [20/20], 196 events versus 88%, [14/16], 112

events). The most frequently reported TEAEs (≥ 15%) in males in the migalastat group were nasopharyngitis (44%) and headache (19%). The most frequently reported TEAEs (≥ 15%) in females in the migalastat group were headache (30%), influenza (25%), nasopharyngitis (25%), diarrhoea (20%), abdominal pain (20%), dizziness (20%), pyrexia (15%), back pain (15%), cough (15%), upper respiratory tract infection (15%), nausea (15%), and urinary tract infection (15%).

In the safety population (0-30 months), the percentage of subjects with TEAEs in the all migalastat group was comparable in females and males (100% versus 95%). The most frequently reported TEAEs (≥ 15%) in males in the all migalastat group were nasopharyngitis (48%), creatine kinase increased (24%), headache (24%), and nausea (19%). The most frequently reported TEAEs (≥ 15%) in females in the all migalastat group were headache (37%), nasopharyngitis (37%), diarrhoea (33%), influenza (30%), abdominal pain (20%), dizziness (20%), pyrexia (20%), arthralgia (17%), bronchitis (17%), cough (17%), palpitations (17%), urinary tract infection (17%), and vomiting (17%).

8.5.1.2. Age

Study AT1001-011

This study included 66 subjects aged ≤ 65 years and 1 subject aged > 65 years (n = 1). No meaningful conclusions relating to differences in safety can be drawn between the two age groups (≤ 65 years versus > 65 years) due to the marked imbalance in subject numbers.

Study AT1001-012

This study included 52 subjects aged ≤ 65 years and 5 subjects aged > 65 years. Only 3 subjects in the migalastat group and 2 subjects in the ERT group were older than 65 years. No meaningful conclusions relating to differences in safety can be drawn between the two age groups (≤ 65 years versus > 65 years) due to the marked imbalance in subject numbers.

8.5.1.3. Race

Study AT1001-011

Of the 67 subjects in the study, 65 (97.0%), were Caucasian and 2 (3%) were non-Caucasian. No meaningful conclusions relating to differences in safety can be drawn between the two racial groups (Caucasian versus non-Caucasian) due to the marked imbalance in subject numbers.

Study AT1001-012

Of the 57 subjects in this study, 48 (48%) were Caucasian, 7 (12%) were Asian, 1 (2%) was Black or African American and 1 (2%) was of multiple racial origin. The number of non-Caucasian subjects in the study is considered too small to meaningfully compare the safety of migalastat in Caucasian and non-Caucasian subjects.

8.5.1.4. Renal impairment at baseline

Study AT1001-011

The study included an assessment of safety in subjects with moderate renal impairment (mGFR$_{iohexol}$ < 60 mL/min/m_2; eGFR$_{MDRD}$ < 60 mL/min/m_2) and in subjects with mild renal impairment or normal renal function (GFR$_{iohexol}$ > 60 mL/min/m^2; eGFR$_{MDRD}$ > 60 mL/min/m^2). There were 10 subjects with moderate impairment at baseline in the safety population based on the mGFR$_{iohexol}$ and 9 subjects with moderate impairment at baseline in the safety population based on the eGFR$_{MDRD}$. The results below are summarised for the subjects with moderate renal impairment based on the eGFR$_{MDRD}$ as data were available for this biomarker for each of the three phases of the study, while data for mGFR$_{iohexol}$ was available for the first two phases of the study but not for the third phase (i.e., OLE).

In Stage 1, all subjects with moderate renal impairment based on the eGFR$_{MDRD}$ experienced a TEAE (5 [100%] subjects in the migalastat group experienced 18 TEAEs; 4 [100%] subjects in

the placebo group experienced 18 TEAEs). The most frequently reported TEAEs based on SOC groupings (≥ 25% subjects) in the migalastat group were infections and infestations (100%; n = 5), general disorders and administration site conditions (40%; n = 2), investigations (40%; n = 2), and renal and urinary disorders (40%; n = 2). At the preferred term level, no TEAE was experienced by more than 1 subject in the migalastat group.

In Stage 2, of the 8 subjects with moderate renal impairment at baseline as assessed by eGFR$_{MDRD}$, 6 (75%) experienced a total of 29 TEAEs. The frequency of TEAEs was the same in both the migalastat-migalastat and placebo-migalastat groups (75% [n = 3]). The most frequently reported TEAEs by SOC groupings (≥ 25% of subjects) in the total population (n = 8) were: respiratory, thoracic, and mediastinal disorders (50% [n = 4]); injury, poisoning, and procedural complications (38% [n = 3]); gastrointestinal disorders (25% [n = 2]); infections and infestations (25% [n = 2]); nervous system disorders (25% [n = 2]); vascular disorders (25% [n = 2); and skin and subcutaneous disorders (25% [n = 2]). At the preferred term level, the most frequently reported TEAEs (≥ 2 subjects) were: nasopharyngitis (25% [n = 3]); ligament injury (25% [n = 2]); and pulmonary embolism (25% [n = 2]).

In *the OLE*, of the 7 subjects with moderate renal impairment at baseline as assessed by the eGFR$_{MDRD}$, 6 (86%) experienced a total of 31 TEAEs. The most frequently reported TEAEs by SOC groupings (≥ 25% of subjects) in the total population (n = 7) were: renal and urinary disorders (43% [n = 3]); gastrointestinal disorders (29% [n = 2]); infections and infestations (29% [n = 2]); musculoskeletal and connective tissue disorders (29%); and nervous system disorders (29% [n = 2]). At the preferred term level, the most frequently reported TEAE (≥ 2 subjects) was proteinuria (43% [n = 3]).

Comment: There were no safety signals in subjects with moderate renal impairment treated with migalastat. However, there were only 9 subjects with moderate renal impairment at baseline based on eGFR$_{MDRD}$ in the safety population (5 in the migalastat group and 4 in the placebo group). Therefore, no definitive conclusions can be made relating to the effects of moderate renal impairment on the safety of migalastat. There were no separate safety data in patients with mild renal impairment, as the safety data in subjects with mild renal impairment and with normal renal function were pooled. There were no safety data in subjects with severe renal impairment.

Study AT1001-012

In the CSR for *Study AT1001-012*, safety data in the body of the report were provided for subjects with moderate renal impairment at baseline based on mGFR$_{iohexol}$ (< 60 mL/min/1.73 m^2). *In the 18-month treatment period*, there were 7 subjects (4 migalastat [30 events], 3 ERT [38 events]) with moderate renal impairment at baseline based on mGFR$_{iohexol}$. In both treatment groups, all subjects with moderate renal impairment experienced TEAEs. The only TEAEs reported in ≥ 2 subjects in either of the two treatment groups (migalastat versus ERT) were gastritis (n = 1 versus n = 2) and arthralgia (n = 0 versus n = 2). *In the safety population (0-30 months)*, there were 7 (14%) subjects in the all migalastat group with moderate renal impairment based on mGFR$_{iohexol}$. All 7 subjects experienced TEAEs, with the total number of TEAEs being 79. TEAEs reported in ≥ 2 subjects were nasopharyngitis (n = 3), influenza (n = 2) abdominal pain (n = 2), vomiting (n = 2), pyrexia (n = 2), protein increased (n = 2), musculoskeletal stiffness (n = 2), dizziness (n = 2), and neuralgia (n = 2).

The CSR (month-30 report) included a *post-hoc* analysis of safety in subjects with baseline protein < 100 mg/24 h and ≥ 100 mg/24 h. The results are discussed below.

In the OLE population, TEAEs in subjects with baseline proteinuria < 100 mg/24 h were reported in 7 (100%) subjects (74 events) treated with ERT for 18 months before switching to migalastat (0-18 months ERT-migalastat group) and 7 (100%) subjects (55 events) treated with migalastat for 12 months after switching from ERT (18-30 months ERT-migalastat group). TEAEs reported in ≥ 2 subjects in either treatment group (ERT-migalastat [0-18 months] versus

ERT-migalastat [18-30 months]) were gastritis (n = 2 versus n = 0), vomiting (n = 2 versus n = 3), pyrexia (n = 2 versus n = 2), bronchitis (n = 2 versus n = 0), headache (n = 2 versus n = 2), nausea (n = 1 versus n = 2), nasopharyngitis (n = 1 versus n = 4), and diarrhoea (n = 0 versus n = 3).

In the OLE population, TEAEs in subjects with baseline proteinuria ≥ 100 mg/24 h were reported in 8 (100%) subjects (69 events) treated with ERT for 18 months before switching to migalastat (0-18 months ERT-migalastat group) and 8 (100%) subjects (62 events) treated with migalastat for 12 months after switching from ERT (18-30 months ERT-migalastat group). TEAEs reported in ≥ 2 subjects in either treatment group (ERT-migalastat [0-18 months] versus ERT-migalastat [18-30 months]) were nasopharyngitis (n = 3 versus n = 1), headache (n = 3 versus n =), diarrhoea (n = 2 versus n = 1), oedema peripheral (n = 2 versus n = 0), influenza (n = 2 versus n = 2), sinusitis (n = 2 versus n = 0), cough (n = 2 versus n = 1), procedural pain (n = 2 versus n = 0), back pain (n = 2 versus n = 0), bronchitis (n = 1 versus n = 2), diabetes mellitus (n = 0 versus n = 2), creatine kinase increased (n = 0 versus n = 2), and muscle spasms (n = 0 versus n = 2).

In the OLE population, TEAEs in subjects with baseline proteinuria < 100 mg/24 h in the all migalastat group (0-30 months safety population) were reported in 22 (100% [22/22]) subjects (241 events). TEAEs reported in ≥ 3 subjects were nasopharyngitis (n = 12), headache (n = 8), diarrhoea (n = 7), vomiting (n = 6), nausea (n = 4), influenza (n = 4), upper respiratory tract infections (n = 4), abdominal pain (n = 3), dyspepsia (n = 3), pyrexia (n = 3), creatine kinase increased (n = 3), arthralgia (n = 3), dizziness (n = 3), palpitations (n = 3), and cough (n = 3)

In the OLE population, in subjects with baseline proteinuria ≥ 100 mg/24 h in the all migalastat group (0-30 months safety population) TEAEs were reported in 28 (97% [28/29]) subjects (357 events). TEAEs reported in ≥ 3 subjects were nasopharyngitis (n = 9), headache (n = 8), dizziness (n = 5), influenza (n = 4), pain (n = 5), cough (n = 5), abdominal pain (n = 4), diarrhoea (n = 4), nausea (n = 4), bronchitis (n = 4), urinary tract infection (n = 4), fall (n = 4), creatine kinase increased (n = 4), protein urine present (n = 4), myalgia (n = 4), arthralgia (n = 3), back pain (n = 3), muscle spasms (n = 3), paraesthesia (n = 3), insomnia (n = 3), oropharyngeal pain (n = 3), sinusitis (n = 3), tinnitus (n = 3), chest pain (n = 3), fatigue (n = 3), influenza like illness (n = 3), and pyrexia (n = 3).

Comment: The number of subjects with moderate renal impairment based on $mGFR_{iohexol}$ is considered too small to make meaningful clinical conclusions relating to the safety of migalastat in patients with renal impairment. There were no data in subjects with severe renal impairment. The safety data in subjects with mild renal impairment were pooled with the safety data in subjects with normal renal function. The *post-hoc* analysis (OLE population) in subjects with baseline urine protein < 100 mg/24 h and ≥ 100 mg/24 h showed no notable differences in the safety profiles between ERT for 18 months (0-18 months ERT-migalastat group) and migalastat for 12 months (18-30 months ERT-migalastat group), or in the all migalastat group (0-30 months).

8.5.1.5. Hepatic impairment at baseline

There were no data on the effect of migalastat in subjects with hepatic impairment.

8.5.2. Safety related to drug-drug interactions and other interactions

There were no safety data relating to drug-drug interactions between migalastat and other therapeutic agents with which it might be co-administered in clinical practice.

8.5.3. Long-term safety

The submission included two Phase III, single-group, open-label, long-term extension studies [AT1001-041; AT1001-042]. The primary objectives of the long-term extension *studies AT1001-041 and AT1001-042* are to evaluate the long-term safety of migalastat. As of 2

November 2015, 85 subjects had entered *Study AT1001-041,* with 13 subjects on-going, and 71 subjects had entered *Study AT1001-042*, with 67 on-going. Subjects entering the two long-term studies were required to have completed previous OLE treatment with migalastat in *studies AT1001-011(Phase III), AT1001-012 (Phase III), or FAB-CL-205 (Phase II)*. The longest duration of exposure to migalastat is 506.6 weeks (or 9.74 years) for a subject from *study FAB-CL-201* who continued treatment in *Study AT1001-041*. The sponsor is discontinuing *Study AT1001-041* for administrative reasons, and subjects from this study are being enrolled into *Study AT1001-042* at the investigators' discretion. There were no exposure or safety data for subjects being treated in *Study AT1001-042*.

In *Study AT1001-041*, 69 (81%) of the 85 enrolled subjects from the three feeder studies experienced at least one TEAE. The most frequently reported TEAEs based on SOC groupings (≥ 20% of subjects) were infections and infestations (49%, n = 42), musculoskeletal and connective tissue disorders (44%, n = 37), gastrointestinal disorders (36%, n = 31), nervous system disorders (35%, n = 30), respiratory, thoracic and mediastinal disorders (21%, n = 18), and cardiac disorders (n = 20%). TEAEs (preferred term), 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). TEAEs reported in ≥ 5% of subjects are summarised below.

Table 86: AT1001-041 – Most common TEAEs (preferred term) reported by ≥ 5% of subjects.

Migalastat 150 mg QOD (n = 85)	
Diarrhoea	14 (16%)
Arthralgia	11 (13%)
Fatigue; Headache; Pain in extremity	10 (12%)
Nasopharyngitis	9 (11%)
Back pain; Pyrexia; Urinary tract infection,	7 (8%)
Abdominal pain upper; Cough; Paraesthesia; Upper respiratory tact infection	6 (7%)
Abdominal distension; Contusion; Hypertension; Oedema peripheral; Pain; Palpitations; Vertigo	5 (6%)
Abdominal pain; Anxiety Dyspnoea; Flank pain; Flatulence; Migraine; Musculoskeletal pain; Proteinuria; Vomiting	4 (5%)

Of the 662 TEAEs reported in *Study AT1001-041*, 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.

There were 31 treatment-emergent SAEs reported by 22 subjects, none of which were considered to be treatment-related. Treatment-emergent SAEs were: cardiac disorders (atrial fibrillation x 2; angina pectoris x1); gastrointestinal disorders (abdominal pain upper x 1; hiatus hernia x1; pancreatitis x1); general disorders and administration site conditions (death x 1; device malfunction x1); hepatobiliary disorder (hepatic infarction x1); infections and infestations (pneumonia x2; lobar pneumonia x1); injury poisoning and procedural

complication (foot fracture x1); musculoskeletal and connective tissue disorders (muscle spasms x1; musculoskeletal chest pain x1); neoplasms, benign, malignant and unspecified, including cysts and polyps (breast cancer metastatic x1; malignant melanoma x1; meningioma x1; papillary thyroid cancer x1; thyroid neoplasm x1); nervous system disorders (brain stem ischaemia x1; pre-syncope x1); not coded (insertion of implantable cardioverter defibrillator x2); psychiatric disorder (conversion disorder x1); renal and urinary disorders (urinary calculus x1); reproductive and breast disorders (priapism x 1; uterine polyp x1); and skin and subcutaneous tissue disorders (angioedema x1).

There 2 deaths in the study: 1 (1%) subject died from a TEAE (Stage III Breast Cancer) deemed to be unrelated to treatment; and 1 (1%) subject was found dead at home (unknown cause of death; unrelated to treatment), with a medical history including transient ischaemic attack, obesity, type 2 diabetes mellitus, hypercholesterolemia, cardiac stent placement, triple bypass surgery, and cardiac pacemaker insertion.

One subject (1.2%) discontinued due to a TEAE (SAE of metastatic squamous cell carcinoma considered to be unrelated to treatment), 9 (10.6%) subjects discontinued due to withdrawal of consent, 7 (8.2%) subjects withdrew at the investigator's discretion, and 1 (1.2%) subject withdrew due to pregnancy.

There was limited information in subjects with laboratory test data. The sponsor stated that there were no more than 8 subjects with a baseline value for whom shifts from baseline could be evaluated. While some shifts from baseline in haematological laboratory parameters were reported, the shifts were not consistent across study visits and occurred in no more than 2 subjects per haematology parameter per visit. While some shifts from baseline in clinical chemistry laboratory parameters were reported, the shifts were not consistent across study visits and occurred in no more than 1 subject per clinical chemistry parameter per visit. No shifts from baseline for urinalysis parameters were reported. No abnormalities of clinical significance were reported in vital sign parameters. The sponsor stated that there were no meaningful increases from baseline in the proportion of subjects with abnormal ECG results.

8.5.4. Phase I studies

In the 10 Phase I studies, 218 subjects received migalastat at various doses and 24 received placebo. The studies were conducted in healthy volunteers, apart from *Study AT1001-015* which included both subjects with renal impairment and subjects with normal renal function. Of the 242 subjects treated in the Phase I studies, 24 (10%) subjects reported headache, including 19 (7.9%) subjects who had received migalastat. No trend related to dose level or route of administration was evident. All other adverse events generally occurred in 1 subject each per study, with usually a single occurrence per subject. No SAEs were reported in the Phase I studies.

8.5.5. Phase II studies

In the 5 Phase II comparative studies, 27 subjects receive migalastat at various doses and regimens, and 23 of these subjects continued treatment with migalastat in the OLE Phase II study [FAB-CL-205]. The range of migalastat doses and regimens explored in these 5 Phase II studies were; BD (25, 100, 250 mg); QD (50, 150 mg), QOD (50, 150, 250 mg), and 3 days on, 4 days off (250 and 500 mg).

In the 5 Phase II comparator studies, few events were reported in ≥ 25% of subjects. TEAEs reported in ≥ 25% of subjects were: 2 (25%) of 8 subjects with cardiac murmur in *Study AT1001-013*; 5 (56%) of 9 subjects with headache (1 mild, 3 moderate, and 1 severe), and 4 (44%) of 9 subjects with nausea in *study FAB-CL-201*; 2 (50%) of 4 subjects with moderate upper abdominal pain in *study FAB-CL-202*; and headache and proteinuria each reported by 2 (40%) of 5 subjects in *study FAB-CL-203*. No TEAEs in *study FAB-CL-204* were reported by more than 2 subjects (22%). TEAEs were generally reported as being mild to moderate in severity and assessed by investigators as being unrelated to treatment.

In the OLE *study FAB-CL-205*, comprising subjects from the 4 Phase II feeder studies continuing treatment with migalastat, arthralgia, fatigue, back pain, pain in extremity, influenza and headache were the most commonly reported TEAEs in the total population (each reported in ≥ 6 subjects [≥ 26%]). In general, TEAEs were reported more frequently in females than in males. Among the most frequently reported TEAEs (≥ 3 subjects at any dose) a higher incidence occurred with the 500 mg dosing regimen (3 days on / 4 days off) compared to the 250 mg (3 days on / 4 days off) and the 150 mg QOD regimens. The rate of TEAEs with the 150 mg QOD regimen was 0.12/treatment-year, compared to 1.48/treatment-year with the 250 mg (3 days on / 4 days off) regimen and 0.73/treatment-year with the 500 mg (3 days on / 4 days off) regimen, based on the number of TEAEs and adjusted for exposure. TEAEs were generally mild to moderate and assessed as unrelated to treatment.

In the 5 Phase II studies, a total of 31 SAEs were reported (including during screening, on treatment and after treatment was discontinued), none of which were considered related to migalastat. The majority of the total number of SAEs were reported in *study FAB-CL-205* (23 SAEs reported in 7 subjects, none of which were assessed by investigators as being related to migalastat). In the 7 (30.4%) subjects in *study FAB-CL-205* with a treatment-emergent SAE, the only event reported in ≥ 2 subjects was atrial fibrillation (n = 2).

8.5.6. Pregnancy and lactation

There were no studies relating to the use of migalastat in pregnant or lactating women. During the clinical development program, pregnancy was reported in 3 female subjects (2 in *Study AT1001-011* and 1 in *Study AT1001-012*). All 3 pregnant women stopped study drug at the time the pregnancy was confirmed. All 3 babies were healthy, 2 delivered vaginally and 1 via a planned C-section.

8.5.7. Overdose

Headache and dizziness were the most commonly reported treatment related AEs reported with migalastat at doses up to 1250 mg and 2000 mg, respectively [FAB-CL-104].

8.5.8. Drug abuse

There were no dedicated studies on the potential for migalastat to be abused. However, given the mode of action drug and the lack of significant mood related CNS treatment effects (e.g., euphoria) it is considered that abuse of migalastat is unlikely.

8.5.9. Withdrawal and rebound

There were no data on withdrawal or rebound effects on migalastat.

8.5.10. Effect on ability to drive and operate machinery

No studies have been conducted to assess the effect of migalastat on the ability to drive or operate machinery.

8.6. Post-marketing data

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

8.7. 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.

8.7.1. Study AT1001-011

In Stage 1 (0-6 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 (6-12 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 (12-24 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 (0-6 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 (6-12 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 (12-24 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 (0-6 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 (6-12 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 (12-24 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.

8.7.2. 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 (0-30 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 (0-30 months) was consistent with the pattern of treatment-related TEAEs in the migalastat group (0-18 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).

8.7.3. Studies AT1001-011 and AT1001-012

No safety issues with possible regulatory impact were identified in subjects treated with migalastat in the two Phase III 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.

8.7.4. 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 III 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 x1); gastrointestinal disorders (abdominal pain upper x 1; hiatus hernia x1; pancreatitis x1); general disorders and administration site conditions (death x 1; device malfunction x1); hepatobiliary disorder (hepatic infarction x1); infections and infestations (pneumonia x2; lobar pneumonia x1); injury poisoning and procedural complication (foot fracture x1); musculoskeletal and connective tissue disorders (muscle spasms x1; musculoskeletal chest pain x1); neoplasms, benign, malignant and unspecified, including cysts and polyps (breast cancer metastatic x1; malignant melanoma x1; meningioma x1; papillary thyroid cancer x1; thyroid neoplasm x1); nervous system disorders (brain stem ischaemia x1; pre-syncope x1); not coded (insertion of implantable cardioverter defibrillator x2); psychiatric disorder (conversion disorder x1); renal an urinary disorders (urinary calculus x1); reproductive and breast disorders (priapism x 1; uterine polyp x1); and skin and subcutaneous tissue disorders (angioedema x1).

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).

9. First round benefit-risk assessment

9.1. 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 III study comparing migalastat 150 mg QOD with ERT over 18 months of randomised, open-label, treatment (Study AT1001-012), and in 1 supportive Phase III 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 III 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.

9.1.1. 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.

9.1.1.1. 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 $eGFR_{MDRD}$; and -2.7 mL/min/1.73 m^2 (95% CI, -4.8, -0.7) for $mGFR_{iohexol}$. 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 $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ 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 $eGFR_{CKD\text{-}EPI}$ in the migalastat group (n = 28) and the placebo group (n = 20) were 0.3 ± 17.05 and 2.0 mL/min/1.73 m^2, respectively. The mean (± SD) annualised changes from baseline at month 6 in $eGFR_{MDRD}$ 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 m^2, respectively. In the OLE population, the mean (± SEM) annualised changes in $eGFR_{CKD\text{-}EPI}$ and $eGFR_{MDRD}$ from baseline at month 24 were -0.30±0.663 and 0.79 ± 1.027 mL/min/1.73 m^2, 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 $mGFR_{iohexol}$ 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 m^2, respectively. In the OLE population, in subjects treated with migalastat (n = 37) for 18 or 24 months the mean (± SEM) annualised change in $mGFR_{iohexol}$ at month 24 was -1.51 ± 1.327 mL/min/1.73 m^2. The results indicate that $mGFR_{iohexol}$ remained stable over 18 or 24 months treatment with migalastat.
- In Study AT1001-011, the mean annualised reductions at month 24 in $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ 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, $eGFR_{CKD\text{-}EPI}$ remained stable over an average of 36 months (range: 18, 54 months). The mean annualised rate of change in $eGFR_{CKD\text{-}EPI}$ over this period in subjects continuing treatment (n = 41) was -0.77 (95% CI: -1.9. 0.39) mL/min/1.73 m^2. Measured GFR ($mGFR_{iohexol}$) was not assessed in Study AT1001-041.

9.1.2. 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.

9.1.3. 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/24h, 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 87: 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/24h; 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/24h; 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/24h; 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/24h, respectively) and albumin (106.6 and

184.0 mg/24h, 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).

9.1.4. 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).

9.1.5. 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.

9.1.6. 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.

9.1.7. 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 (i.e., 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).

9.1.8. 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 0-6, 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.

9.2. 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 III 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 [x1]; post-procedural haemorrhage [x1]). 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 III 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 III 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 III 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 x1; pancreatitis x1); 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).

9.3. 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 (i.e., 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 (i.e., 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 (i.e., 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.

10. 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.

11. Clinical questions

11.1. General

1. In the Australian Specific Annex Document, the sponsor states that an Investigational New Drug (IND) application was submitted to the US FDA on 21 June 2004 and that the IND remains current. The sponsor stated that multiple interactions between the US FDA and Amicus have taken place over the last 9 years. Please indicate the nature of the problem with the US IND for migalastat which has resulted in protracted interaction with the US FDA.

2. Does the sponsor intend submitting data to the TGA supporting approval of migalastat in children and adolescents younger than 16 years of age? If yes, please provide the estimated data of submission. If no, please justify the decision not to provide such data.

11.2. Pharmacokinetics

1. 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.

2. Please provide a formal justification for not submitting a PK study evaluating the impact of hepatic impairment on the PK of migalastat. Does the sponsor intend undertaking such a study?

3. In *study FAB-CL-102*, following oral migalastat HCl 50 mg BD and 150 mg BD statistical analysis of C_{min} values on Days 5, 6, and 7 indicated that steady state had not been reached on Day 7. This was an unexpected finding, given that the mean terminal half-life of migalastat following single dose administration was approximately 2.5 hours. The sponsor is requested to comment on this unexpected finding.

4. In the PK renal impairment 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 (C48) 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 (i.e., 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 no dosage adjustment is indicated for patients with moderate or mild renal impairment. Please justify why a dosage adjustment has not been recommended for subjects with moderate renal impairment, given the approximately 2-fold increased exposure in subjects with moderate renal impairment compared to subjects with normal renal function.

5. In the PPK study [MGM116016], the mean predicted $t_{1/2}$ value in healthy volunteers (n = 51) from *Study AT1001-010* was 3.65 hours (range: 2.98, 4.55 hours) and 20.6 hours (range: 19.0, 23.5 hours) in subjects (n = 62) with Fabry disease from *Study AT1001-010*. However, predicted exposure data were generally similar for the two studies. The relevant data are from the PPK study report MGM116016 for *Study AT1001-011* and *Study AT1001-010*. Please comment on the reasons for the difference in predicted $t_{1/2}$ between the two studies. In particular, please comment on the long $t_{1/2}$ estimated for *Study AT1001-011.*

11.3. Pharmacodynamics

1. The sponsor considered that the results for kidney GL-3 concentration in tissue homogenates presented *study FAB-CL-204* were non-informative. The sponsor stated that accumulation of GL-3 in kidney tissue might be regionally variable, particularly in females because of their heterozygotic expression of both mutant and wild type forms of α-Gal A. Please clarify why accumulation of GL-3 in kidney tissue might be regionally variable?

11.4. Efficacy

1. In *Study AT1001-011*, the pre-specified Stage 1 analysis was based on subjects identified as responsive by the Clinical Trial HEK assay. Subsequent re-analysis of the 67 subjects resulted in 17 subjects (25%) being deemed non-amenable by the validated GLP HEK Assay. Why did the Clinical Trial HEK assay identify such a large proportion of patients subsequently deemed non-amenable as responsive?

2. Please provide the results of the pre-specified primary efficacy endpoint in Stage 1 of *AT1001-011* using the amenable subjects (ITT population) based on the GLP HEK assay (i.e., the responder analysis based on the number of subjects with ≥ 50% reduction from baseline to month 6 in the average number of IC GL-3 inclusions).

3. In *Study AT1001-011*, no primary efficacy endpoint was defined for the *post-hoc* analysis of Stage 1. Please explain the reasoning behind this decision.

4. In *Study AT1001-011*, p-values were provided for the comparisons between migalastat and placebo for the *post-hoc* analysis. However, no comment was provided in the CSR that the significant p-values were nominal rather than confirmatory due to no statistical adjustments being made for multiplicity. Please comment on this matter.

5. In *Study AT1001-012*, lot numbers for the ERT products used in individual subjects were provided. Does the sponsor have any information on whether the lots represented the same formulations of the ERT products and whether the lots represented formulations approved in Australia?

6. Please provide separate tabulated summaries of the amenable GLA mutations based on the GLP HEK assay identified by genotype for all amenable subjects from *studies AT1001-011 and AT1001-012*. For each genotype for each study please provide the number of subjects with the genotype. Please confirm that the tables you provide include the results for all amenable subjects from both studies. Tables were presented by the sponsor in correspondence with the EMA during the course of the CHMP evaluation, but it was not entirely clear which tables contained the correct information. For example, it appears that Tables 4 and 5 in the *Rapporteurs Day 195 Joint CHMP and PRAC Response Assessment Report Clinical – Assessment of the responses to the CHMP/PRAC List of Questions* include different patient numbers for some genotypes provided by the sponsor from those calculated by the CHMP from data spread-sheets provided by the sponsor.

7. In order for a patient to be treated with migalastat it will be necessary to establish that they have an amenable *GLA* mutation. Therefore, the first step in the process will be to determine their genotype. How does the sponsor see this working-out in current Australian clinical practice for patients with Fabry disease (established or de novo) who have not been genotyped? Is genotyping of new patients with Fabry disease part of the routine work-up in Australian clinical practice? In the report of the pre-submission meeting, the sponsor indicated that genotype testing for diagnosing Fabry disease for the clinical trials was conducted in Australia through the NATA-accredited laboratory at the Women's and Children Hospital in Adelaide, South Australia. If migalastat is approved in Australia, does the sponsor envisage that genotyping will be undertaken at this laboratory or another centralised laboratory or will individual units make their own arrangements with local laboratories? How does the sponsor

see funding of genotyping proceeding (e.g., sponsor supported, individual patient payment, Medicare Benefits Schedule item number)?

12. Second round evaluation of clinical data

12.1. General

- ***Question 1: In the Australian Specific Annex Document, the sponsor states that an Investigational New Drug (IND) application was submitted to the US FDA on 21st June 2004 and that the IND remains current. The sponsor stated that multiple interactions between the US FDA and Amicus have taken place over the last 9 years. Please indicate the nature of the problem with the US IND for migalastat which has resulted in protracted interaction with the US FDA.***

Sponsor's response:

The Applicant comments that during recent interactions with the US FDA on the migalastat program, the FDA indicated that Kidney IC GL-3, the primary endpoint in *Study AT1001-011* is currently not considered a basis for an accelerated approval under Subpart H Accelerated Approval Regulation. Statutory requirements do not allow FDA to accept a comparator trial with ERT as a key component for approval since FDA does not consider ERT to have shown clinical benefit. Therefore, *Study AT1001-012* cannot be used in the US in the same way it has been used to demonstrate clinical benefit in the EU, Switzerland and Australia, where it has been presented as a pivotal study.

In the US, Fabrazyme (agalsidase beta) is the only available therapy for Fabry disease. Fabrazyme was approved in 2003 under the Subpart E Accelerated Approval Regulation, using a surrogate endpoint of Kidney Interstitial Capillary globotriaosylceramide (Kidney IC GL-3). At the time of the approval, Genzyme was required to complete three additional clinical studies and continue the patient registry to demonstrate clinical benefit to enable full approval. Genzyme completed the post marketing commitments and submitted the studies. However, from an FDA regulatory viewpoint, Fabrazyme did not demonstrate clinical benefit in Fabry disease and has not been converted to full approval.

Replagal (agalsidase alfa) has never been approved in the US and was only introduced under an expanded access program for a short period, during the Fabrazyme shortage. TKT made an original BLA submission in 2000 and were issued a Complete Response Letter. In 2009, at the request of FDA, Shire (who had acquired TKT) submitted a new BLA application; however, after 3 years of interactions, Shire announced that it was no longer pursuing a marketing application in the US following requests by FDA for additional controlled studies.

The Applicant comments that the US situation for both Fabrazyme and Replagal highlights a key difference with the regulatory landscape in the US compared with other markets across the world where both Fabrazyme and Replagal hold a full approval, and have been the mainstay of treatment for Fabry disease patients since the early 2000s.

The Applicant comments that the migalastat development program was based on the guidance obtained in multiple interactions with FDA and EMA beginning in 2009. Based on this guidance, two Phase III studies were conducted – a placebo controlled study based on a surrogate endpoint of Kidney IC GL- 3 for FDA and an active comparator study based on stabilisation of renal function for EMA. It was expected, for the US and all other markets that conducting two studies would provide cumulative evidence of a positive risk-benefit, even if in diverse regions/countries a different one of the two studies might be considered the pivotal study. EMA and Switzerland, where Galafold is approved, accepted the company position that the comparator study (*Study AT1001-012*) was the pivotal study, with the placebo-controlled study (*Study AT1001-011*) providing strong supporting evidence for the benefit-risk assessment.

Based on recent interactions with FDA, Amicus plans to conduct a new gastrointestinal signs and symptoms trial to provide additional data to demonstrate substantial evidence of effectiveness/clinical benefit per 21CFR 314.50 to support full approval in the US. While these additional data are being collected, Amicus will initiate an Intermediate Expanded Access Program to ensure short-term access to migalastat for patients who are currently on ERT and meet the requirements for the program. In addition, patients who are currently participating in the ongoing extension studies will continue to receive migalastat until approval is received.

Evaluator's comment:

The sponsor's response is satisfactory. The US requires different data for approval of migalastat for the treatment of Fabry disease than that required by Australia and other jurisdictions. This appears to be due to a flow-on effect arising from differences in the registration status of ERT products between the US and other jurisdictions.

- ***Question 2: Does the sponsor intend submitting data to the TGA supporting approval of migalastat in children and adolescents younger than 16 years of age. If yes, please provide the estimated data of submission. If no, please justify the decision not to provide such data.***

Sponsor's response:

Amicus is conducting a global study in paediatric patients aged 2-16 in accordance with a Paediatric Investigational Plan (PIP) agreed with EMA. A waiver has been granted for birth-2 years of age. This global study will be initiated in 2017 with results expected in 2021. The Applicant therefore intends to submit these data in due course to TGA and other regulatory agencies, to support a revised label for paediatric patients.

Evaluator's comment:

The sponsor's response is satisfactory.

12.2. Pharmacokinetics

- ***Question 1: 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.***

Sponsor's response:

Migalastat is a highly soluble, BCS 3 drug. It is well absorbed, and the absolute bioavailability of the 150 mg clinical capsule is approximately 75%. This is consistent with results from the mass-balance Study AT1001-014, where approximately 80% of the radio-labelled dose was recovered in urine. Clinical and marketing formulation dissolution profiles are presented below in Table 1.

Table 88: Batch analysis data for batches of migalastat HCl capsules.

Formulation		Clinical: Mean (range); RSD				Marketing: Mean (range); RSD		
Batch No.	Acceptance Criteria	W014722 (150 mg)	W015082 (150 mg)	W018702 (150 mg)	W018703 (150 mg)	W011387 (150 mg)	W011388 (150 mg)	W11389 (150 mg)
Dissolution (% migalastat released)	Complies with harmmonized pharmacopoiea; not less than 85% dissolved in 30 min (Q=80% at 30 min)	102 (100-104); 1.2	101 (96-104); 3.0	101 (94-106); 4.9	103 (96-108); 3.9	102 100-104); 1.3	103 (102-105); 1.0	102 (100-104); 1.4
	Complies with requirements of current USP (711), Apparatus 2, where Q=80 at 30 min	Early Clinical: Mean (range); RSD						
		8901.001 (25 mg)	8901.002 (25 mg)	8901.003 (25 mg)	8901.004 (25 mg)	8901.005 (25 mg)		
		101 (95-107); 3.7	99 (91-104); 4.5	104 (93-110); 5.6	97 (89-109); 7.7	89 (84-95); 5.2		

As shown, *in vitro* dissolution profiles for early clinical, clinical, and marketing batches at 25 mg and 150 mg strengths are near-identical with complete or near-complete dissolution within 30 minutes. Additionally, in clinical *study FAB-CL-103*, the relative bioavailability of the early clinical capsule at a 100 mg dose (4 x 25 mg capsules) was approximately 100% compared to an oral solution of the same dose administered to healthy volunteers. Therefore, the relative bioavailability of the 25 mg capsule should not be different from the 150 mg clinical or marketing capsules. Given the similarity in dissolution profiles, and the well-characterised pharmacokinetics of plasma and urine migalastat, a relative bioavailability study bridging the clinical and marketed formulations was not considered warranted.

Evaluator's comment:

The sponsor's response is satisfactory.

- ***Question 2: Please provide a formal justification for not submitting a PK study evaluating the impact of hepatic impairment on the PK of migalastat. Does the sponsor intend undertaking such a study?***

Sponsor's response:

The Applicant confirms that a hepatic study was not performed for the following reasons:

- Migalastat is highly water soluble and its primary route of elimination is *via* the kidney.
- Migalastat is largely un-metabolised with 3 glucuronides identified, none of which comprises more than 6% of the radio-labelled dose; the glucuronides were identified only in urine.
- Although 20% of the migalastat dose was identified in feces, it was comprised of unchanged drug; therefore, it is assumed that the 20% recovery of the radiolabelled dose in feces represents un-absorbed drug. The 20% unabsorbed is consistent with the absolute bioavailability of migalastat, 75%.
- Given the PK profile of migalastat, and that hepatic impairment is not characteristic of the clinical profile of Fabry disease, there are currently no plans to perform a hepatic impairment study.

Evaluator's comment:

The sponsor's response is satisfactory.

- ***Question 3: In study FAB-CL-102, following oral migalastat HCl 50 mg BD and 150 mg BD statistical analysis of Cmin values on Days 5, 6, and 7 indicated that steady state had not been reached on Day 7. This was an unexpected finding, given that the mean terminal half-life of migalastat following single dose administration was approximately 2.5 hours. The sponsor is requested to comment on this unexpected finding.***

Sponsor's response:

The Applicant confirms that a statistically significant difference was found between the three C_{min} values 24 hours apart (Days 5, 6 and 7) following BID dosing with 150 mg migalastat HCl (p-value 0.0008 for Helmert's contrasts) (see below).

Table 89: Geometric Mean of Cmin by dose and time (Days 5, 6 and 7).

Dose Level	Time	C_{min}* (mcg/L)
50 mg BID	-48-hour	56.568
	-24-hour	51.333
	0-hour	63.561
150 mg BID	-48-hour	177.567
	-24-hour	158.063
	0-hour	194.905

*Geometric Means of C_{min} by Dose and Time (Days 5, 6 and 7)

Helmert's Contrasts	P-value
Comparison 1	0.9893
Comparison 2	0.0008

- A plausible explanation is that the C_{min} level for one of the subjects was > 100% different from the geometric mean of the group (n = 6). The C_{min} for this subject (150 mg BID) was 69.9 µg/mL (at the -24 hour period), compared to the geometric mean of the group of 158.063 µg/mL. The inclusion of the C_{min} results from this outlier resulted in a CV% of 38.1% for the mean C_{min} value and introduced enough variability to impact the analysis. An explanation for the low Cmin was that the outlier reached t_{max} earlier than all other subjects in the treatment group (1.5 h on Day 1 compared to the range 2.0 h - 4.0 h for other subjects and 2.0 h on Day 7 compared to the range from 2.5 h to 4.0 h for the other subjects). The results for the C_{min} are summarised below.
- Given the short half-life, drug accumulation was not observed following BID dosing.
- The current regimen in Fabry patients is 150 mg QOD, with C_{min} values below or slightly above the lower limit of quantification.
- Therefore, the analysis does not impact the pharmacokinetic profile characterised in the Fabry patient population.

Table 90: Concentration of AT-1001 in plasma (Group 2, 150 mg, Day 7).

Subject ID	Period	-48	-24	0
	1	137.0	141.0	191.0
	1	208.0	230.0	223.0
	1	160.0	205.0	230.0
	1	164.0	69.9	116.0
	1	160.0	141.0	180.0
	1	262.0	238.0	268.0
Arithmetic Mean		191.83	170.82	201.33
± SD		45.591	65.034	52.114
CV%		25.1	38.1	25.9
Minimum		137.0	69.9	116.0
Maximum		262.0	238.0	268.0
Median		162.0	173.0	207.0
Geometric Mean		177.57	158.06	194.90
n		6	6	6

Evaluator's comment:

The sponsor's response is satisfactory.

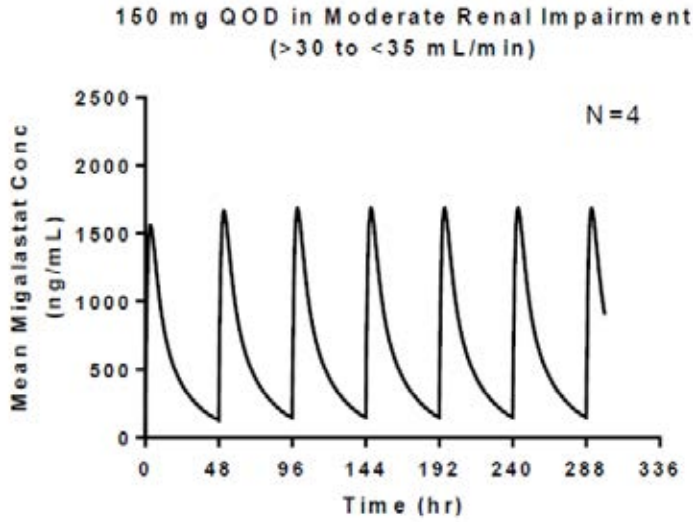
- ***Question 4: In the PK renal impairment study [AT1001-015], after a single oral dose of migalastat HCl 150 mg to subjects with mild, moderate and severe renal impairment the AUC0-t values were 1.2-, 1.8- and 4.3-fold greater, respectively, compared to subjects with normal renal function. In addition, plasma migalastat concentrations at 48 hours after dosing (C48) 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 m² (i.e., 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 no dosage adjustment is indicated for patients with moderate or mild renal impairment. Please justify why a dosage adjustment has not been recommended for subjects with moderate renal impairment, given the approximately 2-fold increased exposure in subjects with moderate renal impairment compared to subjects with normal renal function.***

Sponsor's response:

Subjects with mild renal impairment had C_{48h} plasma migalastat concentrations near the lower limit of quantification (LLOQ), therefore significant accumulation following multiple dosing is not expected. Multiple dose simulations of subjects were performed at the lowest level of moderate renal impairment (30-35 mL/min). Although these showed substantially greater mean C_{48h} concentration than observed in subjects with normal renal function, they did not demonstrate further accumulation following multiple dosing with 150 mg migalastat HCl every other day (QOD), and long-term safety issues would not be expected.

In the Phase I renal impairment study, AT1001-015, following a single dose of 150 mg migalastat HCl, subjects with mild renal impairment had a mean C_{48h} concentration of 9.34 ng/mL, subjects with moderate renal impairment had a much higher mean C_{48h} concentration of 64.5 ng/mL, and subjects with normal renal function had a mean C_{48h} concentration that was below the LLOQ (5.70 ng/mL). Since subjects with mild renal impairment had C_{48h} concentrations that were slightly over the LLOQ, significant accumulation following multiple dosing every other day would not be anticipated. Multiple dose simulations in subjects at the lowest level of moderate renal impairment (30-35 mL/min) did not show relevant additional accumulation beyond that caused by moderate renal impairment. As shown below, C_{48h} concentrations following multiple dosing were similar to the Day 1 C_{48h} concentration. This suggests that in moderate renal impairment, 48 hours is sufficient time for migalastat to clear from the plasma compartment without additional accumulation.

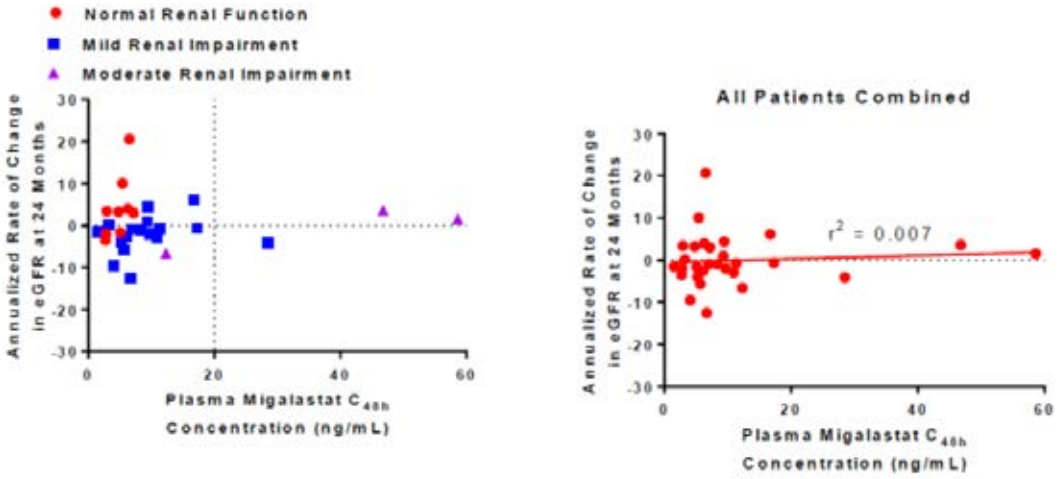
Figure 13: Multiple dose simulations of non-Fabry patients with low-moderate renal impairment (30-35 mL/min).



Additionally, predicted C_{48h} plasma migalastat concentrations do not appear to be correlated with decline in renal function, or with increase in the Fabry biomarker, plasma lyso-Gb3, in Fabry patients enrolled in Study AT1001-011 (see below). This indicates that elevated plasma migalastat C48h concentration does not lead to loss of long-term efficacy.

Scatter plots are presented below from Fabry patients who participated in Phase III study, AT1001-011. Figure 14 presents plasma migalastat C_{48h} concentrations versus annualised rate of change in eGFR from baseline after 24 months by renal function category and overall, respectively.

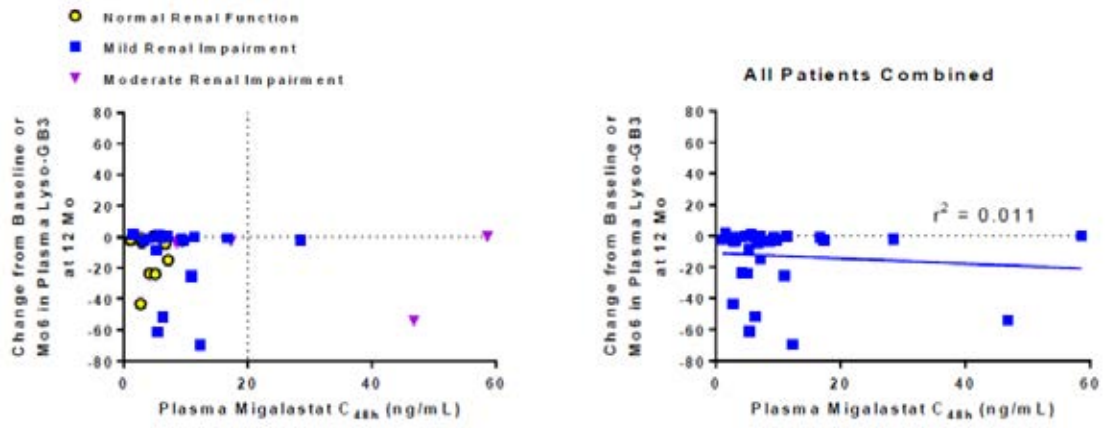
Figure 14: Plasma migalastat C_{48h} concentrations versus annualised rate of change in eGFR at 24 months by renal function group and overall.



Of 32 patients with amenable mutations from Study AT1001-011, 11 patients had normal eGFR (≥ 90 mL/min/1.73 m²), 16 patients had mild renal impairment (< 90 to ≥ 60 mL/min/1.73 m²), and 5 had moderate renal impairment (< 60 to ≥ 30 mL/min/1.73 m²) at 12 months post baseline. Renal function was estimated using the MDRD equation. The r^2 value of 0.007 along with visual inspection of the scatter plots shows there is no correlation between increased C_{48h} concentrations and long-term changes in renal function.

Figure 15 presents plasma migalastat C_{48h} concentrations versus change from baseline or 6 months in plasma lyso-Gb3 after 12 months by renal function category and overall, respectively.

Figure 15: Plasma migalastat C_{48h} concentrations versus change from baseline or 6 months in plasma lyso GB3 at 12 months by renal function group and overall.



In Figure 15 it should be noted that some patients from AT1001-011 received placebo from baseline to Month 6, then migalastat HCl 150 mg QOD from Month 6 to Month 12. Some patients received migalastat HCl 150 mg QOD from baseline to Month 12. Data entered on these scatter plot includes the change from baseline to Month 12 as it applies to those patients who received active treatment for the full 12-month duration, and the change from Month 6 to Month 12 as it applies to those patients who received active treatment for only that duration.
The r^2 value of 0.011 along with visual inspection of the scatter plots shows there is no correlation between increased C_{48h} concentrations and changes in plasma lyso-Gb3.

With regard to adverse events in patients with normal renal function, mild renal impairment, and moderate renal impairment, there were no apparent differences in the safety profile between normal, mild and moderate renal impairment groups, based on their proportion of TEAEs or SAEs.

Based on these results demonstrating lack of significant accumulation and no evidence of long-term safety concerns in patients with mild and moderate renal impairment, labelling was updated with available renal impairment data for subjects with severe renal impairment only.

Conclusions:

- Subjects with mild renal impairment had C48h plasma migalastat concentrations near the lower limit of quantification (LLOQ, 5.88 ng/mL), therefore significant accumulation following multiple dosing would not be anticipated.
- Multiple dose simulations in subjects at the lowest level of moderate renal impairment (30 – 35 mL/min) did not show additional accumulation beyond that observed from single dose administration.
- Increased C48h plasma migalastat concentrations were not associated with loss of long-term efficacy measured by annualised changes in renal function and plasma lyso-Gb3 levels.
- The adverse event profile was similar across categories of renal impairment.

Evaluator's comment:

The sponsor's response is acceptable.

- ***Question 5: In the PPK study [MGM116016], the mean predicted t1/2 value in healthy volunteers (n = 51) from Study AT1001-010 was 3.65 hours (range: 2.98, 4.55 hours) and 20.6 hours (range: 19.0, 23.5 hours) in subjects (n = 62) with Fabry disease from Study AT1001-010. However, predicted exposure data were generally similar for the two studies. The relevant data are from the PPK study report MGM116016. Please***

comment on the reasons for the difference in predicted t1/2 between the two studies. In particular, please comment on the long t1/2 estimated for Study AT1001-011.

Sponsor's response:

The Applicant confirms that the PK data from the *AT1001-011 study* included all Fabry patients regardless of renal function. Migalastat is primarily eliminated via the kidney (75% of the dose). Some Fabry patients had mild or moderate renal impairment which resulted in higher trough (C_{48h}) concentrations. The trough concentrations from these patients impacted the model's overall (mean) estimation of the elimination rate constant, and therefore a more prolonged half-life (20.6 h) than that seen in healthy volunteers (3.65 h).

In *Study AT1001-010*, all subjects were healthy volunteers with normal renal function. Half-life estimations for these subjects were about 4 hours, and consistent with half-life determinations from the other Phase I studies, where concentrations declined to below the lower limit of quantification by 48 hours post-dose.

Evaluator's comment:

The sponsor's response is satisfactory.

12.3. Pharmacodynamics

- ***Question 1: The sponsor considered that the results for kidney GL-3 concentration in tissue homogenates presented study FAB-CL-204 were non-informative. The sponsor stated that accumulation of GL-3 in kidney tissue might be regionally variable, particularly in females because of their heterozygotic expression of both mutant and wild type forms of α-Gal A. Please clarify why accumulation of GL-3 in kidney tissue might be regionally variable?***

Sponsor's response:

The Applicant confirms that due to Fabry being an X-linked dominant disease with little evidence of cross-correction between affected cells, female patients typically display a mosaicism of diseased (with mutant α-Gal A and accumulated GL-3) and healthy (with wild-type A-Gal A and no GL-3) kidney tissue due to X chromosome inactivation. Patchiness in this pattern of mosaicism within kidney biopsies in female patients has been reported in the literature (Mauer M, Glynn E, Svarstad E, Tøndel C, Gubler M-C, et al. (2014) Mosaicism of Podocyte Involvement Is Related to Podocyte Injury in Females with Fabry Disease. PLoS ONE 9(11): e112188. doi:10.1371/journal.pone.0112188)).

Evaluator's comment:

The sponsor did not comment on the reasons why accumulation of GL-3 in kidney tissue might be regionally variable. However, this matter is not critical to approval of migalastat for the proposed indication and will not be pursued.

12.4. Efficacy

- ***Question 1: In Study AT1001-011, the pre-specified Stage 1 analysis was based on subjects identified as responsive by the Clinical Trial HEK assay. Subsequent re-analysis of the 67 subjects resulted in 17 subjects (25%) being deemed non-amenable by the validated GLP HEK Assay. Why did the Clinical Trial HEK assay identify such a large proportion of patients subsequently deemed non-amenable as responsive?***

Sponsor's response:

From its inception, based on the mechanism of action, migalastat has been intended as a treatment only for patients with amenable GLA mutations. The intent was to enroll only patients

with amenable mutations in the Phase III studies; however, the initial clinical trial assay available at the time was not as precise and accurate as the ultimate GLP-validated HEK assay. One of the key factors that improved with the validated HEK assay was the ability to more accurately quantify wild-type α-Gal A activity. This was achieved by the addition of a lysate dilution step which removed a ceiling effect that had resulted in an over-estimation of the % wild-type α-Gal A activity increases being observed with the initial clinical trial HEK assay.

Several GLA mutations that had a 3-6% of wild-type increase with the initial clinical trial assay (meeting the ≥ 3% threshold criteria for amenability) were determined to actually have a <3% of wild type increase (i.e. non-amenable) with the GLP validated HEK assay. One of these non-amenable mutations, i.e. R342Q, was present in 8 patients enrolled in *Study AT1001-011*, thus helping to explain the relatively large number of non-amenable patients randomised in the study.

As noted in the mutation amenability section, 17 patients randomised into *Study AT1001-011* had a non-amenable mutation based on the GLP validated HEK assay.

Evaluator's comment:

The sponsor's response is satisfactory.

- ***Question 2: Please provide the results of the pre-specified primary efficacy endpoint in Stage 1 of AT1001-011 using the amenable subjects (ITT population) based on the GLP HEK assay (i.e., the responder analysis based on the number of subjects with ≥ 50% reduction from baseline to month 6 in the average number of IC GL-3 inclusions).***

Sponsor's response:

The Applicant confirms that in the '*Ad-hoc Stage 1, Stage 2, and Open-label Extension (OLE) Statistical Analysis Plan*' that was finalised after un-blinding Stage 1 data but prior to un-blinding stage 2/OLE data, where analyses in amenable patients was specified, the responder analysis was removed due to its statistical limitations. The responder analysis was impacted by the low baseline Kidney IC GL-3 values (<0.3) in a majority (61%) of patients, especially females. Based on the fact that a large number of patients had relatively low baseline Kidney IC GL-3 levels, the value of the responder analysis was limited. Hence the *ad hoc* Stage 1 analyses (specified in the SAP) focused on assessment of the mean change from baseline, which is the more biologically meaningful and scientifically appropriate endpoint determination, when a substantial number of patients have low baseline Kidney IC GL-3 levels, near the lower limit of measurement.

Evaluator's comment:

The sponsor's response is satisfactory.

- ***Question 3: In Study AT1001-011, no primary efficacy endpoint was defined for the post-hoc analysis of Stage 1. Please explain the reasoning behind this decision.***

Sponsor's response:

The Applicant confirms that it was not considered appropriate to define a *post-hoc* Stage 1 primary endpoint in the '*Ad-hoc Stage 1, Stage 2, and Open-label Extension Statistical Analysis Plan*' that was finalised after un-blinding Stage 1 data but prior to un-blinding stage 2/OLE data. The key *ad-hoc* Stage 1 Kidney IC GL-3 assessment specified in the SAP was the mean change from baseline for subjects with amenable mutations. The key Stage 2 Kidney IC GL-3 efficacy assessments specified in this SAP were the durability of response in Stage 2 as measured by mean change, for subjects with amenable mutations who received migalastat in Stage 1 and the mean change in Stage 2 for subjects with amenable mutations who received placebo in Stage 1.

Evaluator's comment:

The sponsor's response is satisfactory.

- ***Question 4: In Study AT1001-011, p-values were provided for the comparisons between migalastat and placebo for the post-hoc analysis. However, no comment was provided in the CSR that the significant p-values were nominal rather than confirmatory due to no statistical adjustments being made for multiplicity. Please comment on this matter.***

Sponsor's response:

The Applicant confirms that the FACETS Stage 1 (month 0-6) SAP specified that no adjustments for multiplicity would be performed since the primary objective focused on a single measure (kidney IC GL-3) represented at a single time point (change from baseline to month 6), with secondary objectives evaluated as supportive measures. The Stage 2/OLE (month 6-24) SAP, which was finalised while Stage 2 data remained blinded/firewalled, pre-specified analyses in patients with amenable mutations. Of note, the Stage 2/OLE results are more clinically relevant than the Stage 1 results for GFR and LVMi, as these parameters require longer periods of time than 6 months to accurately assess change from baseline.

Overall, the presentation of nominal p-values for secondary endpoints is justified as it provides a more comprehensive understanding of the drug effect in this rare disease. Furthermore, this would align the label presented in Australia with the EU SmPC and the FACETS publication (Germain *et al*., 2016 *N Engl J Med*; 375:545-55; Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat;), and give Australian prescribers a full understanding of the effect of the drug across multiple endpoints, in line with the claimed indication, which is only in the population of Fabry disease patients with an amenable mutation.

Evaluator's comment:

The sponsor's response is satisfactory.

- ***Question 5: In Study AT1001-012, lot numbers for the ERT products used in individual subjects were provided. Does the sponsor have any information on whether the lots represented the same formulations of the ERT products and whether the lots represented formulations approved in Australia?***

Sponsor's response:

The Applicant confirms that ERT was sourced as a commercially available product in Australia and not provided as an investigational product in *Study AT1001-012*. The eCRFs for *Study AT1001-012* capture information for enzyme replacement therapy (ERT) infusion for subjects randomised to ERT, including the ERT lot number. Amicus, as the sponsor of *Study AT1001-012* does not have information on whether the specific lots represented formulations approved in Australia. This information would be provided by the companies providing the ERT.

Evaluator's comment:

The sponsor's response is satisfactory.

- ***Question 6: Please provide separate tabulated summaries of the amenable GLA mutations based on the GLP HEK assay identified by genotype for all amenable subjects from studies AT1001-011 and AT1001-012. For each genotype for each study please provide the number of subjects with the genotype. Please confirm that the tables you provide include the results for all amenable subjects from both studies. Tables were presented by the sponsor in correspondence with the EMA during the course of the CHMP evaluation, but it was not entirely clear which tables contained the correct information. For example, it appears that Tables 4 and 5 in the Rapporteurs Day 195 Joint CHMP and PRAC Response Assessment Report Clinical – Assessment of the responses to the CHMP/PRAC List of Questions include different patient numbers for some genotypes provided by the sponsor from those calculated by the CHMP from data spread-sheets provided by the sponsor.***

Sponsor's response:

The sponsor provided tabulated summaries for the subjects with amenable mutations in studies AT1001-011 (50 subjects) and AT1001-012 (57 subjects). The tables presented the patient-level listing of baseline and response criteria for these studies. For each genotype for each study, the sponsor provided the number of subjects with the genotype. The sponsor confirmed that the provided tables included the results for all amenable subjects from both studies.

Evaluator's comment:

The sponsor's response is satisfactory. The number of subjects with amenable genotypes in Study AT1001-012 and Study AT1001-011 are summarised below. The table is derived from the data provided by the sponsor. The sponsor provided the amenable migalastat mutations identified by protein sequence change.

Table 91: Number of subjects with amenable migalastat genotypes identified by protein sequence change in Study AT1001-012 and Study AT1001-011

Study AT1001-012		Study AT1001-011	
Number of subjects (n)	**Amenable Genotypes**	**Number of subjects (n)**	**Amenable Genotypes**
11	-	11	N215S
7	G85D	7	-
6	A156T	6	-
4	I253T	4	D322E; Y216C
3	L32P; A143T; P259R; R301Q	3	A156T; P250T; R301P
2	G258R; M284T; P293T; D322E; G325R	2	L36W; G183D.
1	G35R; D55V/Q57L; M96I; A97V; R112H; R112G; L243F; D244N; G260A; D264Y; I270T; G271S; F295C; L300P; I317T; R356W; G373S	1	D33G; D55V/Q57L; G85D; R112H; G144V; C174R; M187I; I253S; G260A; Q279E; M284T; M296I; R301Q; Q312R; G328A; R356Q; R363H; L403S; P409T.

- ***Question 7: In order for a patient to be treated with migalastat it will be necessary to establish that they have an amenable GLA mutation. Therefore, the first step in the process will be to determine their genotype. How does the sponsor see this working-out in current Australian clinical practice for patients with Fabry disease (established or de novo) who have not been genotyped? Is genotyping of new patients with Fabry disease part of the routine work-up in Australian clinical practice? In the report of the pre-submission meeting, the sponsor indicated that genotype testing for diagnosing Fabry disease for the clinical trials was conducted in Australia through the NATA-accredited laboratory at the Women's and Children Hospital in Adelaide, South Australia. If migalastat is approved in Australia, does the sponsor envisage that genotyping will be undertaken at this laboratory or another centralised laboratory or will individual units make their own arrangements with local laboratories? How does the sponsor see funding of genotyping proceeding (e.g., sponsor supported, individual patient payment, Medicare Benefits Schedule item number)?***

Sponsor's response:

The Applicant confirms that at this time the majority of Fabry patients diagnosed in Australia already know their genotype and this is documented in the patients' records. In most cases, the patients then proceed to mutation studies for the index case and family members, which is considered standard of care. We understand that Genotyping is not a MBS (Medicare Benefits Schedule Book - Department of Health) listed test. We intend to follow the current practice, and envisage all tests being run through the National Referral Laboratory at the Women and Children's Hospital in Adelaide. The Head of Department [at that laboratory] ….. currently runs a similar service for Fabry patients. If the patient has not had α-GL A genotype determination and it is not covered under the standard of care, then Amicus would cover the cost of this testing.

Evaluator's comment:

The sponsor's response is satisfactory.

13. Second round benefit-risk assessment

13.1. 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.

13.2. 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.

13.3. Second round assessment of benefit-risk balance

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

14. 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.

15. References

1. Wu X, Katz E, et al. A pharmacogenetic approach to identify mutant forms of α-galactosidase A that respond to a pharmacological chaperone for Fabry disease. Hum Mutat 2011;32:965-77,

2. Desnick, R. J. Enzyme replacement and enhancement therapies for lysosomal diseases. J Inherit Metab Dis 2004;27(3):385-410.

3. Schiffmann R, Warnock DG, et al. Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant 2009;24(7):2102-11.

4. Schwarting A, Dehout F, et al. Enzyme replacement therapy and renal function in 201 patients with Fabry disease. Clin Nephrol 2006; 66(2):77-84.

5. Wanner C, Oliveira JP, et al. Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry registry. Clin J Am Soc Nephrol 2015; 5(12):2220-28.

6. Germain DP, Hughes DA, et al. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. New Engl J Med 2016;375:545-55.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au