1 April 2016
EMA/272226/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Galafold

International non-proprietary name: migalastat

Procedure No. EMEA/H/C/004059/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

Abbreviation	Definition
α-Gal A	alpha-galactosidase A
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
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BID	bis in die (twice daily)
BPI	Brief Pain Inventory
CAR	Constitutive androstane receptor
CKD	chronic kidney disease
CI	confidence interval
CLcr	creatinine clearance
C_{max}	maximum observed concentration
C_{min}	minimal observed concentration
CYP450	cytochrome P450
ECG	electrocardiogram
ECHO	echocardiography
eGFR	estimated glomerular filtration rate
$eGFR_{CKD-EPI}$	estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation
$eGFR_{MDRD}$	estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation

Abbreviation	Definition
EMA	European Medicines Agency
ER	Endoplasmic reticulum
ERT	enzyme replacement therapy
FDA	Food and Drug Administration
GAA	Acid α-glucosidase
GCase	Acid β-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
LLOQ	lower limit of quantitation
LV	left ventricular
LVH	left ventricular hypertrophy
LVMi	left ventricular mass index
lyso-Gb_3	globotriaosylsphingosine

Abbreviation	Definition
MEC	Molar Extinction Coefficient
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 AT1001-011 mITT population
NAGA	α-N-Acetylgalactosaminidase
NOAEL	No-Observed-Adverse-Effect Level
OECD	Organisation for Economic Co-operation and Development
OLE	open-label extension
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
P-gp	P-glycoprotein
PK	pharmacokinetic
PXR	Pregnane X receptor
QC	quality control
QD	quaque die (once daily)
QOD	quaque otra die (once every other day)
RBC	red blood cell
rhα-Gal A	Recombinant human α-Gal A
RI	renin inhibitor
SAE	serious adverse event
SD	standard deviation
SEM	standard error of the mean
SF-36v2	Short Form Health Survey with 36 questions, version 2
SGLT1	sodium glucose cotransporter 1
$t_{½}$	terminal phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of occurrence of Cmax
UGT	uridine 5'-diphospho-glucuronosyltransferase
WT	wild type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amicus Therapeutics UK Ltd submitted on 2 June 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Galafold, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 July 2014.

Galafold, was designated as an orphan medicinal product EU/3/06/368 on 22 May 2006. Galafold was designated as an orphan medicinal product in the following indication: Treatment of Fabry disease.

The applicant applied for the following indication: for long-term treatment of adult (18 to 74 years) and adolescent (16 to 17 years) patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see Section 5.1).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Galafold as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that migalastat hydrochloride was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0174/2012 on 27 July 2012

At the time of submission of the application, the PIP P/0174/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no other authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance migalastat hydrochloride contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 10 December 2008, 29 May 2009, 8 March 2012 and 22 May 2014. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Ondřej Slanař

- The application was received by the EMA on 2 June 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 21 May 2015.
- The procedure started on 25 June 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- PRAC assessment overview, adopted by PRAC on 8 October 2015.
- During the meeting on 22 October 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 October 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 December 2015.

- During the CHMP meeting on 17 December 2015, the CHMP concluded that it was no longer appropriate to pursue accelerated assessment as clinical major objections still remained and agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 10 February 2016.
- During the CHMP meeting on 25 February 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP and the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 March 2016.
- During the meeting on 1 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Galafold.

2. Scientific discussion

2.1. Introduction

Fabry disease is a rare, progressive X-linked lysosomal storage disorder, affecting both males and females, with an estimated prevalence of 1:117,000 up to 1:40,000 (Desnick and Schindler, 2001; Meikle *et al*., 1999; Eurordis, 2005). Mutations in the GLA gene result in a deficiency of the lysosomal enzyme, α-galactosidase A (α-Gal A), which is required for glycosphingolipid metabolism (Brady, 1967). Beginning early in life, the reduction in α-Gal A activity results in an accumulation of glycosphingolipids, including globotriaosylceramide (GL-3) and plasma globotriaosylsphingosine (lyso-Gb3), and leads to the symptoms and life-limiting sequelae of Fabry disease, including pain, gastrointestinal symptoms, renal failure, cardiomyopathy, cerebrovascular events, and early mortality (Germain, 2010). Fabry disease encompasses a spectrum of disease severity and age at onset, and can be divided into two main phenotypes, "classic" and "late-onset" (Desnick *et al*., 2001). Classical Fabry disease can affect all 3 major organs (heart, kidney, central nervous system) and in end-stage disease trigger life-threatening events. In contrast, variant α-Gal A mutations may result in less aggressive clinical phenotypes, which are, leading to single organ involvement and late onset disease (Niemann *et al*., 2014) or so called "atypical" Fabry patients.

More than 841 Fabry disease-causing GLA mutations have been identified (data on file by applicant; SmPC section 5.1). Approximately 60% are missense mutations, resulting in single amino acid substitutions in α Gal A (Germain 2010; Gal *et al*., 2006). The majority of missense mutations are associated with the classic phenotype (Filoni *et al*., 2010; Topaloglu *et al*., 1999; Shabbeer *et al*., 2002; Shabbeer *et al*., 2006; Ishii *et al*., 2007). This application considers patients with amenable mutations, i.e. patients with migalastat-responsive GLA mutations. Whether a patient is amenable to migalastat is unrelated to the disease burden they might have/experience. Recent literature indicates that the genotype cannot be translated to a phenotype. For example mutation A143T causes FD in only a limited number of carriers.

For the treatment of Fabry disease the standard treatment is Enzyme Replacement Therapy (ERT), irrespective of the severity of the disease. It consists of intravenous (IV) infusion of manufactured enzyme every 14 days. This is currently the only authorised treatment available to Fabry patients. Two products are available in the European Union, agalsidase beta (Fabrazyme) and agalsidase alfa (Replagal). The indications for these ERT's are: "*<ERT> is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency)*." Based on literature it is known that patients with late onset Fabry disease (also known as atypical or non-classic Fabry patients) show deterioration, requiring treatment to prevent further disease progression. This is the most important clinical rationale to treat late onset patients as advised in the current guidelines.

Migalastat, a low molecular weight iminosugar, is an analogue of the terminal galactose of GL-3. Nonclinical *in vitro* and *in vivo* studies have demonstrated 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 (Ishii *et al.*, 2007), the genotypes of which are referred to as amenable mutations. Migalastat binding stabilizes these mutant forms of α-Gal A in the endoplasmic reticulum, facilitating their proper trafficking to lysosomes where dissociation of migalastat allows α-Gal A to reduce the level of GL-3 and lyso-Gb3 (Yam *et al.*, 2005, Yam *et al.*, 2006; Benjamin *et al.*, 2009).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 123 mg of migalastat (as hydrochloride) as active substance.

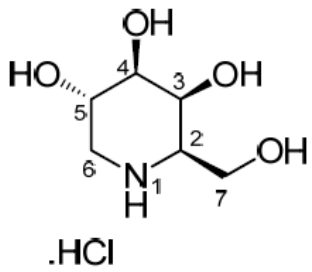
Other ingredients are pregelatinised starch (maize), magnesium stearate (for capsule contents); gelatin, titanium dioxide (E171) and indigotine (E132) (for capsule shell); shellac, black iron oxide and potassium hydroxide (for printing ink).

The product is available in PVC / PCTFE / PVC/Al blister in a pack size of 14 capsules as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information
The active substance is migalastat hydrochloride, a novel active substance not described in any pharmacopoeia. The chemical name of migalastat hydrochloride is (+)- (2*R*,3*S*,4*R*,5*S*)-2-(hydroxymethyl)piperidine-3,4,5-triol, hydrochloride corresponding to the molecular formula $C_6H_{13}NO_4 \cdot HCl$. Migalastat hydrochloride has a relative molecular mass of 199.63 g/mol (hydrochloride salt) and the following structure:

Figure 1: Structure of migalastat hydrochloride



The structure of migalastat hydrochloride is supported by the route of synthesis and confirmed by XRD, ^{1}H-NMR, ^{13}C-NMR, MS, IR and elemental analysis.

The active substance is a white to almost white crystalline solid, which is freely soluble in aqueous media between pH 1.2 and 7.5. These properties are adequate for an oral solid dosage form.

Migalastat hydrochloride contains 4 chiral centres and is manufactured as the 2*R*,3*S*,4*R*,5*S* isomer. It has been demonstrated, as part of the active substance development studies, that no epimers are formed during the manufacturing process and based on these findings it was also concluded that no other diastereoisomers will be formed.

Polymorphism has not been observed for migalastat hydrochloride. The applicant has submitted as part of the MAA full details of chemistry, manufacturing process, quality controls during manufacture and process validation.

Migalastat hydrochloride is considered a new active substance from a quality perspective. The applicant compared its structure with active substances within authorised products in the EU and demonstrated

that it is not a salt, ester, ether, isomer, mixtures of isomers, complex or derivative (e.g. pro-drug or metabolite) of any of them.

Manufacture, characterisation and process controls

The source of the starting material to produce migalastat is controlled by a specification. The manufacturing process development has been performed using some Quality by Design (QbD) principles but no design space has been claimed. Target set-points, normal operating ranges or proven acceptable ranges (PARs) for all the manufacturing process critical process parameters (CPPs) as well as non-CPPs have been described in the dossier. The proposed operating ranges are consistent with the ranges studied and confirmed during development.

Adequate discussion on the carry-over and control of potential impurities in the final active substance has been provided. Potential impurities are sufficiently purged in the process, controlled in the final active substance or a suitable intermediate. The product-related genotoxic impurity C-025487 is controlled. An adequate discussion on genotoxic impurities has also been provided. Screening studies for genotoxic impurities have been performed in accordance with ICH M7 on genotoxic impurities combining an expert rule based methodology with a statistical-based methodology. The absence of control limits for the impurities that were found to be genotoxic has been adequately justified based on batch analysis data and purging studies and is acceptable in view of the ICH M7 option 4 for the control of process related impurities.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. Adequate in-process controls are applied during the synthesis.

Reprocessing is described for the intermediate grade migalastat hydrochloride if it does not comply with the specification. It may be crystallised by performing a recrystallization process. The approach proposed by the Applicant is endorsed.

Several changes have been introduced during the development of the manufacturing process. It was demonstrated by comparative batch analysis data that these changes did not impact the quality of the active substance. The quality of the active substance used in the various phases of development is considered to be comparable with that produced by the proposed commercial process.

The active substance is stored in low-density polyethylene (LDPE) bags inside an opaque polyethylene (PE) container with a natural rubber seal ring, which comply with Regulation (EU) No 10/2011 and with Ph.Eur.3.1.3 (polyolefines).

Specification

The set of active substance specifications have been established in-house by the applicant. The analytical procedures have been described in sufficient detail or reference was made to the relevant Ph.Eur. method. The non-compendial analytical methods have been adequately validated in accordance with the ICH NfG on Validation of Analytical Procedures: Text and Methodology. The stability indicating nature of the HPLC method for assay and related substances has been confirmed by means of forced degradation studies. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analytical data demonstrating compliance with the active substance specification have been provided for three production scale batches. These data confirm consistency of the product quality and manufacturing process.

Stability

Stability data on the active substance have been provided for six production scale batches stored at 30°C/65% RH (18-36 months) and 40°C/75% RH (6 months). The batches were stored in a LDPE bag inside a high-density polyethylene (HDPE) container. The container and contact material are fully representative of the container proposed for routine bulk storage and transport of the active substance.

The following parameters were tested: appearance, assay, related substances, water content, identity and microbial quality.

The analytical methods used were the same as for release and are stability indicating. The stability results showed no trends or changes in any of the tested parameters at both storage conditions.

In addition, the active substance was also demonstrated to remain stable when stored under stress conditions, i.e. in a refrigerator at 5°C (12 months), at 40°C/75% RH fully exposed (3 months), at 50°C/ambient RH (3 months), under freeze/thaw cycling conditions (two repeated cycles of 7 days at -20°C followed by 7 days at 30°C for 1 month) and exposed to ICH Q1B light conditions.

The active substance was shown not to be sensitive to light or humidity exposure, so no precautionary light or humidity protection statements are considered necessary.

Based on the data presented, the proposed retest period of 36 months without any special storage requirements is justified.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Product description

The finished product is formulated as an immediate release, hard capsule containing 123 mg migalastat free base (corresponding to 150 mg of migalastat hydrochloride). The capsules are size 2 hard gelatin capsules with an opaque blue cap and opaque white body printed with "A1001" in black. The product is packed in PVC-PCTFE-PVC/Al blisters. The blisters are contained in a paperboard secondary pack.

Pharmaceutical development

The pharmaceutical development of the finished product contains principles of QbD. The quality target product profile (QTPP) was defined as an immediate release capsule dosage form, which can be swallowed easily, that meets compendial and other relevant quality standards at manufacture and over the proposed shelf-life, and is packaged in a pack that is convenient for the patient and which provides physical and moisture protection. The product design and formulation selection was based on the QTPP.

Based on the QTPP finished product CQAs and CQAs of input and in-process materials were defined.

The relationship between active substance attributes and finished product CQAs was evaluated through Failure Mode and Effects Analysis (FMEA) risk assessment. These attributes are either adequately controlled as part of the drug substance specification (identity, assay and related substances) or it has been sufficiently demonstrated or discussed that the attribute is not critical for the finished product CQAs (PSD, moisture, solid state form).

The following finished product CQAs have been identified and their control strategy described in the dossier:

- Description is controlled by the requirements for capsule size, colour and imprint which are controlled on the empty capsules at release, as IPC during encapsulation and in the finished product.
- Identity of the active substance is controlled as part of the active substance specification as well as the finished product specification.
- Content and uniformity of dosage units are controlled by the acceptance criterion for content in the active substance specification, the screening of migalastat hydrochloride during manufacture, by the IPC tests for mean capsule weight and individual capsule weight during encapsulation and by testing assay and uniformity of dosage units in the finished product specification.
- Drug related impurities are controlled by the active substance specification as well as the finished product specification.
- Dissolution is controlled by the acceptance criterion for disintegration time for the empty capsule shells at release and by the dissolution test in the finished product specification.
- Microbiological quality is controlled by the microbial acceptance criteria for the empty capsule shell and by end product testing.

For the pre-printed hard gelatin capsules the identified input CQAs are controlled through the capsule shell specification: description, water content, disintegration time and microbiological quality.

The list of all excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. All excipients used in the formulation are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. The pre-printed hard gelatin capsules are controlled by an in-house specification.

The compatibility of the excipients with the active substance was confirmed by the results of the formal stability studies.

Subsequently, 25 mg and 250 mg strength capsules (as the hydrochloride salt) were developed for clinical studies in order to provide dosing flexibility (across a range of doses) and convenience of dosing with a simple dosage form.

A 150 mg dosage strength (as hydrochloride salt), equivalent to 123 mg free base, was developed for the Phase III studies and commercialization. This formulation approach was similar to the 25 mg and 250 mg strengths, but a size 2 capsule was selected in order to accommodate the fill weight and the blue colouring agent in the cap of the capsule shell was varied. It was demonstrated that dissolution of the 25 mg and 250 mg capsules used in the phase II clinical studies was similar to that of the Phase III clinical batches.

Formulations used in the open label phase of the Phase III pivotal clinical studies were identical in composition to the primary stability batches and the intended commercial product and only vary from commercial product in terms of print details (the same ink is used). It was demonstrated that these differences did not impact the dissolution of the finished product, and the batches used throughout the clinical development are considered representative of the final commercial product. Routine dissolution testing is performed using the Ph.Eur. paddle apparatus at 50 rpm with 900 ml 0.1N HCl at 37°C as dissolution medium. The development of the dissolution method for quality control of the finished

product has been adequately described. It is recommended that migalastat Capsules 123 mg be taken under fasted conditions. The proposed dissolution medium is considered representative of the acidity of the stomach under fasted conditions.

Although the dissolution method was shown to be discriminatory with respect to cross-linking of gelatin in the capsule shell, once the capsule shell has ruptured and the contents have disintegrated, the method is not discriminating with respect to the dissolution of migalastat because of its high solubility and rapid dissolution across the physiological pH range.

This lack of discriminating power was confirmed by a media-screening exercise using two batches of finished product that differed in active substance manufacturer and capsule shell. The results demonstrated rapid dissolution (about 100% dissolved in 15 minutes) for both tested batches in all dissolution media. No pH sensitivity or difference between the two formulations was detected. Although not discriminating, the applicant concluded that the dissolution method is acceptable as the finished product is designed to produce immediate release, bioavailability is not significantly affected by dissolution and changes in formulation and manufacturing variables do not affect dissolution in media over the range pH 1.2 – 6.8, which is in accordance with ICH Q6A, decision tree #7. This is considered acceptable.

The manufacturing process development has been adequately performed and described according to the ICH Q8-Q10 QbD approach. An early risk assessment was performed across the unit operations to direct experimental activities to support development of a commercial control strategy. The assessment was based on prior knowledge, manufacturing experience with this product and experimental results generated prior to the assessment. Identified failure modes which highlighted attributes and process parameters that could impact product quality were assessed by a FMEA risk analysis tool. The risks were prioritised and used to inform development activities to understand and control the risks to acceptable levels. The potential CQAs and CPPs were subsequently taken into univariate and/or multivariate studies to understand the link between them and the finished product CQAs and establish ranges for the CPPs as elements of the control strategy. Based on the development studies and risk assessments no CPPs have been identified for the manufacturing process, except for the screen size for the screening of the active substance before blending. The output from the experimental work programme and risk assessment was then used to update and enhance the commercial control strategy.

The finished product is packed in PVC blisters sealed with aluminium foil with heat-seal lacquer. The packaging material is usual for oral solid dosage forms and complies with Ph.Eur. and EC requirements. The packaging material meets de USP <671> Class A criteria for moisture permeation. Seal integrity was confirmed by showing no permeation of methylene blue in water under vacuum. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The finished product is packed in blisters that are encased in a paperboard secondary pack (blister sleeve). Removal of the capsule entails pushing through the paperboard and aluminium blister foil material. The chosen packaging represents the best combination of child resistance and user friendly removal of capsules. The integrity of the capsules following removal from the blisters will be further monitored through the company's quality system for any product complaints post authorization and measures for improvement will be considered.

Manufacture of the product and process controls

The main manufacturing process steps are the screening of migalastat hydrochloride and pregelatinised starch, (dry) blending (pre-lubrication and lubrication), encapsulation and packaging.

This is a straightforward standard process. The manufacturing process has been described in sufficient detail. The description of the manufacturing process distinguishes between CPPs and non-CPPs. No design space is claimed (nor has been developed) for the finished product manufacturing process.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for seven production scale batches, demonstrating that the process and operating parameters are suitable to yield finished product of consistent quality. The homogeneity of the final blend before encapsulation is not considered a critical aspect. This was further confirmed by the final batch analysis results of the final product.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance (visual), identification (IR, HPLC), assay (HPLC), related substances (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.) and microbial quality (Ph. Eur.).

Related substances are not tested at release of the finished product but will comply with the specifications if tested. The specification for microbial quality was set in accordance with the Ph.Eur.5.1.4 requirements for non-aqueous preparations for oral use. This is acceptable and skip-testing for this parameter is considered justified based on the batch analysis data and stability data that consistently show compliance with the Ph.Eur.5.1.4 requirements.

The proposed specification of the finished product is considered acceptable.

The analytical methods have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results are provided for seven production scale batches and confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specifications.

The finished product is released on the market based on the above release specifications through traditional final product release testing.

Satisfactory information regarding the reference standard used for assay testing has been presented.

Stability of the finished product

Stability data on the finished product have been provided on three production scale batches stored at 25°C/60% RH (36 months), 30°C/75% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging (i.e. PVC-PCTFE-PVC/Al-blisters).

Samples were tested for description, assay, related substances, dissolution, microbial quality, water content and equilibrium relative humidity (for information). The analytical procedures used are stability indicating.

No changes or trends were seen in any of the relevant stability parameters under all three storage conditions. Results of a photo stability study on one batch of finished product in accordance with ICH Q1B showed that the finished product was not sensitive to light exposure.

In section 6.4 of the SmPC, it is further specified to store the product in the original package in order to protect it from moisture. This storage precaution has been requested due to the sensitivity of gelatin capsules for moisture (in order to ensure that product quality will not be impacted by moisture if kept outside the primary packaging).

Adventitious agents

Gelatin obtained from bovine sources is used in the hard capsules. Valid TSE Certificates of suitability issued by the EDQM have been provided.

The shellac used in the black ink, (pre-printed on the capsule shells) is derived from insects; however, insects are not implicated in BSE/TSE.

No other substances of animal origin are present in the product nor have any been used in the manufacturing of this product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The active substance migalastat has been demonstrated to be very stable as such and also when incorporated in the finished product. The development of the active substance was extensive. It showed a good understanding of the process, critical process parameters and the formation, fate and purge of impurities.

The absence of control limits for the impurities that were found to be genotoxic has also been confirmed based on batch analysis data and purging studies and is acceptable in view of the ICH M7 option 4 for the control of process related impurities.

Dissolution has been identified as a critical process parameter and is controlled by the acceptance criterion for disintegration time for the empty capsule shells at release and by the dissolution test in the finished product specification. Routine dissolution testing is performed using the Ph.Eur. method (paddle apparatus). The development of the dissolution method for quality control of the finished product has been adequately described.

The finished product is packed in blisters that are encased in a paperboard secondary pack (blister sleeve). Removal of the capsule entails pushing through the paperboard and aluminium blister foil material. Evaluation of this packaging in practice showed that pushing the capsules through the blister foil and paperboard was not easy and flexing of the capsules occurred in some cases. This issue was further addressed by the Applicant through a justification that the chosen packaging represents the best combination of child resistance and user friendly removal of capsules. It was further clarified that flexed capsules did not affect the integrity of the capsules. The issue will be further monitored through the company's quality system for any product complaints post authorization and measures for improvement will be considered.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant submitted a detailed non clinical package in support of their application as detailed below.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

In *in vitro* studies using the recombinant human forms of α-GAL A (agalsidase alpha and beta), it was shown that migalastat binds to rhα-GAL A with high affinity. It also stabilizes degradation of the enzymes at different pH's and temperatures.

In studies using cell lines from human volunteers and Fabry patients, it was shown that migalastat can reach intracellular α-GAL A and bind to both wild-type and mutant forms of the enzyme, since increased levels and activity of enzyme were measured. Not all mutant forms were however responsive to migalastat treatment (49 out of 75), and in a similar experiment 23 out of 29 mutants had a Ki in the range of wild-type α-GAL A (21 nM to 68nM range for mutant compared to 21 nM for wild-type).

The effect of increased enzyme activity was sustained for several days after removal of the drug from the test medium, with half-lives that varied depending on the specific mutation, ranging from 11 hours to >120 hours. To further investigate the effect of a wash-out period, Fabry fibroblasts with two specific mutations showed a decrease in GL-3 levels when treated for 7 days with a 3 day wash-out period. In contrast, no decrease in GL-3 level was seen after 10 days continuous treatment, indicating an inhibitory effect of migalastat on enzyme function when it is bound to α-GAL A.

In a study using normal human fibroblasts and thus wild-type α-GAL A, it was shown that the half-life of α-GAL A inhibition (measured as GL-3 turnover) by migalastat was in the order of 2-3 hours, indicating rapid removal of migalastat from the enzyme when treatment is stopped.

These *in vitro* studies indicate that migalastat can bind to a significant number of mutant forms of α-GAL A in the endoplasmic reticulum, it stabilizes the enzyme and allows for trafficking through the Golgi body to lysosomes, where it dissociates from α-GAL A and allows for the enzyme to be active and cleave GL-3 into downstream products.

To better quantify the responsiveness of the specific mutant forms of α-GAL A to migalastat, an *in vitro* assay was developed. To date (March 10th 2016), 850 GLA mutations have been categorised as either amenable (n=269) or non-amenable (n=581).

The data provided show that migalastat binds to human α-GAL A, both wild-type and some mutant forms. Sequence homology for α-galactosidase A between mice, rats, rabbits, dogs, monkeys, and humans is approximately 85%, 86%, 88%, 90%, and 99%, respectively. In addition the Applicant provided data for rat, rabbit, monkey, and human, the Ki values for α-galactosidase A are 7.7, 9.3, 11.4, and 11.2 nanomolar, respectively, similar to that for mouse (10.6 nanomolar). The comparable K_i values between species suggest functional and specific binding in the selected animals.

In vivo studies

A Fabry mouse model was used for *in vivo* pharmacodynamic studies. This mouse model expresses a human mutant α-GAL A transgene on a mouse *Gla* knockout background (hR301Q α-GAL A Tg/KO). This mouse model shows age-dependent accumulation of GL-3 in disease-relevant tissues. Several experiments were performed with this mouse model. After 4 weeks of continuous treatment, α-GAL A tissue levels were increased in skin, heart and kidney, dose-dependently up to 300 mg/kg/day. However, GL-3 reductions were optimal at 30 mg/kg/day). Different dosing regiments however, showed that dosing for 4 days, followed by 3 days wash-out, resulted in a greater reduction in tissue GL-3 than daily dosing at 300 mg/kg/day. These results are is in line with the *in vitro* data and mouse tissue data showing a sustained increased α-GAL A level for several days (half-life of 2-2.5 days) even after migalastat levels have dropped to near zero after a single day. Additionally further studies showed that long term treatment of up to 6 months with the 4 on/3 off regimen resulted in even greater GL-3 reductions in heart and skin, and that migalastat is active in both young and older mice (corresponding to prevention versus reversal of accumulation).

Secondary pharmacodynamic studies

Secondary pharmacodynamics of migalastat were evaluated in vitro. Several assays for enzyme selectivity have been performed by the applicant.

A standard assay of 83 receptors and enzymes showed no significant binding. Specific evaluations using other lysosomal enzymes and lysates from human blood to specifically look for galactose metabolism also showed no significant binding, except for the lysosomal enzyme α-N-Acetylgalactosaminidase (NAGA). Although the affinity of migalastat for this enzyme is 120-fold lower than for α-GAL A, the IC50 of 7 µM (1.4 µg/ml), it is in the range of the clinical Cmax of migalastat of 2 µg/ml. There is high homology between human and rat NAGA, and no effects that could be related to a possible inhibition of NAGA in the rat toxicology studies with more frequent dosing than the proposed clinical dosing regimen were observed.

Additionally, In vitro experiments with migalastat showed 95% inhibition of NAGA, but only at high concentrations which are not expected to be reached using the therapeutic dose. Furthermore, incubation of normal human fibroblasts with migalastat HCl modestly increased NAGA enzyme levels in intact cells, suggesting a lack of detrimental effects on the proteostasis network. Finally, Ki values for NAGA of 6.8 and 8.4 µM, were seen for human and rat NAGA, respectively. Considering that the sequence alignments of monkey, rat, and mouse NAGA indicate 98%, 90%, and 90% homology to the human ortholog, respectively, thishis would suggest that the toxicology species used are suitable to investigate inhibitory effects on NAGA by migalastat.

Due to migalastats molecular structure, the interaction with glucose/galactose transporters is of interest. Interaction with SGLT1, which is predominantly expressed in the gastro-intestinal tract, has been evaluated in this respect, which shows IC50 values of migalastat as a substrate for and inhibitor of SGLT1 which are in excess of the clinical Cmax. Furthermore, interaction with glucose absorption has been investigated in clinical studies, and showed only a marginal reduction in migalastat AUC and C_{max} in subjects having taken a high glucose drink as discussed in the clinical AR.

Data were presented about possible interactions with the SGLT2 transporter. This transporter is predominantly expressed in the kidney where it is involved in glucose reabsorption, and it is the target of several antidiabetic drugs. Affinity for SGLT2 could therefore lead to interactions with SGLT2 inhibitors with potential consequences when these two drugs are taken together. The Applicant has provided data to demonstrate that migalastat is neither a substrate for SGLT2 nor an inhibitor

Safety pharmacology programme

In safety pharmacology studies, migalastat had no effect on the hERG currents when tested up to 47.5 µM. an *in vivo* study in dogs showed also no effect on mean, diastolic, or systolic arterial blood pressure, heart rate, or ECGs, including the QT and corrected QT intervals, when tested up to 100 mg/kg/day. No toxicokinetics were performed, however when extrapolating from other dog studies conducted by the applicant, it is likely that both Cmax and AUC at the high migalastat dose tested in animals are well above the Cmax and AUC values observed in the clinical studies with the recommended dose of migalastat (around 50-fold for Cmax and 20-fold for AUC).

In rats, no effect on any central nervous system was observed at doses tested up to 100 mg/kg. It is recognised that the exposure achieved is lower in rats than dogs non clinical studies. However, extrapolation of toxicokinetics from other studies indicate that the exposure achieved at the high dose was acceptable being likely around 8-fold above the human values for Cmax and 2-fold for AUC.

In rats, no effects on respiratory parameters were seen after treatment with up to 100 mg/kg. In summary the safety pharmacology of migalastat has been sufficiently investigated.

Pharmacodynamic drug interactions

Several studies have been performed to investigate the interaction of migalastat with currently approved enzyme replacement therapies agalsidase alfa and agalsidase beta, both *in vitro* and *in vivo* in rats and the Fabry mouse model. These studies show that concurrent treatment with an ERT and migalastat has an additive effect. This is to be expected since migalastat does not only bind to endogenous mutant α-GAL A, but also to agalsidase, and therefore has a stabilizing effect on these enzymes allowing them to have a longer lasting effect. The applicant indicates that it is unlikely that patients will receive both treatments; however, preclinical studies indicate a potential substantial benefit.

2.3.3. Pharmacokinetics

Methods of analysis

Well-described and validated LC MS/MS methods were used in the toxicokinetic studies. However, some of the toxicokinetic studies included much higher concentrations than the maximum concentration for which the methods were validated.

Absorption

Results of *in vitro* cellular permeability studies in Caco-2 cells indicate that cellular permeability is low and P-gp is not involved in intestinal absorption/elimination. According to the applicant, absorption through paracellular pathways may be involved. This conclusion is not endorsed since it is based on a study with Caco-2 cell monolayers with compromised integrity (by EGTA treatment). Considering the characteristics of the migalastat molecule, it might possibly be a substrate for monosaccharide transporters, which could be responsible for its fast absorption. Besides SGLT1, this has not been investigated and Migalastat is a low affinity substrate for SGLT1.

Absorption was fast in all examined animal species. In mice, rats and rabbits plasma T_{max} was equal to or earlier than the earliest plasma sampling time points at 0.25 – 1 h post dose. In dogs and monkeys, T_{max} was about 1-2 h after oral administration. In a rat radiolabel mass balance study ,comparison of plasma C_{max} 1 h after a single oral dose of 50 mg ^{14}C-migalastat/kg to the same dose of non-labelled migalastat suggests that at t_{max} most of the circulating material consists of unmetabolised migalastat.

Plasma pharmacokinetics and toxicokinetics

Oral bioavailability was high (up to 100%) in mice and not investigated in other animal species. In a rat mass balance study absorption was at least about a third of the oral dose after a single oral dose of 50 mg ^{14}C-migalastat/kg based on urinary excretion .. No information regarding degree of absorption or bioavailability was available for the other laboratory species used in the toxicity studies.

After IV administration, male mice had a plasma elimination $t_{1/2}$ of < 1 h, clearance of 1.5-2.5 L/h/kg and Vss 0.4-0.8 L/kg. The short elimination half life was considered due to the relatively low distribution volume. IV plasma pharmacokinetics was not studied in the other species used for toxicity studies.

After oral administration, $t_{1/2}$ in mice (both sexes) was < 1 - 3.3 h and exposure of females appeared slightly higher compared to males. In repeated dose toxicity studies , toxicokinetic data in orally treated male and female rats, dogs and monkeys showed mostly $t_{1/2}$ values of 1.5 – 5 h, 2 - 7 h and 3 - 5 h respectively, with higher values in some rat (up to 8h) and monkey studies (up to 12 h) with no clear gender difference. In general, the increase of AUC_{0-t} was less than dose-proportional, in particular at higher doses and no evidence of accumulation was observed.

In pregnant rabbits, orally treated from GD6 – GD19, exposure increased slightly in asupra proportional manner with exposure observed at GD19 being about twice as high as the one observed at GD6. The accumulation observed in this species may be due to reabsorption from the intestinal tract or to coprophagia, the latter is also suggested by rising plasma concentrations 10 - 18 h after the dose. Since this is observed only in rabbits, it does not appear to be clinically relevant.

In the animal studies , C_{max} and AUC_{0-t} level achieved were far higher than those in humans, considering also that inclinical studies, the dosign regimen is once every other day compared to once to twice daily in the animal studies.

Distribution

In animal (CD-1 mouse, Sprague-Dawley rat, and cynomolgus monkey) and human plasma, at concentrations of 1 – 100 µM, migalastat did not bind significantly to plasma proteins.

In male Sprague-Dawley rats the blood to plasma ratio of ^{14}C Migalastat related radioactivity indicated no preferential distribution to blood cells.

Tissue distribution studies in mice and rats indicated distribution to the major excretory organs and to target tissues relevant for the pharmacodynamic indication of migalastat (kidney, heart, brain, skin, muscle, spleen, liver). The concentration in brain is delayed compared to plasma and other examined tissues, indicating slower penetration of brain compared to the other tissues. Tissue/plasma ratio's of in particular in brain and in spleen indicated a slower clearance from these tissues than from plasma.

The distribution to target tissues relevant for the pharmacodynamic indication of migalastat was assessed. Other tissues, such as intestinal tract, pancreas, organs of the reproductive system, pigmented tissues and low-perfused tissues such as fat tissue were not included as considered relevant by the applicant. As chronic toxicity studies did not reveal other target organs of toxicity, it can be concluded that the provided study is adequateand considered sufficient,.

In the pre-postnatal rat toxicity study significant distribution of migalastat to foetal plasma to rat milk was observed.(see details below)

Metabolism

In vitro biotransformation:

Hepatocytes from Sprague-Dawley rats, cynomolgus monkeys, or humans did not metabolise ^{14}C-migalastat during incubation for 1 – 4 h.

In vivo biotransformation:

Plasma: After a single oral dose of 50 mg ^{14}C-migalastat/kg in 3 male Sprague Dawley rats, plasma radioactivity at 1 – 12 h post dose consisted mainly of unchanged parent compound, and small amounts of (unidentified) metabolites. *Excreta*: After a single oral dose of 50 mg ^{14}C-migalastat/kg in Sprague Dawley rats (3/sex), most of ^{14}C migalastat related radioactivity excreted up to 24 h post dose in urine and up to 48 h in faeces consisted of unchanged parent compound. About 10-14% of the dose was excreted as metabolites in faeces and only about 3-10% in urine, and summed for urine + faeces about 16 (females) – 21 (males) % of the dose.

Excretion

In rats, after a single oral dose of 50 mg/kg ^{14}C-migalastat, radiolabel was primarily excreted in the faeces (51-67%) and urine (17-38%), within 24-48 hours. Excretion in expired air was examined in one rat of each sex (dose 1500 mg/kg) and was negligible. Excretion in bile was not studied. Therefore, it cannot be assessed whether the material excreted in faeces has been absorbed.

2.3.4. Toxicology

The applicant provided a complete toxicity assessment from animal studies. A single dose otoxicities studies were performed in in both rats and dogs at high doses that greatly exceed the intended clinical dose. Prolonged exposure to migalastat was evaluated in pivotal toxicology studies in rats up to 26 weeks and in Cynomolgus monkeys up to 39 weeks. In addition, shorter repeat dose toxicity studies were performed in mice, rats, dogs and Cynomolgus monkeys and in transgenic galactosidase A knockout mice in a combination study with Fabrazyme. Developmental and reproductive toxicity studies were performed in rat and rabbit, carcinogenicity studies were performed in rat and transgenic mice coding for an oncogene promoter.

Single dose toxicity

Single dose toxicity studies were conducted in Sprague-Dawley rats at a dose of 1500 mg/kg and in Beagle dogs at a dose of 316 mg/kg. The high dose was well tolerated in both rats and dogs.

Repeat dose toxicity

Repeat dose toxicity studies in mice

A 28 day study in mice showed that migalastat was relatively well tolerated at doses up to 2000mg/kg/d. At high doses, irritation of the large intestine and, apoptosis of the mesenteric lymph node was observed, which is considered to result from local irritation due to high concentrations of migalastat in the intestine rather than systemic toxicity. In mice, migalastat exposures increased dose proportionally up to 1000 mg/kg/d, and supra proportionally at higher concentration. C_{max} increase was less than dose proportional and accumulation was considered to be negligible. Exposures and C_{max} were higher in females given 1000 or 2000 mg/kg/d than males. Additionally, in the carcinogenicity study, females were given half the dose than males showed comparable exposures. Therefore, it can be considered that the difference in exposure may be a species specific gender effect.

Repeat dose toxicity studies in rats

A 5 day repeat dose toxicity study in rats revealed no toxicologically relevant findings at doses up to 1500 mg/kg/d. A 14 week study in rats was similarly well tolerated and showed only procedure related changes as result of oral gavage and mild irritation due to high concentrations of migalastat in the stomach. Long term exposure was evaluated in rats in a 26 week toxicity study. There were no changes in clinical observations with the exception of soft faeces in the high dose group (1500 mg/kg bid). There were also no changes in body weight, body weight gain or food consumption, haematology or serum chemistry changes. Urine pH was decreased in high dose treated animals and was reversible but is not considered to be of toxicological relevance. The spleen was considered to be the target organ at the highest dose tested: increased spleen weight was partially reversible and minimal to slight increased lymphoid follicles were observed from the low dose group onwards. In the high dose group, this was not fully reversed at the end of recovery. The findings in spleen were observed in absence of secondary immune changes. These findings in spleen were not observed in the pivotal repeatdose toxicity study in monkeys and therefore not considered to be a relevant finding.

A combination study with Fabrazyme in rats did not show adverse synergistic effects.

In rats, exposure and Cmax increased in a less than dose proportional manner in both males and females and while no accumulation was noted in a 14 day study, in the 26 week study accumulation was noted at all dose levels (28.7, 10.9 and 4.3% at dose levels of 100, 500, and 1500 mg/kg/day, respectively on Day 181). Exposures were above the intended clinical exposure.

Toxicokinetic data

Repeat dose toxicity study in dogs

A 5 day repeat dose toxicity study in dogs with doses up to 500 mg/kg revealed no toxicologically relevant findings. Similarly, migalastat was devoid of toxicity in a 14 day repeat dose study in dogs with the exception of an increase in liquid faeces in the high dose group, considered to be likely migalastat related. In dogs, exposures and C_{max} increased in a less than dose proportional manner. Due to the low number of animals, there is high inter-animal variability in exposure and may have resulted in observed differences between males and females, the latter having a higher exposure.

Repeat dose toxicity studies in Cynomolgus monkeys

In a 14 day repeat dose toxicity study in monkeys, observed findings were related to blood parameters in males receiving upwards of 200 mg/kg/d migalastat, and were considered likely due to the intubation for gavage. In the 39 week repeatdose toxicity study in monkeys, there were no deaths, or changes in body weight, cardiovascular parameters, urinalysis or gross pathology. Slightly decreased red blood cell count and haemoglobin values were however noted in females given 500 mg/kg/d after 169 days. The reduced values normalised at the end of study period and after recovery. The findings are considered to be of no toxicological relevance despite being statistically significant. Similarly, an increase in GGT on day 84 and onwards in animals given 200 mg/kg/d migalastat was attributed to a few animals with higher GGT activity, and higher values were also seen at earlier time-points in control animals and pre-test. This finding was therefore considered not of relevance. In animals given 200 mg/kg/d and upwards, minimal dilatation of lymphatics in duodenum at terminal sacrifice was noted slightly higher in the treatment group than in the control group. There are no other related findings that would suggest toxicity, nor are there gross pathology findings that are correlated to this finding. Therefore the toxicological relevance is considered to be of limited relevance.

In monkeys, exposure increased less than dose proportionally without differences in male and female exposures. Cmax increased in a less than dose proportional manner between 50 and 200 mg/kg/day but was more or less comparable between 200 and 500 mg/kg/day in both the 14 day and the 39

week studies. Overall, there was no accumulation of migalastat after 14 days or 39 weeks across the entire dose range and exposures were well above those intended for clinical use.

Genotoxicity

Migalastat is not genotoxic *in vivo* or *in vitro*.

Carcinogenicity

Carcinogenicity studies were conducted in mice and rats.

Migalastat was well tolerated in a 26-week transgenic (rasH2) mouse carcinogenicity study without changes in body weight, clinical signs or macroscopic findings related to treatment with migalastat. Mice carried the oncogene promoter rasH2. There were no microscopic findings in any migalastat treated animals that could be related to treatment. One palpable mass was detected in a female animal treated with 500mg/kg migalastat at week 16 and result of metastasis

In the long term rat carcinogenicity study, decreased body weight was observed in male rats after 84 weeks despite generally comparable food intake across all groups. This effect was more pronounced in females. There are no differences in mortality compared to the control groups. There were no differences in frequency of clinical signs or ophthalmology compared to controls that were related to migalastat treatment. The incidence of thymic cysts was increased in female rats in all groups including controls compared to males, although the incidence was higher in migalastat treated animals. Formation of cysts in aging female rats is a common observation and therefore not likely related to migalastat treatment.

The incidence of pancreas islet cell adenoma was significantly increased in males treated with 800/1200 mg/kg/d migalastat and was above the incidence rate observed in historical controls. Migalastat is an iminosugar, and thus, the pancreas cannot be excluded as a possible target organ. After ruling out several non-genotoxic or hormonal mechanisms, absence of islet cell hyperplasia or any morphologic islet changes in chronic toxicity studies and the fact that proliferative endocrine lesions are a common background finding, the weight of evidence supports the fact that the observed islet cell adenoma in high dose treated males is not a migalastat related effect.

Reproduction Toxicity

Male rats receiving migalastat showed drastically reduced fertility parameters in all migalastat groups despite comparable mating performance with the control group and in absence of changes in sperm parameters including mean sperm count, sperm motility or morphology. After a 4-week recovery period, females became pregnant, suggesting a migalastat related effect on male fertility. There were no apparent changes in anatomy or organ weight. Consistent with reduced fertility, the number of corpora lutea and thenumber of implantations are reduced in the migalastat females group. Similarly, post implantation loss was high in migalastat group. These findings were fully recoverable and corpora lutea, implantation, pre and post- implantation loss were comparable in all groups including controls. Increased lymphoid infiltrate in both left and right epididymis of high dose treated males was also been observed in some control animals and a treatment related effect was ruled out which was also confirmed by independent peer-review. Furthermore, based on the chemical and pharmacological similarities between migalastat and miglustat, in which infertility is also seen in male animals, it is hypothesized that infertility in migalastat treated male rats is likely based on one or more of the mechanisms of miglustat. While no effect was observed on sperm morphology or motility after treatment with migalastat, it remains possible that biochemical changes in acrosome composition may result in failure of sperm to complete capacitation and/or the acrosome reaction resulting in failure of

sperm to penetrate and/or activate the oocyte. No toxicokinetic analysis was available for this study. However, considering that the doses are comparable to the ones used in the rat repeat dose toxicity studies, it can be assumed that exposures are comparable. Since a NOEL for fertility in males was not established, a second study in rats, was performed at lower doses.In this study, reduced fertility and corresponding pregnancy parameters comparable to the previous study occurred at the highest dose tested (25 mg/kg/day) despite any change in mating performance. Exposure at the highest dose tested was 6663 ng.h/ml, which is considered to be below the intended human exposure.

As miglustat, another iminosugar is also known to induce fully recoverable infertility in males, the effect is likely to be class-related. Therefore, migalastat is considered to have an adverse effect on male fertility in rats above 10 mg/kg/day, which may be relevant for humans. In contrast, no effects of migalastat were seen on fertility in female rats at doses up to 1000 mg/kg/d migalastat. Therefore, migalastat is not considered to have an effect on female fertility.

Embryofoetal toxicity of migalastat was evaluated in rats and rabbits..

Anomalies such as dilated renal pelvis were observed with increased incidence in migalastat groups in comparison to control (litter incidence: 16% control group, 27.3 %, 32% and 31.8% in 100 mg/kg/d, 500 mg/kg/d and 1500 mg/kg/d, respectively), but lacked a dose-response relationship and were below historical control incidence rates. The NOAEL in the embryofetal toxicity study was 1500 mg/kg. PK data taken from repeat-dose study indicate that the margins to human target exposure (AUC) are only 1.9 to 2.4 in females and males, respectively.

In rabbits, maternal toxicity was apparent at the highest dose and manifested as anorexia and reduced food intake. The exposure exceededs the human exposure by more than 20-fold on gestation day 6 at the lowest dose tested. There were no pathological changes in females that could be considered treatment related. However, due to the maternal toxicity, post implantation loss was dose dependently increased from 300 mg/kg/day onwards and 7 females in the high dose group were euthanized due to anorexia after abortion. Post implantation loss was considered to be related to increased resorption incidence and consistent with the observed female toxicity. Foetal weights in the high dose group were decreased. Increased incidences of minor skeletal malformations and delayed ossification were considered consistent with maternal anorexia. Foetal malformations were in line with historical control and also comparable to control group animals, therefore considered to be spontaneous findings and not treatment related. In conclusion, there is no evidence of teratogenic potential of migalastat in the rabbit, although maternal toxicity is apparent from the mid dose onwards. Therefore, the NOAEL for both maternal and offspring animals is 120 mg/kg/day in rabbit.

Effects of migalastat on pre- and postnatal development were evaluated in rats, without any adverse effects in paternal or offspring animals. Similarly, there were no adverse effects in F2 offspring resulting from migalastat administration to F0-generation animals with the exception of slightly increased post-implantation loss in the mid and high dose groups. No dose-relationship was noted and the mean percentage post-implantation loss in the high dose group remained within the historical control range; thus not considered to be treatment related. In conclusion, there is no evidence of pre- or postnatal toxicity resulting from migalastat in rat. Migalastat is excreted in milk. The NOAEL is considered to be the highest dose tested, 1000 mg/kg/day.

2.3.5. Ecotoxicity/environmental risk assessment

Table 1 Summary of main study results

Substance (INN/Invented Name): migalastat			
CAS-number: 108147-54-2 (migalastat); 75172-81-5 (migalastat hydrochloride)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	pH metric method	-0.76±0.05	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.76	not B
PBT-statement :	migalastat is not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined	0.00077	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)	not investigated		

Conclusions on studies for migalastat

The refined PEC_{sw} is 0.00077 µg/l, which is below the action limit of 0.01 µg/l. Migalastat is neither PBT nor vPvB. A further assessment is not deemed necessary and Migalastat is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The pharmacological activity migalastat has been demonstrated both *in vitro* and *in vivo* using recombinant human forms of α-GAL A. According to the Applicant, homology for α-galactosidase A between mice, rats, rabbits, dogs, monkeys, and humans is approximately 85%, 86%, 88%, 90%, and 99%, respectively. , The Ki values for α-galactosidase A are 7.7, 9.3, 11.4, and 11.2 nanomolar,in rat, rabbit, monkey, and human respectively, similar to that for mouse (10.6 nanomolar). These comparable K_i values between species suggest functional and specific binding in the selected animals.

In the repeated dose toxicity studies, the animals were dosed twice daily. This is not in line with the dosing regimen proposed for clinical use, of every other day. The consequence of twice daily dosing could be that instead of stabilization and activation of the enzyme, inhibition of the enzyme occurs due to prolonged exposure, as discussed in the pharmacodynamics section. Less frequent dosing might have resulted in low exposures, and an exaggerated pharmacology of enzyme activation would be difficult to detect since the healthy animals used in the toxicity studies have active enzyme already. Therefore the dosing regimen used in the repeated dose studies is acceptable.

In general exposure multiples in animals were far above those in humans, especially when it is taken into account that migalastat is administered to humans every other day, whereas animals were exposed daily.

In summary, preclinical data indicated that the best substrate reduction was observed with less-frequent dosing compared to daily dosing due to sustained elevated α Gal A in the absence of chaperone. The 30 mg/kg less-frequent dosing was significantly better than 10 mg/kg and not significantly different from higher doses. Based on these data, less-frequent dosing regimens were evaluated in clinical studies, targeting the exposure seen in mice following administration of 30 mg/kg, which corresponds to the exposure associated with the 150 mg dose in human.

Exposure to the parent compound was high in all species used in the pivotal toxicity studies, therefore, it is acceptable that metabolism was only studied in one species (rats) since no major metabolites were identified in humans,

Chronic and high exposure to migalastat in rodent and non-rodent resulted in very limited toxicity. Spleen is the target organ in one pivotal rat repeat dose study, but this was not replicated in other species and therefore likely not clinically relevant. Migalastat has no genotoxic potential *in vitro* or *in vivo*.

In carcinogenicity studies, the incidence of benign pancreatic islet cell adenoma was increased in high dose migalastat treated rats above the one seen in historical controls. Proliferative lesions were not observed in pancreas during chronic testing, and non-genotoxic and hormonal pathways could be ruled out. Because endocrine proliferative lesions are common in rat, migalastat is not genotoxic, and because non-genotoxic and hormonal mechanisms were ruled out it is not considered to be relevant for humans.

Migalastat induces profound male infertility at clinically relevant exposures. The effect is fully reversible after cessation of treatment and is also observed for another iminosugar, miglustat, thus considered likely to be a class effect. Minimal epididymal lymphocyte infiltration was observed in high dose treated males and was not considered to be treatment related, nor the cause of the observed infertility.

Migalastat had no adverse effects on embryofoetal, pre- and postnatal development in rats, and did not induce maternal toxicity. . In contrast, maternal toxicity is seen in rabbits at high exposures . As a result, post implantation loss was dose dependently increased. Consistent with maternal anorexia, foetal weights in the high dose group were decreased as were minor skeletal malformations and delayed ossification. Foetal malformations were considered to be in line with historical controls and comparable to control group animals,. Therefore this was considered to be spontaneous and not treatment related. In conclusion, there is no evidence of teratogenic potential of migalastat in the rabbit, although maternal toxicity is apparent from the mid dose onwards.

The high plasma concentration range in dogs and rabbits exceeded the QC range and the range validated in the analytical validation reports. Therefore, the toxicokinetic data of the high (rabbit) and mid – high (dogs) dose groups should be interpreted with caution as values should only be considered approximations of exposure. , However considering the high exposure achieved in animal studies, (even in the low dose studies) compared to the exposure planned in human this shortcoming has no implications for the toxicological risk assessment

2.3.7. Conclusion on the non-clinical aspects

The pharmacology and toxicology of migalastat have been sufficiently characterised and support the use in humans. The relevant findings have been adequately mentioned in the SmPC section 5.3.

2.4. Clinical aspects

2.4.1. Introduction

The migalastat clinical development program comprised 20 studies and included patients with both the classic and late-onset phenotypes of Fabry disease. The design of the clinical program was based on relevant guidelines (guideline on clinical trials in small populations (CHMP/EWP/83561/2005)) as well as discussions with the Scientific Advice Working Party.

Six Phase 2 and four Phase 3 studies (two pivotal and two open-label long-term extension studies) have been conducted in 180 patients with Fabry disease, of whom 168 (89M, 79F) have been exposed to migalastat (Figure 1). An additional two patients have received migalastat through physician-initiated compassionate use programmes.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

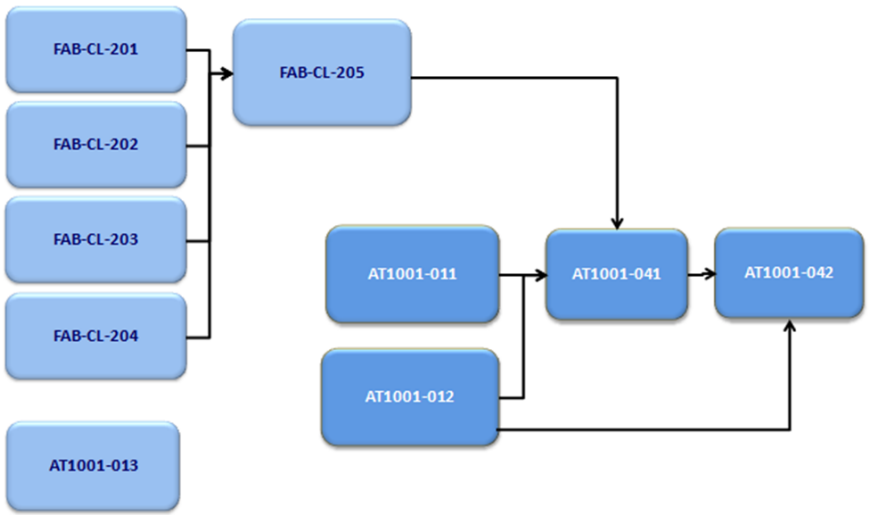


Figure 1: Overview of Migalastat Phase 2 and 3 Studies

- Tabular overview of clinical studies

- **Table 2: Overview of Phase II and III studies**

Study Number	Study Design	Study Objective(s)	Patients (Type, No., Mean Age [range])	Treatment (Dosage, Form, Dose, Route)	Primary Endpoint
Phase 3 Studies					
AT1001-012	18-month active-controlled, randomised, open-label multinational study with optional 12-month open-label extension (OLE)	Compare the efficacy and safety of migalastat to ERT in patients with Fabry disease who were currently receiving ERT and had migalastat-responsive mutations in *GLA*	Patients with Fabry disease with migalastat-responsive *GLA* mutations who were receiving ERT n= 56 (24M/32F) Migalastat:n= 36 (16M/20F) ERT: 22 (9M/13F) 48.9 (18-72) years	Period 1(18-month OL): Migalastat 150 mg capsule QOD (oral) or IV ERT (agalsidase alfa or agalsidase beta) Period 2 (12-month OLE): Migalastat 150 mg capsule QOD	Key endpoints: Annualised rates of change in $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ from baseline to Month 18
AT1001-011	6-month double-blind (DB), randomised, placebo-controlled study (Stage 1) followed by 6 month open-label treatment (Stage 2) and an optional 12-month open-label extension (OLE)	Stage 1: Compare the effect of migalastat versus placebo on kidney GL-3 as assessed by histological scoring of the number of IC GL-3 inclusions. Stage 2: Assess the efficacy, safety, and PK of migalastat	Patients with Fabry disease with migalastat-responsive *GLA* mutations who were ERT-naïve or ERT-free ≥6 months 67 (24M/43F) Migalastat-migalastat: 34 (12M/22F) Placebo-migalastat: 33 (12M/21F) 42.2 (16-68) years	Stage 1(6 months DB): Migalastat 150 mg capsule QOD or placebo QOD (oral) Stage 2 (6 months OL) + optional OLE (12 months): Migalastat 150 mg capsule QOD	Key endpoints: Stage 1: Proportion patients with a ≥ 50% reduction from baseline to Month 6 in the average number of IC GL-3 inclusions Stage 2: Annualised rates of change in $eGFR_{CKD-EPI}$ -EPI and $mGFR_{iohexol}$ from baseline to Month 12
AT1001-041	OL extension study evaluating long-term safety and efficacy in	Evaluate long-term safety, efficacy, and PD in patients who completed	Patients with Fabry disease with migalastat-responsive *GLA* mutations who	Migalastat 150 mg capsule QOD	Key endpoints: change from baseline in $eGFR_{CKD-EPI}$ -EPI, cardiac

	patients who participated in studies AT1001-011, AT1001-012, or FAB-CL-205	treatment in a previous study of migalastat	completed a previous study of migalastat Ongoing		parameters
AT1001-042	OL extension study evaluating long-term safety and efficacy in patients who participated in studies AT1001-011, AT1001-012, or AT1001-041	Evaluate long-term safety, efficacy and PD in patients who completed treatment in a previous study of migalastat	Patients with Fabry disease with migalastat-responsive *GLA* mutations who participated in a previous study of migalastat Ongoing	Migalastat 150 mg capsule QOD	As for AT1001-041

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Study Number	**Study Design**	**Study Objective(s)**	**Patients (Type, No., Mean Age [range])**	**Treatment (Dosage, Form, Dose, Route)**	**Primary Endpoint**
Phase 2 Studies					
FAB-CL-201	OL, multicentre, repeat dose escalation study	Evaluate the safety, tolerability, PK, and PD of different dosages of oral migalastat in patients with Fabry disease	Patients with Fabry disease Eligible-enrolled patients: 9 (9M) 36.7 (17-58) years Dosed screening failures: 6 (6M) 42.7 (20-63) years	Migalastat capsule(s): 25 mg BID Days 1-14 100 mg BID Days 15-28 250 mg BID Days 29-42 25 mg BID Days 43 to 84 Optional Extension Period: 25 mg BID or 50 mg QD Day 85 to Week 48 or 96	PD assessments included: α-Gal A activity in leukocytes and skin GL-3 levels in plasma, urine, and skin.
FAB-CL-202	OL, multicentre, repeat dose study	Evaluate the safety, tolerability and PD of oral migalastat in patients with	Patients with Fabry disease 4 (4M) 33 (18-65) years	Migalastat capsule 150 mg QOD 12 weeks with optional 36-week extension	PD assessments included: α-Gal A activity in PBMCs,

		Fabry disease			kidney, and skin GL-3 levels in urine, kidney, plasma, and skin.
FAB-CL-203	OL, multicentre, repeat dose study	Evaluate the safety, tolerability and PD of oral migalastat in patients with Fabry disease	Patients with Fabry disease 5 (5M) 41.6 (31-55) years	Migalastat capsule 150 mg QOD 24 weeks with optional 24-week extension	PD assessments included: α-Gal A activity in PBMCs, skin, and kidney GL-3 levels in urine, plasma, kidney, and skin
FAB-CL-204	OL, multicentre, repeat dose study	Evaluate the safety, tolerability, PK, and PD of different dosages of oral migalastat in female patients with Fabry disease	Female patients with Fabry disease Migalastat 50 mg: 2 (2F) 49.0 (36-62) years Migalastat 150 mg: 4 (4F) 44.8 (37-59) years Migalastat 250 mg: 3 (3F) 44.0 (42-47) years	Treatment Period: Migalastat capsules 50 mg, 150 or 250 mg QOD for 12 weeks Optional Extension Period: continue same dose regimen as in treatment period for additional 36 weeks	PD assessments included: α-Gal A activity in leukocytes, kidney and skin GL-3 levels in urine, kidney, plasma, skin
FAB-CL-205	OL extension study for patient completing study FAB-CL-201, FAB-CL-202, FABCL-203, or FAB-CL-204	Evaluate the long-term safety, tolerability, PK, and PD of oral migalastat in patients with Fabry disease	Patients with Fabry disease who participated in a previous Phase 2 study of migalastat 23 (14M/9F) 43.1 (19-66) years	Migalastat capsule(s) 150 mg QOD Dose escalation phase (DEP): migalastat 250 mg (3 days on/4 days off) for 2 months followed by migalastat 500 mg (3 days on/4 days off) Following the DEP, migalastat 150 mg QOD	PD assessments included: α-Gal A activity in leukocytes GL-3 levels in urine, plasma, and kidney

2.4.2. Pharmacokinetics

The pharmacokinetic (PK) behaviour of migalastat has been well-characterised in healthy volunteers and patients with Fabry disease. The clinical pharmacology of migalastat was characterised in ten Phase 1 studies (FAB-CL-103, AT1001-016, FAB-CL-101, FAB-CL 102, FAB-CL-104, AT1001-014, MGM115806, AT1001 015, AT1001-010, and AT1001-018). Additional PK and pharmacodynamic (PD) data were obtained from five Phase 2 and 3 studies in patients with Fabry disease (AT1001-013, FAB-CL-201, FAB-CL-204, FAB-CL-205, and AT1001-011).

Urinary recovery indicates that migalastat is absorbed for at least 77%. Solubility data showed that migalastat has a solubility of more than 500 mg/ml over the pH range of 1.2 to 7.5. Based upon solubility data and excretion data migalastat can be considered a BCS Class III (high solubility/low absorption).

One analytical LC-MS/MS method has been applied for the analysis of migalastat in plasma. Validation suggested that the method was adequate. Stability was shown covering study sample handling and storage. This was also adequate in urine. Based upon the analytical reports, performance were within normal criteria with acceptable reproducibility.

Absorption

After oral administration, maximum migalastat plasma concentrations are observed after about 2.5 – 3.5 h. The absolute bioavailability of migalastat is about 75%.

A high fat, high caloric meal decreased migalastat AUC and C_{max} by about 37 and 40%, respectively. A decreased absorption is also observed when migalastat is taken 1 h before a high fat meal and a light meal, i.e. AUC was 37 and 42% lower, and C_{max} 15 and 18% lower, respectively. Also after intake of migalastat 1 h after intake of a light meal AUC and C_{max} was decreased (40 and 39%, respectively).

Concomitantly intake of migalastat with a glucose drink showed a small decrease in AUC and Cmax by 14 and 10%, respectively. This latter study was carried out to confirm the impact of a glucose drink on migalastat pharmacokinetics, as migalastat appeared to be a substrate, although with low affinity, for SGLT1 (sodium-dependent glucose cotransporter).

In clinical studies, migalastat was administered 2 h before or 2 h after food intake. Furthermore, patients were instructed to take migalastat at the same time of the day. This is in line with the SmPC recommendations. Based upon migalastat plasma concentration under fasting conditions at 2 h after administration and at t_{max} , the applicant suggested that absorption was about 87% of the dose. Therefore it was considered that intake of a meal 2 hours after intake of migalastat would not impact the absorption of migalastat. This seems reasonable. Although not evaluated, it was expected that intake of migalastat 2 h after intake of a meal would not impact migalastat absorption. This assumption seems to neglect that 2 h after food intake, a considerable amount of food may be still in the stomach, with possible food interaction. As the SmPC recommendations were in line with the supportive clinical studies, this issue was considered adequately addressed.

Three capsule formulations (25, 150 and 250 mg) and an oral solution without excipients were used in the clinical studies. The oral solution is bioequivalent to the 25 mg capsule.

. The 150 mg capsule is shown to be dose proportional to the 250 mg capsule. The 150 mg commercial capsule formulation is considered similar to the 150 mg capsule formulation used in the clinical studies.

For the 25 mg capsule, the difference in the amount of active substance was compensated by the amount of pregelatinised starch. No bioequivalence study is carried out to proof that the capsule

formulations are bioequivalent. This is acceptable, as 1) migalastat is highly soluble, 2) the qualitative compositions are similar 3) a difference in the amount of starch does not affect bioavailability as shown by the bioequivalence between the 25 mg capsule and the oral solution and 4) the capsule formulations show a very rapid dissolution at pH 1.2 (900 ml, 50 rpm).

Based upon these data it is expected that the capsule formulations are bioequivalent.

Linear pharmacokinetics is observed in healthy subjects up to 1250 mg single oral doses. At the higher 2000 mg dose no further increase in AUC is observed. Linear pharmacokinetics is also observed up to 150 mg oral b.i.d. doses.. Dose proportionality was also confirmed in patients with Fabry disease over the 25 – 250 mg dose range after single dose, as well as after b.i.d. and q.o.d. dosing.

No unexpected accumulation is observed after multiple dosing b.i.d. or q.o.d dosing. At the recommended 150 mg q.o.d., very low pre-dose levels are observed at day 14 and 84 (<1% of Cmax). Considering the short elimination half-life, steady state is expected to be reached within a few days.

Migalastat pharmacokinetics shows a moderate between-subject variability of about 25 – 35%. Intra-subject variability was not evaluated.

Migalastat pharmacokinetics between healthy subjects and Fabry patients are comparable.

Dose and q.o.d. dosing scheme is recommended based on nonclinical studies demonstrating that, compared to daily administration, greater GL-3 reductions were observed using less-frequent dosing regimens, including an every other day regimen, and this was further confirmed in vivo (see clinical part).

Distribution

Migalastat does not bind to plasma proteins and as such, drug-drug interactions due to protein displacement are not expected with migalastat.

Based upon limited animal data, migalastat is widely distributed to body tissues, it may cross the blood-brain barrier, and it may transfer over the placenta and may be excreted into milk.

Patients with Fabry disease receiving migalastat showed increased α-gal A activity and/or substrate (GL-3) reduction in clinically relevant tissues, such as skin, peripheral blood mononuclear cells, and kidney. The volume of distribution (Vz) of about 60 l indicates that it is larger than total body water (about 42 l for a 70 kg subject).

Metabolism

In vitro data show that migalastat is not a substrate of CYP enzymes. This is confirmed *in vivo*, showing that migalastat is not extensively metabolised.

The major circulating component in plasma was migalastat, representing approximately 77% of the sample radioactivity. Other circulating components were formed by dehydrogenation followed by O-glucuronidation (M1, M2 and M3). These metabolites were minor representing only approximately 5%, 2% and 6% of the sample radioactivity, respectively.

Elimination of migalastat in human following oral administration was mainly by direct renal excretion with approximately 55% of the administered dose detected as unchanged migalastat in urine. Metabolism via dehydrogenation and O-glucuronide conjugation was a minor route of elimination with metabolites representing approximately 4% of the dose in human urine. Total radioactivity recovery in urine was about 77%. A further 20% of the administered dose was detected as unchanged migalastat in faeces, which may represent unabsorbed migalastat or material either directly secreted in the bile or

conjugated and then hydrolysed in the gastrointestinal tract. The total recovery of the radioactive dose was 97.6%.

Urinary recovery of mainly the intact drug was confirmed in several other studies.

Elimination

The plasma elimination half-life of migalastat is about 3.5 – 4.5. CL after i.v. administration was about 9.3 l/h. After oral administration at the 150 mg dose CL/F was about 11 – 14 l/h. Renal clearance was about 7 l/h, in line with the normal glomerular filtration rate of 6 l/h.

Special patient groups

Population pharmacokinetic analysis did not show a difference in migalastat clearance between male and female subjects and an effect of age on clearance. Further, based upon population pharmacokinetic analysis, no effect of race on the clearance of migalastat is observed.

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 bodyweight are subject to a lower exposure (difference about 40%). This is considered however not clinically relevant.

Migalastat is eliminated to a great extent renally as intact drug. As such, an impact of an impaired renal function on the pharmacokinetics of migalastat is expected. Indeed, a mild, moderate and severe impaired renal function increased systemic exposure 17%, 81% and 353%, respectively. Consequently, Galafold is not recommended for use in patients with Fabry disease who have estimated GFR less than 30 mL/min/1.73 m^2.

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

Special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	19	0	0

Interactions:

In vitro, migalastat appeared not to be an inducer of CYP1A2, CYP2B6 and 3A4.

In vitro data show that migalastat is not a substrate of P-gp or CYP enzymes. Based upon *in vivo* data, migalastat is a substrate for uridine 5'-diphospho-glucuronosyltransferase (UGT), however this is only a minor elimination pathway. As such, it is not expected that migalastat inhibits UGT.

In vitro, migalastat does not inhibit 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 and appeared not to be an inhibitor of BCRP, MDR1 and BSEP human efflux transporters and OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K human uptake transporters. *In vitro*, migalastat is not a substrate of BCRP, MDR1, BSEP, OAT1, OAT3, OCT2, MATE1 and MATE2-K.

In vitro migalastat appeared not to be an inhibitor of P-gp.

Based upon the available *in vitro* data, no interactions are expected on CYP and transporters level.

In vivo, co-administration of migalastat with agalsidase resulted in increased exposures to agalsidase; at the 150 mg single dose level an increase of 2.0 to 4.2-fold is observed. Agalsidase did not affect the pharmacokinetics of migalastat. This interaction is adequately described in the SmPC section 4.5.

2.4.3. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

The pharmacodynamic (PD) properties of migalastat were investigated in five Phase II trials (see Table 2). Results from the PD studies showed that migalastat increased α-Gal A activity in peripheral blood mononuclear cells (PBMCs) and corresponding decreases in plasma GL-3 were observed in patients with migalastat-responsive mutations.

Dose selection was based on findings from preclinical and PD studies, the optimal dosage was found to be 150 mg QOD. This was based on the optimal increase of α-Gal A activity in peripheral blood mononuclear cells (PBMCs) and corresponding decreases in GL-3 (in urine, blood, skin etc.). Increases in PBMC α-Gal A activity and decreases in GL-3 observed with migalastat 150 mg QOD dose were not further enhanced when patients switched to higher, less frequent doses (250 and 500 mg, 3 days on/4 days off; FAB-CL-205), supporting the selection of the 150 mg QOD regimen for study in Phase 3 trials. Patients were selected based on GLA genotyping (by HEK analysis; discussed below) whether they had an amenable mutation or not.

Fabry disease-causing *GLA* missense mutations, carboxyl-terminal nonsense mutations, 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, generally qualify for *in vitro* testing. These types of mutations are generally associated with mutant forms that may be physically unstable, prone to inefficient or aberrant folding, have deficient lysosomal trafficking, and/or show increased levels in cultured cells upon binding and stabilization by migalastat (Lemansky *et al.*, 1987; Ishii *et al.*, 1993; Ishii, Kase *et al.*, 1996; Ioannou *et al.*, 1998;Fan 1999; Desnick *et al.*, 2001; Garman and Garboczi 2002; Bernier, Lagace *et al.*, 2004; Desnick 2004; Garman and Garboczi 2004; Yam *et al.*, 2005; Yam *et al.*, 2006; Ishii *et al.*, 2007; Shin *et al.*, 2008; Benjamin *et al.*, 2009). Thus, Fabry patients with these types of mutations may show increased total cellular α-Gal A activity after treatment with migalastat. This has been shown in the pivotal studies (AT1001-011 and AT1001-012) were increases in α-Gal A were observed after migalastat 150 mg QOD treatment. No changes in α-Gal A were observed after placebo treatment. In ERT treated patients α-Gal A could not be measured due to interference with the administered enzyme.***GLA* Genotype Testing used for Patient Identification**

The standard diagnostic for Fabry disease includes GLA genotyping to confirm the presence of a mutation. A GLA mutation that is predicted to be responsive to migalastat was a key eligibility criterion throughout the clinical development program. During Phase 2, an *in vitro* assay was developed in human embryonic kidney-293 (HEK) cells, which identifies mutant forms of α Gal A that are responsive to migalastat. In this assay, the mutant form of α-Gal A being tested is expressed in HEK cells, which are cultured in the absence and presence of migalastat. An increase in α-Gal A activity in the presence of migalastat indicates that the specific mutant form was stabilised by migalastat and trafficked into the lysosome. For Phase 3 enrolment, a preliminary HEK assay was used to identify patients with responsive mutations. The criteria for a mutation to be considered responsive were: a relative increase in α-Gal A activity ≥1.2-fold above baseline and an absolute increase in α Gal A activity ≥3% of wild-type (WT) after incubation with 10 μM migalastat. The concentration of 10 μM is the approximate C_{max} of migalastat in the plasma of patients with Fabry disease following a single oral dose of 150 mg

(Johnson *et al.,* 2013). In patients with Fabry disease, α-Gal A increases of approximately 1 to 5% of normal activity *in vivo* are considered to be clinically meaningful (Desnick, 2004). A reference table that categorised GLA mutations, according to the preliminary HEK assay, was compiled and used to determine eligibility for the pivotal Phase 3 studies of migalastat.

GLP HEK assay (a.k.a. migalastat amenability assay)

During the conduct of the Phase 3 studies, the preliminary HEK assay (see above) was transferred to a qualified third-party laboratory, Cambridge Biomedical, for analytical and GLP validation. 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. After assay validation, the *in vitro* responses to 10 μM migalastat of the 531 known mutant forms of α-Gal A were re-tested in the GLP HEK assay, including those from all patients enrolled in the Phase 2 pharmacodynamic studies (FAB-CL-201 to FAB-CL-204) and the pivotal Phase 3 studies (AT1001-011 and AT1001-012). The criteria for amenability in this assay were the same as in the preliminary HEK assay (see above).

For clinical validation of the GLP HEK assay, the mutant forms of α-Gal A categorised as amenable in the HEK assay were compared to the observed α-Gal A activity in PBMCs of male patients with Fabry disease (n=51) after migalastat treatment in Phase 2 and 3 clinical trials. These analyses showed a high degree of consistency between the two sets of results. The predictive values were estimated to be:

- Sensitivity: 1.0
- Specificity: 0.88
- Positive predictive value: 0.95
- Negative predictive value: 1.0

Additional analyses of the Phase 3 clinical studies demonstrated that the GLP HEK assay results are highly predictive of changes in kidney IC GL-3 and plasma lyso-Gb3, which are considered biomarkers.

The positive predictive value of the HEK assay on a patient level is 95% (i.e. some patients deteriorate during migalastat treatment due to non-amenability). This uncertainty necessitates a warning to be included in the SmPC with regards to the need of monitoring of treatment after 6 months and regularly thereafter. Further given a specificity of 88%, about 12% of the patients will be wrongly identified as non-amenable. It should be concluded that the HEK assay has its limitations in the identification of amenable and non-amenable patients. The HEK assay is acceptable as it identifies a population of amenable patients that would respond to migalastat treatment (see efficacy conclusions).

The mutant forms of α-Gal A categorised as amenable in the HEK assay are also associated with corresponding changes in disease substrate in patients. High sensitivity and specificity were seen in the comparisons of α-Gal A activity in the HEK assay to reductions in male kidney IC GL-3 (sensitivity 1.0, specificity 1.0, positive predictive value 1.0, negative predictive value 1.0), male plasma lyso-Gb3 (respectively: 1.0, 1.0, 1.0, 1.0), and male and female plasma lyso-Gb3 (respectively: 0.93, 0.69, 0.84, 0.85).

These results support the clinical validation of the GLP HEK assay and the utility of the pharmacogenetic reference table in identifying the target population for treatment with migalastat.

The GLP HEK assay was based on the preliminary HEK assay, and included modifications to increase the level of quality control, rigor, precision, and consistency. Comparison of the results from the GLP HEK assay and the preliminary HEK assay showed that 475 of 531 (89%) mutations were maintained

in the same category, whereas 56 of 531 (11%) mutations changed categories after analytical validation. Mutations that do not meet the amenability criteria are referred to as non-amenable. Further the applicant considers mutations not tested non-amenable. To date, 850 GLA mutations have been categorised as either amenable (n=269) or non-amenable (n=581). Non-amenable mutations also include mutations that do not qualify for testing such as large deletions, insertions, truncations, frameshift mutations, and splice site mutations. 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. 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, splice site mutations are not testable in the GLP HEK assay because this assay uses recombinant *GLA* cDNA; thus, the mutant α-Gal A is expressed independent of pre-mRNA splicing. To date, 850 GLA mutations have been categorized as either amenable (n=269) or non-amenable (n=581).

In the indication, it is stated that patients should be amenable to migalastat as follows: "*Galafold is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (*see list of mutations in section 5.1*)*" In section 5.1, two tables are included: one table including the GLA mutations that are amenable to migalastat and one table with the mutations that are considered not amenable to migalastat which include mutations not investigated yet. It is emphasized by the applicant that only mutations that were tested are included in one of the tables.

Table 3 presents a summary of the patients in Phase 3 studies, overall and for those with amenable and non-amenable mutations.

Table 3: Summary of Phase 3 Patients with Amenable GLA Mutations Based on GLP HEK Assay (ITT and mITT Populations).

Study	Total Number of patients[a)]	Amenable (n)[b)]	Non-amenable (n)
AT1001-012	60	56	4
AT1010-011	67	50	17
Total	127	106	21

a) ITT population; b) mITT population was defined as those patients having an amenable mutation to migalastat.

The reference table (e.g. table with known mutations that are amenable or non-amenable to migalastat *in vitro*) will be updated by the applicant as new amenable mutations are identified. It is anticipated that on a yearly basis 30 to 40 new mutations will be identified. It is expected that as a result of registration this number will temporarily be higher and the SmPC will be updated regularly to reflect the scientific knowledge.

Dose selection pharmacology studies

- *Study FAB-CL-201*

Study FAB-CL-201 was a dose-escalation study in which 9 adult male patients received oral migalastat 25 mg BID, 100 mg BID, and 250 mg BID each for 2 weeks. At the end of the dose escalation phase, patients received 25 mg migalastat BID for 6 weeks after which they could enter an optional extension phase and receive 50 mg QD, giving a total treatment duration of up to 97 weeks in some patients. An additional 6 patients were dosed screen failures who received migalastat 150 mg QD for 2 weeks.

- Study FAB-CL-202/ Study FAB-CL-203

In two other studies (FAB-CL-202 and FAB-CL-203) five and four male patients respectively were included to further investigate the optimal dosing regimen of migalastat 150 mg QOD. Patients received migalastat administered as a QOD regimen for either 12 or 24 weeks, followed by an optional extension phase, giving a cumulative treatment duration of 48 weeks. All male patients (18 to 65 years) were hemizygous for Fabry and had to have residual α-Gal A activity. These patients are considered non-classic male Fabry patients.

- Study FAB-CL-204

Similar to study FAB-CL-201, nine female Fabry patients were enrolled in study FAB-CL-204. The female Fabry patients were heterozygous for Fabry and had to have residual α-Gal activity. Five of the 9 female patients were amenable to migalastat. Additional post hoc analysis demonstrated that female subjects with amenable mutations demonstrate a response to migalastat in reduction of urine GL-3 and kidney IC GL-3, compared with subjects with non-amenable mutations.

Patients in the PD studies were not stratified according to ERT exposure status. Post hoc analysis showed a consistent trend observed in patients with amenable mutations independent of the pre-treatment with ERT. These results are in line with those reported in the phase 3 studies.

In male Fabry patients, 25 mg, 100 mg, and 250 mg BID and 150 mg QOD migalastat increased leukocyte α-Gal A activity in almost all patients, even those with very low α-Gal A activity at baseline (studies FAB-CL-201 through FAB-CL-203). Decreases in urine GL-3 were seen in 3 male Fabry patients whose α-Gal A mutant forms were classified as amenable to migalastat based on the *in vitro* HEK assay (Study FAB-CL-202). Decreases in urine GL-3 were inconsistent in studies FAB-CL-201 and FAB-CL-203 in male Fabry patients. Renal interstitial capillary GL-3 in the last available biopsy (Week 12, 24, or 48), scored histologically using the fully quantitative Barisoni method (Barisoni *et al.*, 2012), tended to decrease relative to baseline in patients whose α-Gal A mutant forms were amenable to migalastat based on the *in vitro* HEK assay (Study FAB-CL-202 and FAB-CL-203). GFR, 24 hr urine protein excretion, 24 hr creatinine clearance was collected at baseline of all patients. All patients were considered having a (near) normal renal function. After treatment with migalastat no clinical meaningful differences were observed. Baseline cardiac MRIs were abnormal in most patients. After treatment some patients (16 had available data) showed improved LVEF and increase in LVESi. The data indicate that migalastat may have some beneficial effects on cardiac parameters. This should be confirmed in the phase III studies.

In female Fabry patients treated with 50 mg (n=2), 150 mg (n=4), or 250 mg (n=3) migalastat QOD (Study FAB-CL-204), increases in leukocyte α-Gal A activity were seen in all patients by Week 24. At Week 48, eight of nine patients maintained this increase. Decreases in urine GL-3 were seen by Week 48 for seven of the nine patients. The earliest and most consistent declines in urine GL-3 were seen in the three patients who received 150 or 250 mg migalastat and whose α-Gal A mutant forms were amenable to migalastat based on the *in vitro* HEK assay. Renal interstitial capillary GL-3 in the last available biopsy (Week 48 or 12), scored histologically using the fully quantitative Barisoni method (Barisoni *et al.,* 2012), decreased relative to baseline in six of the nine patients. Of the six female patients having an abnormal cardiac MRI three showed no improvement. The three others showed some improvement.

- Study FAB-CL-205

Study **FAB-CL-205** is a Phase 2 open-label, non-comparative, long-term extension study in 23 patients who transitioned from the completed studies FAB-CL-201 to FAB-CL-204. Depending on the protocol amendment in force at the time of enrolment, patients either started on migalastat 150 mg QOD then entered a dose-escalation period, or they directly entered the dose-escalation period. The dose-escalation period evaluated migalastat 250 mg and 500 mg given as a 3 days on/4 days off

regimen. Following safety and pharmacodynamic data review indicating that the 150 mg QOD regimen offered a more favourable benefit-risk profile, the protocol was amended and the majority of patients returned to migalastat 150 mg QOD. Data in male patients with an amenable mutation demonstrate that migalastat showed improvement in α-Gal A activity. In contrast in male patients with non-amenable mutation no noteworthy increase in α-Gal A activity was observed.

Of the 23 patients enrolled, 8 had paired kidney biopsy samples (baseline from their previous feeder study, Visit 8, and Visit 12) available for evaluation. For these 8 patients, a decline in IC GL-3 inclusions was seen in the 5 patients in Visit 8 and 4 patients in Visit 12 with amenable mutations, and was variable in the 3 patients with non-amenable mutations.

Due to the limited number of patients, the results of the above pharmacological studies lack proper statistical analysis. No clear relationship between the various groups (different dosing regimen, amenable/non-amenable patients) could therefore be demonstrated. However due to the nature of the disease this is acceptable.

Based on the phase 2 studies, the 150 mg QOD dosing regimen was selected for the phase 3 studies. The pharmacological studies showed increases in α-Gal A activity and decreases in GL-3 with migalastat 150 mg QOD. These parameters were not further enhanced when patients switched to higher, less frequent migalastat doses (250 mg and 500 mg, 3 days on/4 days off). Although the data are limited, clinical based justification was provided, concluding that the data support the selection of the 150 mg QOD regimen.

Important biochemical parameters

The focus of clinical assessment is based on the following of biochemical parameters as these that are considered of key importance for the efficacy outcome and clinically important to the Fabry patient.

Alfa-galactosidase A (α-Gal A) activity

Due to the mode of action of migalastat –(e.g. stabilization of the galactosidase enzyme) - increased activity of the enzyme would confirm the mode of action. It should be noted that measurement of α-Gal A activity is less relevant in women since Fabry is a recessive X-linked disease. Women are heterozygotes, thus they have one intact gen copy left on X chromosome that expresses the α-Gal protein.

Lyso-Gb3

Lyso-Gb3 is a deacylated form of Gb3 which has been identified as a storage product in Fabry disease (Aerst, *et al.,* 2008) and considered a sensitive marker (Rombach *et al.,* 2010; Togawa *et al.,* 2010). Of note, there are at least six other lyso-Gb3 analogues known at present. In plasma lyso-GB3 is the main isoform (Boutin *et al.,* 2014). Plasma lyso-Gb3 in males is known to be higher than the plasma lyso-Gb3 concentrations in females Therefore, sensitive analysis is required to observe a small change of lyso-Gb3 in women.

Based on plasma lyso-Gb3 concentration, Fabry patients can be divided in different Fabry phenotypes (Smid *et al.*, 2015) as follows : Patients with classical Fabry disease (defined as males with lyso-Gb3 about 50- 100 nmol/l) and females with plasma lyso-Gb3 concentration about 0-20 nmol/l) (Lukas *et al., 2013;* Smid *et al.*, 2015*)*.

At baseline, the patients in the placebo controlled study had a mean lyso-Gb3 level of 47.3 ± 62.2 nmol/l in the treatment group and 41.9 ± 39.1 nmol/l in the placebo group. Given the large variation in the observed lyso-Gb3 levels, both individual and absolute (uncorrected) values are analysed to get complete information on the magnitude and of the effect and its variation. The results revealed that a

considerable number of data points were not entered in the database but this was later corrected. Analysis of the data further support the observed decrease in lyso-Gb3 in patients treated with migalastat despite a considerable variability.

GL-3 inclusions

In Fabry disease, accumulation of GL-3 (also known as zebra-bodies) can be observed in all body tissues. In the placebo controlled study, renal biopsies are taken to investigate whether GL-3 inclusions are present in the interstitial capillaries to definitely confirm the diagnosis Fabry. At baseline, 30/34 patients in the migalastat groups versus 30/33 patients in the placebo group had GL-3 inclusions in the kidney interstitial capillary (migalastat 0.922 ± 1.64 GL-3 inclusion per IC; placebo 0.645 ± 0.80 GL-3 inclusions per IC). 7 patients were excluded since they did not have biopsies at both baseline and month 6. Additionally, a large variation in scoring GL-3 inclusions was observed between the different pathologists. Therefore, upon request, the applicant submitted intra- and inter-observer reliability data. However, when considering the intra- and inter-observer reliability, the applicant stated that most results are between 2SD. This is per definition true as ±2SD encompasses with 95.4% of the observations within the 2SD assuming a normal distribution. Further analysis applying Pearson's correlation revealed an acceptable intra- and inter-observer reliability.

eGFR

In Fabry disease patients, renal function can deteriorate over time. Therefore, one of the treatment goals is the stabilization of renal function. GFR is used to estimate the renal function based on serum creatinine and depending on the formula used by weight or age and gender and race. The applicant used $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol,}$ and GFR_{mrd}. $eGFR_{CKD\text{-}EPI}$ and $mGFR_{iohexol}$ are considered the best approach for calculation/estimation of GFR.

> *$eGFR_{CKD\text{-}EPI}$ is calculated as GFR = 141 x min(Scr/κ, 1)α x max(Scr/κ, 1)-1.209 x 0.993Age 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.*
>
> *$mGFR_{iohexol}$ = measured glomerular filtration rate as assessed by plasma clearance of iohexol*

The eGFR is analyses in this assessment report, since it is currently considered the most sensitive estimation for the renal function. The above method however could provide an over or under estimation of the GFR of about 15 ml/min/1.73 m^2 in the ranges mentioned in the studies[1].

Baseline data from phase II and phase III studies indicate that the included Fabry patients (male and female) had a (near) normal renal function according to the stages of Chronic Kidney Disease (CKD). Patients had proteinuria to some extent, classifying them either stage 1 or 2.

Cardiac parameters

At baseline the majority of patients included in the study reported little cardiac problems in terms of LVMi which was considered to be in the upper normal ranges. However, some patients had abnormal LVMi and/or LVH at baseline.

Repeated measurements of the LVMi in non Fabry patients showed a variability of about 0.3 g/m^2 for the same investigator and the observed intra-reader variation is considered to be between 4.5 and 6.3 g/m^2 [2].

[1] *J. Hougardy, P. Delanaye,, A. Le Moine, J. Nortier*. "Estimation of the glomerular filtration rate in 2014 by tests and equations: strengths and weaknesses.". Rev Med Brux. *2014. Sep;35(4):250-7*

[2] A. Armstrong, S. Gidding, O. Gjesdal, et al. LVM Assessed by Echocardiography and Cardiac Magnetic Resonance, Cardiovascular Outcomes, and Medical Practice. JACC Cardiovasc Imaging. 2012 Aug; 5(8): 837–848.

2.4.4. Discussion on clinical pharmacology

In the four phase II studies FAB-CL-201 to FAB-CL-204 , 18 males and 9 female Fabry patients were included. Study FAB-CL-205 was an extended open label (OLE) study that included 23 patients (14 males/9 females) from FAB-CL-201 to 204.

Based on the inclusion criteria and baseline α-Gal A activity, the included patients are considered to be Fabry disease patients. All patients had residual α-GAL A activity, except for one patient in study FAB-CL-201 who had zero activity. In addition all patients had lyso-Gb3 concentrations that where below the cut-off lyso-Gb3 value for classical Fabry disease (e.g. 50-100 nmol/L) for male patients and for classical female patients (0 - 20 nmol/L). The mean renal function was (near) normal renal function (for age), e.g. eGFR ≈90 ml/min/1.73 m^2 on a group level. Notwithstanding the near normal mean value, some of the patients (9/27) included in the PD studies had mild to severe renal insufficiency (GFR < 90 ml/min/1.73 m^2) andall patients had proteinuria. Most patients (10/18 males and 6/9 females) had an abnormal cardiac MRI at baseline.

In summary, this indicated that, within the PD studies, a considerable number of patients had a disease burden considered to be in line with the disease spectrum observed in the general Fabry population.

In general, protocol deviations were rather high and raised concerns. The high number of deviations were caused by the reporting of each missing lab value due to missed visits as a separate deviation. However, this type of deviation should not affect results of studies, which was considered reassuring and finally acceptable.

Patients were selected to be responsive to migalastat in patient-derived lymphocytes (test for α-GAL A activity). If the HEK assay demonstrated increased α-Gal A activity (i.e. a relative increase in α-Gal A activity ≥1.2-fold above baseline and an absolute increase in α-Gal A activity ≥3% of wild-type (WT) after incubation with 10 μM migalastat), patients were considered to be responder (or defined as amenable) to migalastat and then included in the study.

In the open label extension study FAB-CL-205, urine levels of GL-3 were decreasing for several weeks in treatment-responsive subjects. Nevertheless, the same trend as in previous studies was observed as the GL-3 levels started to rise in final week of study. However, this was mainly driven by the value of one patient (GFR below 30 mL/min/1.73 m^2).

A range of doses and regimens were explored in 27 subjects (18 males and 9 females): twice daily (25, 100, 250 mg), per day (50 mg), QOD (50,150, 250 mg), and 3 days on-4 days off (250, 500 mg). Generally, it appears that doses above 150 mg did not show any additional effect; however no formal analysis across studies was provided by the applicant. This approach could be acceptable considering the small number of patients included in phase II studies. In addition, results from Phase III studies further confirmed the efficacy and safety profile of 150 mg dose of migalastat.

After treatment with migalastat, the majority of patients considered amenable to migalastat showed an increased α-Gal A activity and a decrease in urine GL-3 after 48 weeks of treatment. Some of the patients showed improved of cardiac anatomy (e.g. LVMi, LVH).

In contrast, patients considered non-responders did not show any improvement of clinical significance for above parameters. No additional beneficial effects were observed when dosing migalastat in dosage of 250 or 500 mg.

The applicant demonstrated that the GLP HEK assay results are predictive in selecting patients with amenable mutations (i.e. responder to migalastat), based on the data from the Phase 3 clinical studies. The mutant forms of α-Gal A categorised as amenable in the HEK assay are also associated

with corresponding improvements in disease substrate in patients. High sensitivity and specificity were seen in the comparisons of α-Gal A activity in the HEK assay to reductions in male kidney IC GL-3 (sensitivity 1.0, specificity 1.0, positive predictive value 1.0, negative predictive value 1.0), male plasma lyso-Gb3 (respectively: 1.0, 1.0, 1.0, 1.0), and male and female plasma lyso-Gb3 (respectively: 0.93, 0.69, 0.84, 0.85).

269 mutations are amenable to migalastat to date. The applicant agreed to include the reference tables listing all amenable and non amenable mutations tested and reviewed by the CHMP in SmPC section 5.1. The reference tables in SmPC section 5.1 will also be published on a specific website managed by the applicant. Considering the high number of mutations, from a clinical perspective, a reference to a website including a search tool is considered very helpful, in support of the SmPC information to allow Health Care Providers to search for the patient mutation and find out whether a specific GLA mutation has been classified as amenable to treatment with migalastat. From a legal and regulatory perspective, the principle of a website to provide the list of amenable and non amenable mutations listed in the latest approved SmPC with a search tool is considered to be acceptable, provided that the website will only duplicate information already present in the SmPC and that no promotional content should be provided in the website. (see discussion later in the report)

As new mutations are tested, a variation will be submitted to CHMP for review and update of the tables listed in section 5.1 of the SmPC. Following approval, the website will be updated.

2.4.5. Conclusions on clinical pharmacology

The mode of action of migalastat enabling galactosidase to be partially functional in the lysosome has been demonstrated.

Patients included in the pharmacologic studies encompassed the whole spectrum of Fabry disease (classic and non-classical). Results from the PD studies showed that migalastat increased α-Gal A activity in peripheral blood mononuclear cells (PBMCs) and corresponding decreases in plasma GL-3 were observed in patients with migalastat-responsive mutations.

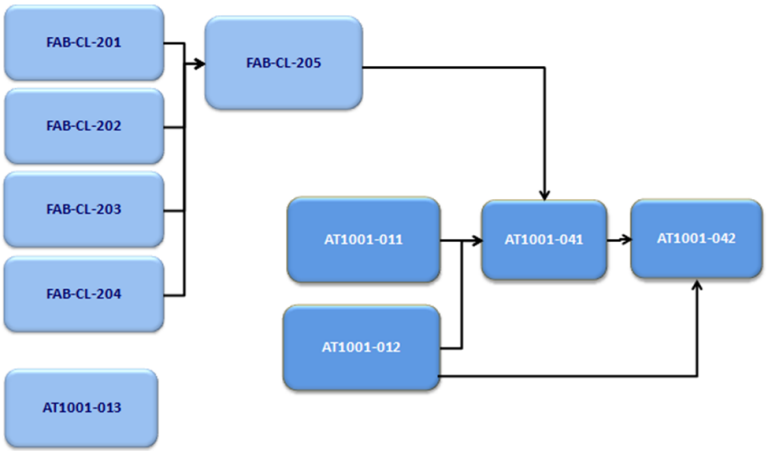
Mean renal function was near normal at baseline with some patients suffering from mild to severe renal insufficiency. Migalastat did not show improvements of renal function expressed as an increase of eGFR.

Based on the phase 2 studies migalastat 150 mg QOD was chosen as the optimum dosage for which an increase of α-GAL A activity and reduction of GL-3 was optimal and as such this dosage was considered to be an acceptable dose regimen to be evaluated in the phase 3 clinical program.

2.5. Clinical efficacy

Figure 2 depicts the phase 2 and phase 3 clinical programme.

Figure 2: Overview of Migalastat Phase 2 and 3 Studies



2.5.1. Dose response studies

The phase 2 open label studies FAB-CL-201 to FAB-CL-204 were conducted in 27 patients (9 female and 18 male patients) with Fabry disease, all of whom received migalastat. In phase 2 study FAB-CL-205 14 males and 9 females Fabry patients were included. These studies are discussed in the clinical pharmacology section.

Based on these studies migalastat 150 mg QOD was chosen as the optimum dosage for which an increase of α-GAL A activity and reduction of GL-3 was optimal.

One open-label Phase 2 study (AT1001-013) was performed in 20 patients with Fabry disease that received migalastat co-administered with agalsidase. The objective of this study was to evaluate the interaction between migalastat and agalsidase. This study is discussed in the pharmacokinetic part of this report as clinical efficacy was not studied only the increase of enzyme activity in WBC.

It is noted that migalastat is not intended for concomitant use with ERT and the applicant is considering performing a phase 2 repeated dose study co-administering migalastat with ERT. This might be a valuable treatment option in patients that are considered non-amenable to migalastat and those that have a marginal response to ERT, therefore, such study is encouraged.

Efficacy of migalastat was investigated in two pivotal studies (AT1001-011 and AT1001-012) in 124 patients with Fabry disease, of whom 70 received migalastat, 24 received active comparator (15 of whom later received migalastat), and 33 received placebo (30 of whom later received migalastat). Two Phase 3, non-comparative, open-label, long-term extension studies (AT1001-041, AT1001-042), in which 67 patients received migalastat in AT1001-041 and 17 patients received migalastat in AT1001-042 as of 13 October 2014. Study AT1001-042 is an ongoing study in which all patients will be enrolled from study AT1001-012 or AT1001-041. The last patient is expected to be enrolled into study AT1001-042 in the first quarter of 2016. The study reports of AT1001-041 and AT1001-042 are not included in the dossier. However relevant safety data and data on renal and cardiac efficacy at 30-months were included in the application . This will be sufficient for further assessment of maintenance. However the final study reports should be submitted upon completion.

2.5.2. Main studies

2.5.2.1. Study AT1001-011 (Placebo controlled)

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

Methods

Study AT1001-011 consisted of two stages and a 12 month open-label extension (Figure 3). Stage 1 consisted of Screening (up to 2 months) and a 6-month, double-blind, randomised, placebo-controlled treatment period that compared the safety and PD of migalastat versus placebo in migalastat-responsive patients with Fabry disease who were ERT-naïve or had not received ERT for at least the 6 months before Screening. Patients were randomised in equal proportions to receive either oral migalastat (administered at 150 mg QOD) or matching placebo. Randomisation was stratified by sex.

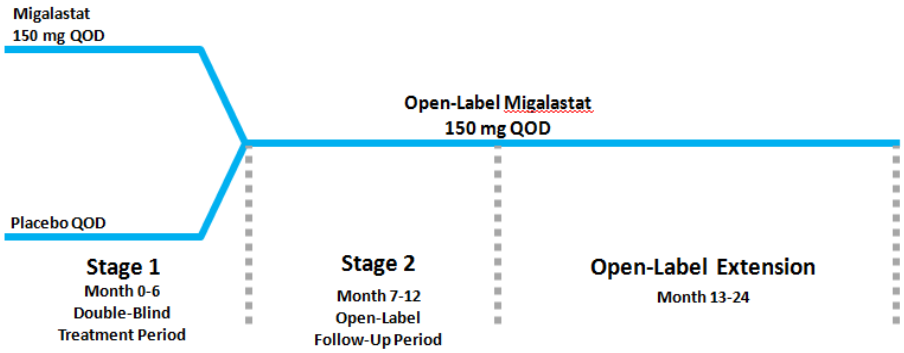


Figure 3: AT1001-011: Study Design

- **Study participants**

The most important inclusion criteria were: confirmed diagnosis of Fabry Disease, patients over 16 years of age; naïve to ERT or had not received ERT for at least the 6 months before Screening; a confirmed GLA mutation shown to be responsive to migalastat in the HEK-assay; Urine GL-3 ≥4 times the upper limit of normal (ULN) at Screening. The diagnosis algorithm was not part of the study protocol therefore diagnosis should be further justified in some patients

- **Treatments**

  Migalastat (150 mg QOD) taken orally in 150-mg capsules.

  Placebo QOD taken orally in matching capsules.

Duration of Treatment

Study AT1001-011 consisted of two stages (figure 2 above):

- Stage 1: 6-month double-blind

- Stage 2: 6-months open label part
- Open label extension part: 12 months

- **Objectives**

The primary objective in Stage 1 was to compare the effect of migalastat versus placebo on kidney GL-3 inclusions assessed by histological scoring of the number of GL-3 inclusions per interstitial capillary (IC).

- **Outcomes/endpoints**

The primary endpoint was the proportion of patients (ITT population) with a ≥50% reduction from baseline to month 6 in the average number of GL-3 inclusions per IC; secondary endpoints were the percent change from baseline in GL-3 inclusions per IC and percent ICs with zero GL-3 inclusions. Other secondary endpoints included urine GL-3; $eGFR_{CKD\text{-}EPI}$, $mGFR_{iohexol}$; $eGFR_{MDRD}$; and 24-h urine protein, albumin, and creatinine. Cardiac parameters were assessed by echocardiography (ECHO). Patient-reported outcomes for quality of life, pain, and gastrointestinal symptoms were assessed using the SF-36v2, the Brief Pain Inventory short form (severity component; BPI), and the Gastrointestinal Symptom Rating Scale (GSRS).

In Stage 2, all patients received migalastat 150 mg QOD for up to 6 months. Patients who received placebo during Stage 1 were switched to migalastat (placebo-migalastat group) and patients who received migalastat during Stage 1 continued on migalastat (migalastat-migalastat group). Patients completing both Stage 1 and Stage 2 were eligible to participate in a 12-month, open-label migalastat extension phase (study AT1001-041). The efficacy endpoints evaluated for Stage 2 and the open-label extension included $eGFR_{CKD\text{-}EPI}$, $mGFR_{iohexol}$, $eGFR_{MDRD}$, LVMi, SF-36v2, BPI short form, GSRS, mean number of GL-3 inclusions per IC (Stage 2), and plasma lyso-Gb_3.

- **Sample size/randomisation**

A total of 180 patients consented to participate and 67 patients (ITT population) were randomised in study AT1001-011. Thirty-four patients were randomised to migalastat (12 males and 22 females; mean age of 40.0 ± 13.3 years) in Stage 1, and 33 were randomised to receive placebo (12 males and 21 female patients; mean age of 44.5 ± 10.2 years).

- **Statistical methods**

The statistical analyses were based on the Stage 1 SAP, the Stage 2 SAP, and the Plasma Lyso-Gb3 Exploratory Endpoint SAP. The Stage 2 SAP was finalized prior to receipt of the Stage 2 and open-label extension datasets. The Stage 2 SAP included post hoc analyses of Stage 1 data and prespecified analyses of Stage 2 and open-label extension data.

Analysis Populations–Stage 1 SAP

The Intent-to-Treat (ITT) Population included all randomized patients. The Modified Intent-to-Treat (mITT) Population included all randomized patients who had received at least 1 dose of study drug and underwent a renal biopsy at both Baseline (Visit 1) and Month 6 (Visit 4). The Per Protocol (PP) Population included all randomized patients who had received at least 1 dose of study drug, had both the Baseline (Visit 1) and Month 6 (Visit 4) kidney biopsy performed, and had no major protocol violations. The Safety Population included all randomized patients who received at least 1 dose of study drug.

Analysis Populations–Stage 2 SAP

In addition to the mITT, ITT, and Safety Populations, the analysis populations specified in the Stage 2 SAP included the Stage 2 Population and the Open-Label Extension Population. The Stage 2 Population

included all randomized patients who completed Stage 1 and continued in the study for Stage 2. The Open-Label Extension Population included all randomized patients who completed Stage 2 and continued in the open-label extension.

The primary endpoint analysis for Stage 1 compared the proportion of successes (i.e., percentage of patients with a ≥ 50% reduction from Baseline [Visit 1] to Month 6 [Visit 4] in the average number of IC GL-3 inclusions) in each treatment group using the exact Cochran-Mantel-Haenszel test stratified by sex. A p-value < 0.05 (2-sided) was required to conclude a statistically significant treatment effect. The frequency and percentage of successes for each group were calculated and presented.

The superiority design is acceptable and based on results known from patients with "classical" Fabry disease this is acceptable. As the included patients are considered atypical patients the beneficial effect to be expected might be lower. As no formal study size calculation is made in these rare disease, there might be an increased risk of a type II error.

- **Results**

Baseline data/number analysed

A total of 64 patients completed Stage 1: 34 in the migalastat group and 30 in the placebo group; 63 of the 64 entered Stage 2 (33 patients in the migalastat-migalastat group and 30 patients in the placebo-migalastat group).

A total of 31 patients in the migalastat-migalastat group and 29 patients in the placebo-migalastat group completed Stage 2. Of the patients who completed Stage 2, 29 in the migalastat-migalastat group and 28 in the placebo-migalastat group entered the open-label extension. Two patients in the migalastat-migalastat group discontinued during the open-label extension (one due to pregnancy, and one who was lost to follow-up); one patient in the placebo-migalastat group withdrew consent. Study drug compliance was high (98 to 99%) and similar between treatment groups in all stages of the study.

The two groups were comparable with respect to baseline disease characteristics (seeTable 4). A total of 17/67 (25.4%) of patients had previously been treated with ERT and 19/67 were receiving ACEIs, ARBs, or RIs at baseline (6/34 of the migalastat group and 13/33 of the placebo group). An additional post hoc analysis was submitted further elucidating the baseline disease severity. Of the patients included in study 011 46 out of 67 patients (60%) had more than 2 organ systems involved at the start of treatment (i.e. migalastat).

The applicant provided the individual patient data (disease symptoms, lyso-Gb3, LVMi, eGFR, GLA mutation α-Gal A activity). No baseline plasma GL3 was provided by the applicant. Baseline α-Gal A activity in males migalastat (n=9) 1.4 ± 3.1 nmol/h/mg and placebo (n=9) 0.5 ± 0.5 nmol/h/mg. The individual patient data (amenable patients only) was used to confirm the diagnosis and treatment eligibility conform the requirements as published by Biegstraaten *et al*. (2015). According to the publication of Smid[3]. the gold standard is a biopsy demonstrating GL-3 inclusions (zebra bodies) in the cell. In study 011, 60/67 patients in the ITT population (mITT 45/50 patients) had a renal biopsy and average number of GL-3 inclusions per IC varied from 0.02 to 5.96 (min, max), confirming the diagnosis of FD in these patients. For all patients the diagnosis could be confirmed.

Analysis of the database for study 011,showed that for eGFR, LVMi, the various time points were adequately entered. For lyso-Gb3, the data points were less complete. This is due to the addition of lyso-Gb3 as important endpoint during the study and before data lock point.

[3] Smid BE, Van der Tol L, Cecchi F, Elliott PM, Hughes DA, Linthorst GE, et al. Uncertain diagnosis of Fabry disease: consensus recommendation on diagnosis in adults with left ventricular hypertrophy and genetic variants of unknown significance. Int J Cardiol. 2014;177(2):400–8.

The applicant diagnosed 14 male patients in this study as having classic Fabry disease. For further details, please refer to paragraph Clinical studies in special populations (subparagraph *Male patients with classical FD*).

The mean $eGFR_{CKD-EPI}$ at baseline was 94.6 ml/min/1.73 m^2 (95.4 in the migalastat group and 93.8 in the placebo group) which are considered to be normal GFR values. Based on urine protein:creatinine ratio (migalastat 31.9 ± 44.2 mg/mmol; placebo 41.4 ± 55.1 mg/mmol) it may be concluded that these patients are considered to have normal renal function but with proteinuria (CKD stage 1 or 2 (The Renal Association)). This is also reflected by the fact that 19/67 patients received concomitant angiotensin converting enzyme inhibitor (ACEI); angiotensin receptor blocker (ARB) or a renin inhibitor (RI).

Table 4: Baseline disease Characteristics AT1001-011 (Safety Population)

		Treatment Group		
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
	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 (33)
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 (28)
Number of subjects who were previously on ERT	n (%)	5 (15)	12 (36)	17 (25)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; $eGFR_{MDRD}$ = estimated glomerular filtration rate assessed by the Modification of Diet in Renal Disease equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; RI = renin inhibitor; SAP = statistical analysis plan.

Notes: The $eGFR_{MDRD}$ is calculated as GFR = 175 x (1/Serum Creatinine in mg/dL1.154) x (1/Age in years0.203) x 0.742 [if female] x 1.212 [if black].

24-hour urine collection start and stop times were recorded. If collection times were less than or greater than 24 hours, urine parameters were standardized to a 24-hour collection period as per the SAP.

Urine albumin:creatinine ratio is calculated as mg of albumin per 24-hour urine collection/mmol creatinine per 24-hour urine collection.

- **Primary Efficacy Endpoints**

The primary endpoint in Stage 1 (month 6) was the kidney IC GL-3 responder analysis (defined as ≥50% reduction from baseline in the average number of GL-3 inclusions per IC). In all randomised patients (ITT), a response was seen in 13/34 of patients in the migalastat group and 9/33 of patients

in the placebo group (p=0.3), indicating that most patients did not achieve the >50% reduction from baseline. Based on the responder analysis, it is concluded that the primary endpoint has **not** been met.

The mean percent change in the average number of GL-3 inclusions per IC in the ITT population was -8.0 ± 105.3 for migalastat versus 13.0 ± 90.5 for placebo (p=0.097).

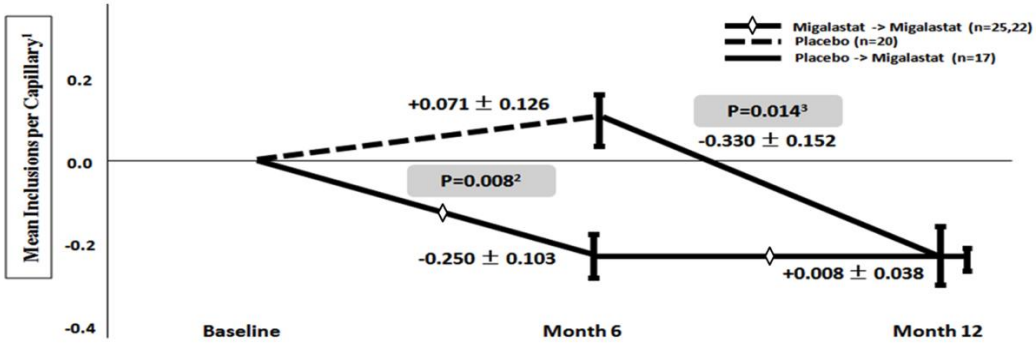
For measurement of GL-3 inclusions in the kidney interstitial capillaries each patient had a kidney biopsy performed at baseline, at month 6 and month 12. Two pathologists scored total GL-3 inclusions per 300 interstitial capillaries from which the mean was calculated. According to the MAH, reduction in kidney IC GL-3 is a recognised treatment outcome and was the basis for initial approval of Fabrazyme (Eng *et al.,* 2001). It was noticed that there was high variability in scoring of GL-3 inclusions by the observers. Considering the intra and inter observer reliability, it was stated that most results are between 2SD. This is per definition true, as ±2SD encompasses 95.4% of the observations assuming a normal distribution. Based on this information, no conclusions on reproducibility can be drawn.

- **Secondary endpoints**

GL-3 Inclusions per Kidney Interstitial Capillary - Change from baseline.

A post hoc analysis of Stage 1 results was performed in the 50/67 patients with amenable mutations. The change from baseline analysis demonstrated that 6 months treatment with migalastat was associated with a greater reduction in the average number of GL-3 inclusions per IC that was statistically significant compared to placebo: -0.250±0.103 versus +0.071±0.126, respectively; p=0.008; shown below in Figure 4. Based on literature, a qualitative correlation between GL-3 inclusions and clinical outcome can be assumed. However, a quantitative relation cannot be established. Therefore, the GL-3 inclusions in renal tissue cannot be used for the prediction of the clinical benefit of migalastat.

Figure 4: AT1001-011: Change from Baseline in the Mean Number of GL-3 Inclusions per Kidney Interstitial Capillary



[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 interstitial capillary. 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 least squares 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.*

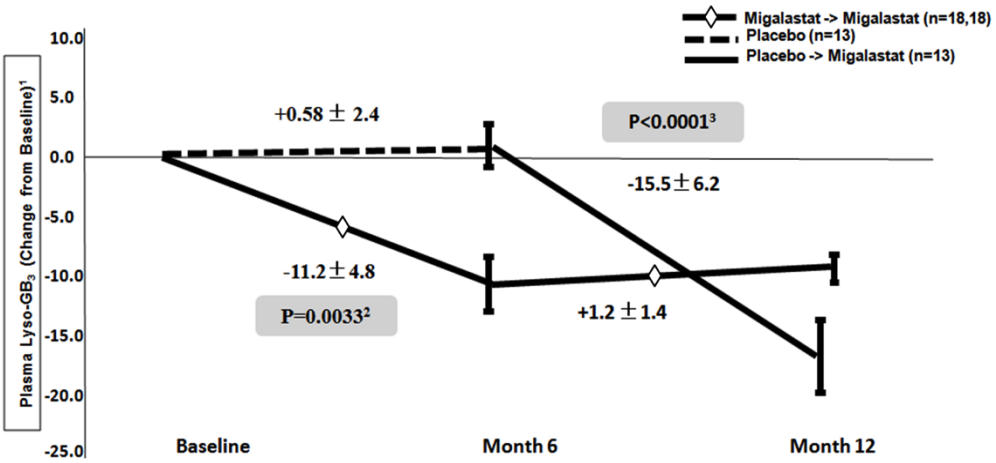
In patients switching from placebo to migalastat in Stage 2 (the placebo-migalastat group, mITT), a statistically significant reduction in the mean number of GL 3 inclusions per IC (± SEM) was observed (0.330±0.152; p=0.014), thus replicating the IC GL-3 reduction seen in the cohort who received migalastat in Stage 1 (Figure 4). The reduction in the mean number of GL 3 inclusions per IC remained stable in the migalastat-migalastat group (patients who had received migalastat in Stage 1 followed by an additional 6-month treatment with migalastat in Stage 2). After 6 months of treatment with migalastat no further improvement of GL-3 inclusions could be observed.

Though a tertiary endpoint the least squares mean difference for the change in percentage of kidney IC with zero GL-3 inclusions was 7.3%, in favour of migalastat versus placebo (p=0.042). In patients with non-amenable mutations, no difference between migalastat and placebo in the mean number of GL-3 inclusions was observed.

Plasma Lyso-Gb3

Plasma lyso-Gb3 at baseline was 47.3 ± 62.2 nmol/l in the migalastat group and 41.8 ± 39.1 nmol/l in placebo group. After 6 months of treatment, the lyso-Gb3 concentration in the migalastat group was 36.1 ± 45.9 nmol/l in the placebo group this was 42.2 ± 43.1 nmol/l (Figure 5). The reduction in plasma lyso-Gb_3 was maintained when patients randomised to migalastat in Stage 1 continued for an additional 6 months of migalastat treatment in Stage 2. The patients switching from placebo to migalastat in Stage 2, followed a similar trend as observed for the patients on migalastat in stage 1.

Figure 5: AT1001-011: Absolute Change in Plasma Lyso-Gb_3 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] *Analysis of covariance (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.*

In study 011, male patients with multi-organ failure at baseline higher lyso-Gb3 levels (n=5; 136.6 ± 50.15 nmol/l) compared to male patients who did not have multi-organ failure (n=13; 12.9 ± 5.71 nmol/l) were observed. As expected the reduction of lyso-Gb3 level was more pronounced in male patients with multi-organ failure (-29.4% versus -8.1%). Similar trend was observed when patients previously on placebo were included in the analysis (open label part of study 011).

Taking the renal severity into account, no conclusion can be drawn due to the limited numbers. Numerically, migalastat showed larger reduction of lyso-Gb3 over placebo. Similar results were seen

when stratified by male and female patients with baseline plasma lyso-Gb3 levels for Males > 51 nmol/L + Females > 1.19 nmol/L versus Males < 51 nmol/L + Females < 1.19 nmol/L (thresholds for male classic FD and female FD patients (Smid *et al., 2015*)).

Renal Function

Baseline $eGFR_{CKD-EPI}$ values were migalastat group 95.4 ± 28.5 ml/min/1.73 m^2 and placebo 93.8 ± 20.6 ml/min/1.73 m^2. These are considered normal values for age.

After 6 months of treatment with migalastat 150 mg QOD eGFR values increased (1.8 ± 2.3 ml/min/1.73 m^2) whereas in the placebo treated group eGFR declined (-0.3 ± 7.5 (ml/min/1.73 m^2). Analysis of the GFR results in Stage 2 of AT1001-011 showed that renal function remained stable over 18 to 24 months of migalastat treatment (24 months in the patients treated with migalastat in Stage 1, 18 months in the patients treated with placebo in Stage 1).

These results, across all three methodologies used, demonstrate stabilisation of renal function in migalastat-treated patients. The change in renal function in migalastat-treated patients is comparable to the annual decline in renal function in healthy adults, [a change in eGFR of -1 mL/min/1.73 m^2/year (Stevens et al., 2006)]. The data also suggests that renal function remains stable up to 36 months.

A comprehensive survey of published reports of renal function in untreated patients with Fabry disease revealed annual changes in eGFR (mL/min/1.73 m^2) between -2.2 and -12.2 (Eng *et al.,* 2001; Schiffmann *et al.*, 2001; Branton *et al.*, 2002; Schwarting *et al.*, 2006; Tahir *et al.*, 2007; Tennankore *et al.*, 2007; Schiffmann *et al.*, 2009; West *et al.*, 2009; Wanner *et al.*, 2010).

Table 5: AT1001-011: Annualised GFR Change at Month 18/24 (mITT-amenable Population).

GFR Method	N	Mean (±SEM) [95% CI]
$eGFR_{CKD-EPI}$	41	-0.30 (0.66) [-1.65, 1.04]
$eGFR_{MDRD}$	41	+0.79 (1.03) [-1.28, 2.87]
$mGFR_{iohexol}$	37	-1.51 (1.33) [-4.20, 1.18]

Glomerular filtration rate (GFR) measured in mL/min/1.73 m^2/year.

$eGFR_{CKD-EPI}$=estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation; $eGFR_{MDRD}$=estimated glomerular filtration rate based on the Modification of Diet in Renal Disease equation; $mGFR_{iohexol}$ =measured glomerular filtration rate; mITT-amenable=patients with amenable mutations in the modified intent to treat population; N=number of patients with data; SEM=standard error of the mean.

The long-term effect of migalastat on renal function was assessed by evaluating annualised change in $eGFR_{CKD-EPI}$ in patients who continued from AT1001-011 into extension study AT1001-041. In these patients, $eGFR_{CKD-EPI}$ remained stable over an average of 38 months (minimum 18 months, maximum 55 months (n=1)). The annualised rate of change over this period was -0.77 (95% CI: -1.94, 0.39) mL/min/1.73 m^2/year. Post hoc data showed similar trend for the subgroups of patients with ≥2 organ systems (n=36; -0.8 ± 3.8) involved and patients with mutations associated with classic phenotype (n=24; -0.6 ± 4.5). Further analysis indicated also that the GFR remained stable independent of the renal function at baseline, age and gender.

Cardiac parameters

LVMi

Baseline LVMi values in the migalastat group (n=30) was 91.7 ± 28.0 g/m^2 and placebo (n=29) was 97.7 ± 32.2 g/m^2. These are considered normal values for age (Cain *et al.*, 2009). The long-term

effect of migalastat on cardiac parameters was assessed by evaluating LVMi in patients who continued from AT1001-011 into extension study AT1001-041 (36 months in the patients treated with migalastat in AT1001-011 Stage 1, and 30 months in the patients initially treated with placebo in AT1001-011 Stage 1). These patients demonstrated further reductions in LVMi up to Month 30/36, beyond the effect seen at Month 18/24 (Table 6). This reduction was larger in patients with LVH at baseline. Post hoc data showed similar trend for the subgroups of patients with ≥2 organ systems (n=4; -30.0 ± 17.5) involved and patients with mutations associated with classic phenotype (n=2; -21.9 ± 4.2).

Table 6: LVMi (g/m^2) Change from Baseline up to Month 30/36 after Migalastat Treatment in Studies AT1001-011 and AT1001-041.

Statistic	All Patients (N=48)	LVH at Baseline (N=11)
Baseline		
N	44	11
Mean (SD)	96.5 (32.9)	138.9 (37.1)
Change at Month 18/24		
n	27	8
Mean Change (95% CI)	-7.7 (-15.4, -0.01)	-18.6 (-38.2, 1.0)
Change at Month 30/36		
n	15	4
Mean Change (95% CI)	-17.0 (-26.2, -7.9)	-30.0 (-57.9, -2.2)

Additional data were submitted for LVMi during the assessment and showed that mean changes 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.

Further, the descriptive statistics suggest a stronger effect in male patients compared to female, younger patients appear to be showing more improvement than elderly patients. However, there are largehe variability, prohibiting any definite conclusions.

Other cardiac parameters

Regarding other cardiac parameters based on echocardiography like in study AT1001-012, LV ejection fraction, fractional shortening, systolic and diastolic functional grades were generally normal at baseline and no clinical significant changes were noted.

Gastrointestinal Symptoms (GSRS)

The GSRS was assessed in AT1001-011 but not in AT1001-012. The GSRS outcomes in AT1001-011 indicate the benefit of migalastat in improving the gastrointestinal symptoms in Fabry disease (

Table 7).

Table 7: Changes in the Gastrointestinal Symptoms Rating Scale

GSRS	Diarrhoea		Reflux		Indigestion		Constipation		Abdominal Pain	
Treatment Group	Migalastat	Pbo	Migalastat	Pbo	Migalastat	Pbo	Migalastat	Pbo	Migalastat	Pbo
Mean Baseline Values (n)										
All Patients	2.3 (28)	2.1 (22)	1.4 (28)	1.4 (22)	2.5 (28)	2.4 (22)	1.9 (28)	2.0 (22)	2.1 (28)	2.3 (22)
Patients with Symptoms at BL	3.2 (17)	3.1 (11)	2.1 (10)	2.6 (6)	2.8 (23)	2.7 (19)	2.5 (17)	2.4 (15)	2.4 (22)	2.9 (15)
Change from Baseline to Month 6 (Stage 1, Double-blind)[a]										
All Patients	**-0.3**[b]	+0.2	-0.1	+0.2	-0.1	-0.1	+0.1	+0.2	0.0	0.0
Patients with Symptoms at BL	-0.6	+0.2	**-0.6**[b]	+0.6	-0.2	-0.2	+0.2	+0.1	-0.1	-0.1
Mean Change (95% CI) from Baseline (Migalastat) or Month 6 (Placebo) to Month 24 (OLE Migalastat)										
All Patients	**-0.5 (-0.9, -0.1)**[c]		-0.2 (-0.5, +0.2)		**-0.4 (-0.7, -0.0)**[c]		**-0.4 (-0.7, +0.0)**[d]		-0.2 (-0.5,+0.1)	
Patients with Symptoms at BL	**-1.0 (-1.5, -0.4)**[c]		-0.6 (-1.5, +0.2)		**-0.5 (-0.8, -0.1)**[c]		**-0.5 (-1.1, +0.0)**[d]		-0.2 (-0.6, +0.1)	

BL = Baseline; GSRS = Gastrointestinal Symptoms Rating Scale; OLE = open-label extension; Pbo = placebo | Cell shading and bold font of results indicates significant or borderline significant changes from baseline. [a] Least squares means for change from baseline; [b] $p \leq 0.05$ using ANCOVA; [c] Statistically significant based on 95% CIs; [d] Borderline statistically significant based on 95% CIs. | Sources: AT1001-011 CSR Table 14.2.12.1b-1, Table 14.2.12.1b-3, Table 14.2.12.1c-1, and Table 14.2.12.1c-3.

White blood cell α-Gal A Activity

In AT1001-011, among males with amenable mutations, increases of ~2.6 nmol/h/mg in α-Gal A activity were maintained through Month 24. As expected, PBMC α-Gal A activity did not change for male patients with non-amenable mutations throughout the study.

Patient-Reported Outcomes (SF-36v2 and BPI)

In the AT1001-011, comparison of migalastat and placebo in the SF-36v2, for patients with amenable mutations and abnormal baseline values, numerical improvements were found across the study (24 months of treatment for the migalastat-migalastat group and 18 months of treatment for the placebo-migalastat group) for the vitality subscale (mean increase: 4.0) and the general health domain (mean increase: 4.5).

2.5.2.2. Study AT1001-012

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

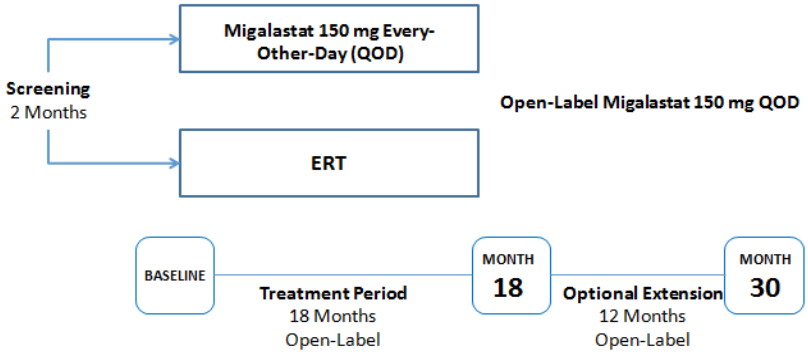
Methods

Study AT1001-012 is an active-controlled, randomised, open-label multinational study for which the applicant has received SA. The study was designed to only compare the efficacy and safety of oral migalastat to intravenous ERT in patients with Fabry disease who were receiving ERT prior to study entry and who had migalastat-responsive *GLA* mutations(.. The study was not powered to demonstrate non inferiority, e.g. normal statistics were used. Strictly spoken, the study is considered a "randomised

stop study" in which patients quit ERT treatment and start with a new intervention in this case oral migalastat.

The applicant received SA on the conduct of the study (EMEA/CHMP/SAWP/540686/2008). The CHMP agreed with the applicant that due to small number of available patients it would be difficult to recruit treatment naïve patients. The use of both Replagal (agalsidase α) and Fabrazyme (agalsidase ß) as comparative ERT was agreed upon. Although it would have been preferable to have only one active comparator, this would have reduced the number of patients to be included. The study was structured in two periods (Figure 6). The first period was an 18-month open-label treatment in which ERT-experienced patients were randomised 1.5:1 to switch from ERT to migalastat (150 mg QOD) or continue with ERT. Randomisation was stratified by sex and proteinuria (<100 mg/24 h; ≥100 mg/24 h). The second period is a 12-month open-label extension that is currently ongoing. Patients who received migalastat during the first period continued to receive migalastat in this extension. Patients who received ERT during the first period discontinued ERT and switched to migalastat.

Figure 6: AT1001-012: Study Design



- **Study participants**

Most important inclusion criteria were: patients with confirmed Fabry disease over 16 years of age; ERT treatment initiated at least 12 months prior visit 2; a confirmed GLA mutation shown to be responsive to migalastat in the HEK-assay; Glomerular filtration rate (GFR) ≥30 mL/min/1.73 m^2.Diagnosis was made by the treating physician and was considered plausible based on the available information in the dossier. In addition, it was demonstrated that that all patients were eligible for treatment in accordance with the recent treatment guideline (Biegstraaten *et al*., 2015).

- **Treatments/duration of treatment**

The ERT used as active controls were agalsidase alfa (Replagal) and agalsidase beta (Fabrazyme). Throughout the course of this study, commercially available agalsidase for intravenous infusions was prescribed by the patient's treating physician and was administered in accordance with the approved prescribing information.

Patients were enrolled in period 1 of the study receiving either migalastat or ERT for 18 months. After finalising period 1, patients could continue in the extended phase (period 2) for an additional 12 months.

- **Objectives**

The primary objective of this study was to compare the efficacy and safety migalastat to ERT in patients with Fabry disease who were currently receiving ERT and who had migalastat-responsive mutations in GLA, the gene that encodes α-galactosidase A (α-Gal A).

- **Sample size**

Approximately 50 patients were planned to be enrolled. A total of 68 patients consented to participate, and 60 patients were randomized. Of these patients, 36 were randomized to the migalastat group, and 24 were randomized to the ERT group. Efficacy was analysed in the modified Intent-to-Treat (mITT) Population, which consisted of 52 patients; safety was analysed in the Safety Population (all patients who received at least 1 dose of study drug), which consisted of 57 patients.

- Randomisation

Eligible patients were randomized in a 1.5:1 ration to either to ERT treatment and start treatment with migalastat or to continue on ERT. Randomization was stratified by sex and proteinuria (<100 mg/24 h; ≥100 mg/24 h).

- **Statistical methods**

The Intent-to-Treat (ITT) Population included all randomized patients. The mITT Population included all randomized patients with mutations amenable to migalastat in the validated Good Laboratory Practice (GLP) HEK assay that received at least 1 dose of study drug and had both the baseline and a post baseline efficacy measure of $mGFR_{iohexol}$ and a post baseline measure of $eGFR_{CKD\text{-}EPI}$. Efficacy analyses were performed using the mITT Population. Each patient was analysed according to his or her original randomized treatment group.

The Per Protocol (PP) Population included all patients in the mITT Population who completed the 18-month randomized treatment period and did not have the following protocol violation: change in the use of ACEIs, ARBs, or renin inhibitors (RIs) during the 18-month treatment period. Analyses using the PP Population analysed patients according to the actual treatment received. The Safety Population included all randomized patients who received at least 1 dose of migalastat or ERT. All safety analyses were performed using the Safety Population and analysed patients according to the actual treatment received.

The use of a non-inferiority design for the comparative study was discussed during scientific advice (EMEA/CHMP/SAWP/540868/2008), CHMP was in the view that descriptive statistics could only be accepted if an active control and a historical comparison with placebo regarding clinical endpoints if the study duration would be sufficiently long. No historical control data in atypical Fabry patients was submitted. The proposed study is considered a "randomized stop-study", in which patients are switched from ERT to migalastat without a period of being untreated. So it will be difficult by definition to demonstrate clinical significant differences between the two interventions. Due to the lack of a placebo arm in this study the through effect of migalastat on GFR, LVMi and other parameters cannot be concluded. The mITT Population included all randomized patients with mutations amenable to migalastat in the validated Good Laboratory Practice (GLP) HEK assay that received at least 1 dose of study drug and had both the baseline and a post baseline efficacy measure of $mGFR_{iohexol}$ and a post baseline measure of $eGFR_{CKD\text{-}EPI}$. Efficacy analyses were performed using the mITT Population.

Both treatments were declared comparable as a >50% overlap of the 95% confidence intervals (CIs) and a difference of least squares (LS) mean annualized rate of change no greater than 2.2 mL/min/1.73 m^2 between the 2 treatment groups could be demonstrated.

- **Outcomes and estimation**

Annualized Change in GFR (Primary Efficacy Parameters)

The primary efficacy parameters were the annualized rates of change in both $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$.

The CKD-EPI based on cystatin C alone underestimates GFR, whereas the CKD-EPI formula based on creatinine alone overestimates GFR in comparison to mGFR. The combination of the two markers into the same formula gives the most accurate estimate of mGFR. Therefore, the CHMP proposed to use the CKD-EPI formula based on creatinine and cystatin C serum markers as an additional secondary end point.

Change from baseline to 18 months for $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ were taken as secondary endpoints.

Additional subgroup analysis was performed by the applicant.

- **Results**

Number analysed

A total number of 68 patients were enrolled into the study and 60 patients were randomised. Out of these only 56 amenable patients were analysed as four (4) patients were post-hoc considered as non-amenable.

The original data files submitted by the applicant contain evaluable data for 57 patients (53 amenable and 4 non-amenable) as three patients did not receive the study drug. Thirty-six (36) patients received migalastat and twenty-one (21) received ERT.

Analyses were performed on the mITT population (34 patients in the migalastat group and 18 patients in the ERT group) or Safety Population (36 patients in the migalastat group and 21 patients in the ERT group).

All efficacy analyses were carried out using the mITT Population. The analyses of the primary efficacy parameters were also performed on the ITT and PP Populations as supportive analyses.

No major protocol deviations were made.

With respect to the HEK analysis this was considered GLP compliant after patients were already randomized. Four patients initially randomized to have amenable mutations were considered non-amenable based on GLP-HEK assay.

Baseline data

Some patients had genetic mutations for which the relation with disease activity is disputed (for example A143T).

The submitted individual patient data show that about all data points for eGRF were entered in the CRF in the controlled phase. For LVMi up to 22% of the data-points were not entered for a given time point in the controlled phase of the study, while for lyso-Gb3 up to 40% of the data-points was missing for a given time point in the controlled phase of the study. In the extension phase the percentage of data-points not entered in the CRF varied from 8% (eGFR) to 52% (lyso-Gb3).

Demographics were comparable in both treatment groups. Patients in the migalastat group (16 males and 20 females) were 50.5 ± 13.76 years and in the ERT group (9 males and 12 females) 46.3 ± 14.9 years. Five patients were ≥65 years up to 72 years of age (migalastat n=3; ERT n=2). Most patients were receiving agalsidase α (37/57) at baseline; 19/57 patients received agalsidase ß. For one patient,ERT at baseline was not collected. A total of 27/57 of patients was receiving ACEIs, ARBs, or

RIs. Medical history and prior and concomitant medication were comparable between the groups. In this comparative study, about 70% of the patients had multiple organ involvement this suggests a reasonable disease burden for most patients.

Additional post hoc analysis performed by the applicant showed that of the patients included in study 012, 40 out of 56 patients (70%) had more than 2 organ systems involved prior the start of ERT.

Table 8: Baseline Characteristics (Safety Population) (AT1001-012).

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 m²)	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 m²)	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)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; eGFRCKD-EPI = estimated glomerular filtration rate assessed by the Chronic Kidney Disease Epidemiology Collaboration equation; ERT = enzyme replacement therapy; GFR = glomerular filtration rate; GLA = gene encoding α-galactosidase A; GLP = Good Laboratory Practice; HEK = Human Embryonic Kidney; mGFRiohexol = measured glomerular filtration rate as assessed by plasma clearance of iohexol; RI = renin inhibitor.
Notes: Percentages are based on the number of patients in the Safety Population.
The ERT at Baseline was not collected for 1 patient in the migalastat group.
Baseline for the migalastat group was defined as the last non missing measurement taken prior to the first migalastat dose date (including unscheduled assessments). In the case where the last non missing measurement and the first dose date coincided, that measurement was considered pre-Baseline. For the ERT group, Baseline was defined as the last day prior to or equal to the first dose of ERT, where the first dose was defined as the dose of ERT after randomization date (on Visit 3).
$eGFR_{CKD-EPI}$ is calculated as GFR = 141 x min(Scr/κ, 1)α x max(Scr/κ, 1)-1.209 x 0.993Age 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.
24-hour urine collection start and stop times were recorded. If collection times were less than or greater than 24 hours, urine parameters were standardized to a 24-hour collection period.
Amenable GLA mutations categorized by the GLP HEK assay.

Based on the original data files the total number of patients (amenable as well as non-amenable) available for analysis was 56 patients.

The mean $eGFR_{CKD-EPI}$ at baseline was for migalastat: 89.6 ± 22.2 ml/min/1.73 m^2, and 95.8 ± 19.2 ml/min/1.73 m^2 in the ERT group. Mean $mGFR_{iohexol}$ was 82.4 ± 18.1 ml/min/1.73 m^2 for migalastat and 83.6 ± 23.9 ml/min/1.73 m^2 for ERT.

All patients had proteinuria at baseline based on the urine protein: creatinine ratio (migalastat group 19.9 ± 21.5 mg/mmol; ERT group 12.8 ± 16.3 mg/mmol). Thus, these patients are considered having a near normal kidney function (normal renal function is defined as eGFR about 90 ml/min/1.73 m^2) with proteinuria (CKD stage 1 or 2).

Primary Efficacy Endpoints

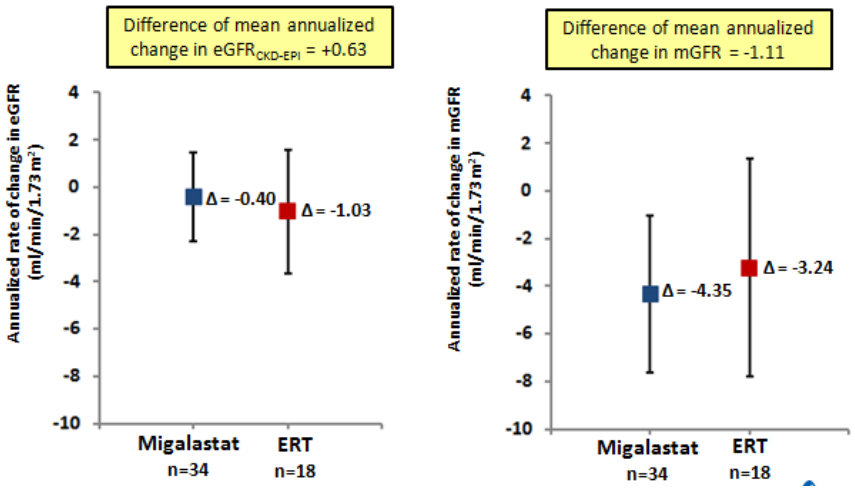
The primary efficacy parameters were defined as follows:

- *Annualized change in $mGFR_{iohexol}$ as assessed by plasma clearance of iohexol from Baseline through Month 18.*
- *Annualized change in estimated GFR (eGFR) assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation ($eGFR_{CKD-EPI}$) from Baseline through Month 18.*

The pre-specified criteria for comparability between migalastat and ERT were:

- *difference between the means for annualised change in GFR for migalastat and ERT within 2.2 ml/min/1.73 m^2 per year, and*
- *>50% overlap of the 95% confidence interval (CI) between migalastat and ERT.*

Figure 7: Annualised Change in GFR from Baseline to Month 18 – ANCOVA (mITT Population) (AT1001-012).



Data represent least square means and 95% confidence intervals

$eGFR_{CKD-EPI}$= estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation; ERT=enzyme replacement therapy; $mGFR_{iohexol}$=measured glomerular filtration rate.

Mean annualised rate of change in $_{eGFRCKD-EPI}$ was -0.40 mL/min/1.73 m^2 (95% CI: -2.272, 1.478) in the migalstat group compared to -1.03 mL/min/1.73 m^2 (95% CI: -3.636, 1.575) in the ERT group.

Figure 7 depicts the difference in the mean annualised rate of change between migalastat and ERT from baseline to 18 months which was +0.63 for $eGFR_{CKD-EPI}$ and -1.11 for $mGFR_{iohexol}$, and the overlap of the 95% CIs of the changes from baseline was 100%.

This is within the pre-specified parameters as laid down by the applicant (above). The variance of the +0.63 for $eGFR_{CKD-EPI}$ is not known. As per definition the difference should be smaller than 2.2. Therefore the 95%CI of the given difference (+0.63) should not include the 2.2. The lower bounds of the 90% and 95% confidence intervals were -2.0348 and -2.5662, respectively. The lower bound of the 95% CI therefore exceeds the defined 2.2 difference. However this is considered less relevant and comparability might be assumed. Change from baseline to 18 months for $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ were taken as secondary endpoints. For both these endpoints, there seem to be no difference between migalastat and ERT. Change from baseline to month 30 showed an annualised rate of -1.718 ± 2.55 for $eGFR_{CKD-EPI.}$ (95% CI -2.653, -0.782).

A post hoc sensitivity analysis was conducted to calculate the 90% and 95% confidence intervals of the difference in annualized rate of change in $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$ between migalastat and ERT. Based on this analysis, the lower bounds of the difference for mean $eGFR_{CKD-EPI}$ were -2.03 and -2.57, respectively. For $mGFR_{iohexol}$ the lower bounds were respectively -5.81 and -6.74, reflecting higher variability in determining $mGFR_{iohexol}$.

A subgroup analysis, based on $eGFR_{CKD-EPI}$, showed that patients with <u>low</u> baseline 24-hour urine protein (<100 mg/24 h) compared to patients with <u>high</u> baseline values (≥100 mg/24h) tend to benefit slightly more from migalastat treatment compared to ERT. The annualized rate of change <100 mg/24h was 1.4 ± 5.0 ml/min/1.73 m^2 and for ≥100 mg/24h -2.3 ± 2.8 ml/min/1.73 m^2. The analysis of the results related to the seriousness of the renal insufficiency indicated that the magnitude of the effect in not related to the eGFR at baseline.

Subgroup analysis based on $mGFR_{iohexol}$ only showed that patients with low baseline 24-hour urine protein (<100 mg/24 h) slightly benefit from migalastat over ERT.

However overall, the numbers are too small to draw definite conclusions.

<u>Secondary endpoints</u>

Secondary endpoints of importance are urine GL-3, 24-hour urine protein, the composite endpoint (based on renal, cardiac, cerebrovascular events and death), LVMi, quality of life (SP-36 questionnaire), and change in plasma lyso-GL-3 from baseline.

<u>Urine GL-3</u>

There was a trend for a greater decrease in urine GL-3 (normalised to creatinine in the same sample) from baseline to Month 6 in the migalastat group (-361±878 ng/mg creatinine), compared with the placebo group (-147±969 ng/mg creatinine) in patients with amenable mutations.

At the end of Stage 2, for patients with amenable mutations, after 12 months of treatment with migalastat the mean change for urine GL-3 was -304 ng/mg creatinine in the migalastat-migalastat group (from baseline) and -469 ng/mg creatinine for the placebo-migalastat group (change from Month 6).

These results should be interpreted with caution, as the significance of urinary GL-3 has not been established yet. Furthermore, this parameter is not optimal in female patients, as a considerably high percentage of female Fabry patients do not have any elevations of urinary GL-3 before treatment.

24-hour urine protein

At baseline, the mean 24-hour urine protein was 259.6 ± 422.22 mg/day in the migalastat group and 417.4 ± 735.5 mg/day in the ERT group in the mITT population. The mean change from baseline to month 18 was: 49.2 ± 199.5 mg/day for the migalastat group and 194.5 ± 690.8 mg/day for the ERT group.

Baseline 24-hours urine-albumin:creatinine ratio in the migalastat group was 13.55 ± 28.91 mg/mmol and in the ERT 21.89 ± 47.08 mg/mmol. Change from baseline to month 18 was for migalastat 5.78 ± 19.66 mg/mmol and 14.34 ± 40.20 mg/mmol for ERT. As patients (27/57) also received concomitant ACEI, ARB or RI medication the results may be cofounded. However data indicate that proteinuria prior and after 18 months of treatment did not change in a clinically significant manner.

LVMi and Other Cardiac Parameters

Echocardiography (ECHO) was performed to measure parameters including LVMi, LV mass, LV fractional shortening, LV ejection fraction, and the systolic and diastolic functional grades. The mean baseline LVMi, was 95.3 ± 22.7 g/m^2 in the migalastat group and 92.9 ± 25.7 g/m^2 in the ERT group (mITT). In normal healthy patients of similar age (about 50 years), the LVMi is 92 to 95 g/m^2 (Cain *et al.,* 2009) suggesting a near normal LVMi in the study patients. In the overall population, LVMi decreased from baseline to month 18 in the migalastat group (mean change, -6.6 ± 12.1 g/m^2; 95% CI, -11.0, -2.1) and did not notably change from baseline in the ERT group (mean change, -2.0 ± 14.9 g/m^2; 95% CI, -11.0, 7.0).

Based on the additional data submitted, it was demonstrated that the effect could be maintained up to 30 months of migalastat treatment. The change from baseline to 30 months was -3.77 ±13.15 g/m^2 (95% CI -8.873, 1.328) for patients with LVMi at baseline and -9.96 ± 9.33 g/m^2 (95% CI -16.630, -3.288) for patients with LVH at baseline.

Subgroup analysis shows that LVMi decreased from baseline to month 18 (

Table 9) in both males and females in the migalastat group (mean change: 13 males, -9.4 ± 12.6 g/m^2; 18 females, -4.5 ± 11.6 g/m^2). In the ERT group LVMi decreased from baseline to month 18 in females (n=7) as well (-7.2 ± 9.4 g/m^2); in males (n=6) LVMi increased from baseline to month 18 (4.1 ± 18.5 g/m^2).

Table 9: Subgroup Summary of LVMi: Change From Baseline (mITT Population) (AT1001-012).

Parameter	Statistic	Treatment Group	
		Migalastat	ERT
Male	n	13	6
Change From Baseline to Month 18 (g/m^2)	Mean	-9.415	4.050
	SD	12.6103	18.4977
	Median	-7.740	4.815
	95% CI[a]	(-17.036, -1.795)	(-15.362, 23.462)
Female	n	18	7
Change From Baseline to Month 18 (g/m^2)	Mean	-4.529	-7.213
	SD	11.6077	9.3814
	Median	-6.205	-7.720
	95% CI[a]	(-10.301, 1.244)	(-15.889, 1.463)
Subjects With Abnormal Baseline LVMi[b]	n	13	5
Change From Baseline to Month 18 (g/m^2)	Mean	-8.406	4.496
	SD	10.6704	20.4531
	Median	-7.970	6.980
	LSMean[c]	-6.563	3.862
	SE(LSMean)	4.1887	6.6877
	95% CI[c]	(-15.689, 2.564)	(-10.710, 18.433)
	Difference LSMeans (Migalastat minus ERT)	-10.425	
	95% CI[d]	(-28.864, 8.015)	
	p-value[d]	0.2416	

CI = confidence interval; ECHO = echocardiography; ERT = enzyme replacement therapy; LS = least squares; LVMi = left ventricular mass index; mITT = modified Intent-to-Treat.
a 95% CI is based on the mean.
b Only subjects with both a Baseline and a Month 18 visit are presented.
c LS means and CI based on the model that includes the treatment groups, baseline LVMi, sex, age and baseline 24-hour urine protein stratification factor.
d p-value and 95% CI calculated on the difference from the LS Means.
Notes: Ranges: LVMi (g/m2): Normal: 43-95 (female), 49-115 (male), mildly abnormal: 96-108 (female), 116-131 (male); 109-121 (female), 132-148 (male); severely abnormal: ≥ 122 (female), ≥ 149 (male).
The baseline value had been modified as the value obtained at the last visit just prior to first dose of study drug. However, because the baseline visit could occur over multiple days, the ECHO assessment at Baseline sometimes occurred after first dose of study

Subgroup analysis in 18 patients with abnormal baseline LVMi[4] values showed that there was a trend for a greater decrease from baseline to month 18 in LVMi in the migalastat group (difference in LS means, -10.4 g/m^2;

[4] *Abnormal LVMi defined by applicant as mildly abnormal: 96-108 (female), 116-131 (male); 109-121 (female), 132-148 (male); severely abnormal: ≥ 122 (female), ≥ 149 (male). Also refer to Table 9.*

Table 9). This data suggests that migalastat can further normalize LVMi in patients with abnormal LVMi values.

Post hoc analyses showed a similar trend for patients with multi-organ involvement at baseline and patients with mutations associated with the classic phenotype (Table 10). Post-hoc analysis further shows that the percent decreases from baseline were greatest for patients with baseline LVH (-7.1% for migalastat *versus* +3.2% for ERT-treated patients), and were also greater for patients in the upper half of the normal range compared to patients in the lower half of the normal range. However, there is a considerable variation due to the limited number of patients included and the missing values and no statistical significant difference could be demonstrated. Further, the descriptive statistics suggest a more pronounced effect in male patients compared to female, younger patients appear to be showing more improvement than elderly patients. Again the variation is large, prohibiting any statistical difference to be demonstrated.

Table 10: LVMi Change in Patients with Multi-organ Disease at Baseline or Classic Phenotype (Study AT1001-012)

	All patients (LS Mean)		Patients with multi-organ disease at baseline		Patients with mutations associated with classic phenotype	
	Migalastat Mean (SD, n)	ERT Mean (SD, n)	Migalastat Mean (SD, n)	ERT Mean (SD, n)	Migalastat Mean (SD, n)	ERT Mean (SD, n)
LVMi CFB (all)	-6.6 (12.1, n=31)	-2.0 (14.9, n=13)	-7.9 (12.5, n=26)	-1.5 (15.4, n=12)	-8.9 (17.5, n=11)	-5.3 (14.0, n=5)
LVMi CFB (LVH at Baseline)	-8.4 (10.7, n=13)	+4.5 (20.5, n=5)	-9.6 (10.1, n=12)	+4.5 (20.4, n=5)	-11.1 (13.4, n=4)	-4.7 (16.5, n=2)

SD = standard deviation; CFB = change from baseline to Month 18; ERT=enzyme replacement therapy; LVMi = left ventricular mass index; LVH = left ventricular hypertrophy [Normal LVMi: 43-95 (female), 49-115 (male)].

Left Ventricular Ejection Fraction (LVEF)

The mean baseline LVEF, was 64.0 ± 2.9% in the migalastat group and 61.1 ± 4.2% in the ERT group (mITT). According to Cain *et al.,* (2009) mean values for LVEF in male is 64-65% and for females 69%. The mean change from baseline to month 18 was comparable between the migalastat group (-1.1 ± 3.0 %) and the ERT group (-0.5 ± 4.1%). One patient in each treatment group had an abnormal LVEF at baseline. At month 18, all patients had a normal LVEF with the exception of 1 patient in the migalastat group (who was also abnormal at baseline), and 3 patients in the ERT group (1 of whom was abnormal at baseline).

Other cardiac parameters

The left ventricular posterior wall thickness in diastole decreased in the migalastat group from baseline to month 18 (mean change, -0.035 cm) but not in the ERT group (mean change, 0.029 cm) in the mITT Population. No notable changes from baseline were noted for the migalastat group or the ERT group in the mITT population in functional diastolic grade, functional systolic grade, or intraventricular septum wall thickness. Most subjects in the mITT population were in the normal range for left ventricular fractional shortening, and there was no notable difference between treatment groups in mean percentage of left ventricular fractional shortening at any time point.

Composite Clinical Outcomes

Based on the number of patients in each treatment group who experienced death or one of the following specific renal, cardiac, or cerebrovascular events:

• *Renal events: a decrease in $eGFR_{CKD-EPI}$ ≥15 ml/min/1.73 m^2, with the decreased eGFR <90 ml/min/1.73 m^2 relative to baseline; an increase in 24h urine protein ≥33%, with the increased protein ≥300 mg relative to baseline.*

• *Cardiac events: myocardial infarction, unstable cardiac angina, new symptomatic arrhythmia (requiring anti-arrhythmic medication, direct current cardioversion, pacemaker, or defibrillator implantation), congestive heart failure (New York Heart Association Class III or IV).*

• *Cerebrovascular events: stroke, transient ischemic attack.*

Analysis of the composite clinical outcome endpoint indicated some benefit of migalastat in the most important organ systems (kidney, heart, and brain) that contributed to the morbidity and mortality in Fabry disease (Table 11).

Table 11: Number (%) of Patients in the mITT Population who Experienced Composite Outcomes (AT1001-012).

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

ERT=Enzyme replacement therapy; mITT=modified intent to treat

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

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

When looking at a consistent effect on all disease manifestations (defined as beneficial effects on renal and cardiac function as well as in the pharmacodynamic (lyso-Gb3)) this can only be assessed in the classic male population. After analysis of males with the classical phenotype, it can be concluded that only complete data of 7 classic male patients were available (lyso-Gb3 at 6 months, LVMi and GFR at 24 months) of these 5 (62.5%) showed a beneficial effect on all three parameters. The two remaining patients lacked a beneficial response in either lyso-Gb3 or LVMi. Further, one patient showed deterioration on all parameters.

Patient-Reported Outcomes (SF-36v2 and BPI)

The Short Form Health Survey with 36 questions, version 2 [SF-36 v2] and questions based on the Brief Pain Inventory short form, severity component (BPI) were used to collect patient-reported outcomes. For the BPI and the SF-36 v2, there were no notable changes from baseline at any time point for either the migalastat or the ERT group in study AT1001-012

Disease Substrates

Comparison of Migalastat and ERT on Plasma Lyso-Gb3

Lyso-GB3 is a deacylated form of Gb3 which has been identified as a storage product in Fabry disease (Aerst, *et al.,* 2008) and considered a sensitive marker (Rombach *et al.,* 2010; Togawa *et al.,* 2010).

Baseline plasma lyso-Gb3 levels are presented in Table 12. Mean baseline values for migalastat (9.1 ± 10.8 nmol/l) and ERT (17.6 ± 20.7 nmol/l) suggest that these patients were atypical Fabry patients at diagnosis.

Table 12: Plasma lyso-Gb3 change from baseline to month 18 (AT1001-012).

		Treatment group	
Parameter	**Statistic**	**migalastat**	**ERT**
Number of Subjects in the Modified Intent-to-Treat Population	N	34	18
Lyso Gb-3 Average by Time point (nmol/L)			
Baseline	n	32	17
	Mean	9,064	17,648
	SD	10,8217	20,7824
	SEM	1,913	5,0405
	Median	6,345	9,65
	Min, Max	0,80, 59,07	0,85, 73,40
Treatment Period Month 18			
Actual	n	31	15
	Mean	11,024	15,846
	SD	15,5978	18,6469
	SEM	2,8015	4,8146
	Median	7,397	6,413
	Min, Max	1,01, 87,37	0,84, 62,50
Change from Baseline	n	31	15
	Mean	1,728	-1,926
	SD	5,5332	4,8872
	SEM	0,9938	1,2619
	Median	0,55	-0,043
	Min, Max	-2,27, 28,30	-11,90, 2,57
	95% CI	(-0,301, 3,758)	(-4,632, 0,781)

Notes: 95% CI is based on the mean.

Patients 2301-1152, 5003-1851, 2006-1401, 4103-2752 have non-amenable GLA mutations based on GLP HEK assay.

The data showed that plasma lyso-Gb3 levels remained low and stable for up to 18 months following switch from intravenous ERT to oral migalastat in patients with amenable mutations (Figure 8). ERT slightly favouring over migalastat.

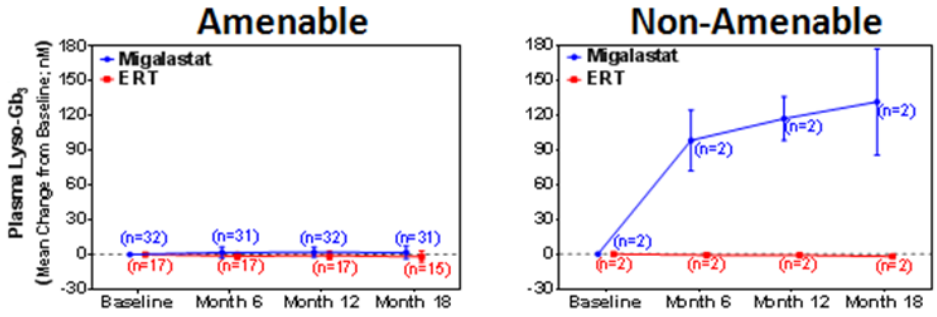
On a patient level, the results could be considered consistent (i.e. patient did not deteriorate). Plasma lyso-Gb3 was maintained or decreased in 10/18 patients (61%) on continued ERT and for migalastat this was 11/32 patients (34%). When accepting a variation of plasma lyso-Gb3 ⩽-1.0 nmol/l[5] , 22/32 (69%) patients remained stable and in the ERT arm 12/18 (67%) patients.

Of the four patients considered as non-amenable with the updated GLP HEK-assay, two patients (both male) showed increased plasma lyso-Gb3 concentrations after switching from ERT to migalastat. The two other patients (one male, one female) who remained on ERT had stable low plasma lyso-Gb3 concentrations. As these patients have a non-amenable mutation, there is no effect to be expected of migalastat on lyso-Gb3.

The observed differences in plasma lyso-Gb3 in patients with amenable *versus* non-amenable mutations further substantiate the accuracy of the GLP HEK assay in categorizing GLA mutations (see

GLP HEK assay (a.k.a. migalastat amenability assay)

Figure 8: Change in Lyso-Gb_3 from Baseline to Month 18 in Patients with Amenable Mutations versus Non-Amenable Mutations (AT1001-012).



ERT=enzyme replacement therapy; Lyso-Gb_3=globotriaosylsphingosine

Peripheral Blood Mononuclear Cell (PBMC) α-Gal A Activity

Assessment of WBC α-Gal A activity is less relevant in females because females are mosaic (i.e., express both the mutant and wild type α-Gal A). Therefore, only the data on males are considered for the assessment. At baseline, the male patients had an α-Gal A activity of 2.9 ± 3.4 nmol/h/mg in the migalastat group and in the placebo group the α-Gal A activity was 1.1 ± 2.3 nmol/h/mg.

The mean increase in PBMC α-Gal A activity from baseline to month 18 was 5.4 ± 4.6 nmol/h/mg in the migalastat group (Table 13). Results were consistent with the data from the PD studies. There was no change from baseline in the ERT group (mean change, -0.4 ± 1.4 nmol/h/mg). Based on the PD data from study AT1001-013, it was observed that α-Gal A activity after infusion with galactosidase-α or -ß also increased for a duration of2 hrs after which gradually the α-Gal A activity declined.

The results demonstrated that the increased α-Gal A activity in the migalastat group is consistent with the mechanism of action of migalastat, which binds to and stabilises amenable mutant forms of the enzyme, facilitating their proper trafficking to lysosomes.

[5] Given a SD of 4.9 in the ERT treated population after 18 months this deterioration should be considered conservative.

Table 13: WBC α-Gal A Activity for Males: Change From Baseline to Month 18 (mITT Population).

Parameter	Statistic	Treatment Group	
		Migalastat	ERT
Number of Subjects in the mITT Population	N	34	18
WBC α-Gal A Activity (nmol/h/mg)			
Baseline	n	14	8
	Median	1.840	0.300
	Mean	2.856	1.139
	SD	3.3815	2.2681
	Min, Max	0.16, 11.20	0.10, 6.71
Treatment Period Month 18			
Actual	n	14	7
	Median	8.545	0.470
	Mean	8.249	0.796
	SD	7.3289	1.0331
	Min, Max	0.48, 22.86	0.10, 3.04
Change from Baseline	n	14	7
	Median	6.580	0.040
	Mean	5.393	-0.437
	SD	4.5975	1.4295
	95% CI	(2.738, 8.047)	(-1.759, 0.885)
	Min, Max	-0.04, 12.92	-3.67, 0.30

α-Gal A = α-galactosidase A; CI = confidence interval; ERT = enzyme replacement therapy; mITT = modified Intent-to- Treat; WBC = white blood cell.

Notes: 95% CI is based on the mean.

Summary of main efficacy results

The following tables (Table 14 and

Table 15) summarise the efficacy results from the main studies (AT1001-011 and AT1001-012) supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of efficacy for trial AT1001-011

Title: 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.			
Study identifier	AT1001-011		
Design	A two-stage trial with a 6 months double-blind randomized, placebo-controlled part and a 6 months open-label extension part, followed by an 12 month extension part (=AT1001-041).		
	Duration of main phase stage 1: Duration of main phase stage 2: Duration of Run-in phase: Duration of Extension phase:		6 months 6 months not applicable 12 months
Hypothesis	Superiority		
Treatments groups	Migalastat		150 mg QOD , 6 months, n= 34
	Placebo		placebo, 6 months, n= 33
Endpoints and definitions	Primary endpoint	% change >50% reduction of GL-3 inclusion per kidney IC Change from baseline to month 6	% reduction of more than 50% reduction of GL-3 inclusion bodies per kidney IC were scored
	Secondary endpoint	GL-3 inclusion per kidney IC Change from baseline to month 6	reduction of GL-3 inclusion bodies per kidney IC were scored
	Secondary	plasma Gb-3	absolute change of plasma Gb-3 change from baseline to month 6
	Secondary endpoint	change from baseline to month 18 $eGFR_{CKD-EPI}$	change from baseline to month 6 for $eGFR_{CKD-EPI}$
Database lock	n/a		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	modified Intent to treat		
Descriptive statistics and estimate variability	Treatment group	migalastat	Placebo
	Number of patient	34	33
	Primary endpoint % change in patients >50% reduction of GL-3 inclusions from baseline to month 6	-40.6	-28.1
		p= 0.3	
	Primary endpoint % change in average GL-3 inclusions from baseline to month 6	-40.8	-5.6
		p= 0.0.97	
	Secondary endpoint reduction of GL-3	-0.25 ± 0.1	0.1 ± 0.1

	inclusions (mean±SD)	p= 0.008	
	secondary endpoint plasma GL-3 (mean±SD)	-11.2 ± 4.8	0.6 ± 2.4
		p= 0.003	
	$eGFR_{CKD-EPI}$ change from baseline to month 6 (mean±SD)	1.8 ± 9.0	-0.3 ± 7.5
	reduction of LVMi form baseline to month 30/36 mean (95% CI)	-17.0 (-26.2, -7.9)	-
	reduction of LVH from baseline to month 30/36 mean (95% CI)	-30.0 (-57.9, -2.2)	-
Notes	Note that during the double blinded 6 months period no significant clinical effects could be observed between treatment and placebo.		
Analysis description	**Other, specify:**		
patient reported outcomes	Mean increase of 4.0 points was observed in patients on migalastat for 24 months compared to patients only 18 months on migalastat treatment. In the general health domain an increase of 4.5 point was observed		

Table 15: Summary of efficacy for study AT1001-012

Title: A Randomized, Open-Label Study to Compare the Efficacy and Safety of AT1001 and Enzyme Replacement Therapy (ERT) in Patients With Fabry Disease and migalastat-Responsive GLA Mutations, Who Were Previously Treated With ERT.			
Study identifier	AT1001-012		
Design	Randomised, open-label study to evaluate the efficacy and safety of migalastat HCl 150 mg QOD compared to ERT over 18 months in male and female patients with Fabry disease who were receiving ERT and who have migalastat-responsive mutations.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		18 months not applicable 12 months
Hypothesis	Equivalence; descriptive statistics		
Treatments groups	migalastat		Migalastat 150-mg capsules, administered orally QOD 18 months; n=34
	ERT[#]		intravenous ERT conform product label, 18 months; n=18
Endpoints and definitions	primary endpoint	annualised changes in gromular filtration rate $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$	yearly change in GFR based on the CKD-EPI equation and $mGFR_{iohexol}$ change from baseline to month 18.
	Secondary endpoint	change from baseline to month 18 $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$	change from baseline to month 18 for $eGFR_{CKD-EPI}$ and $mGFR_{iohexol}$
	Secondary endpoint	left ventricular mass index (LVMi)	assessment of LVMi by ECHO. Change from baseline to month 18. Separate for males and females change from baseline. And patients with abnormal values at baseline.
	Secondary endpoint	composite clinical outcome	composite clinical outcome, as assessed by the number of patients who experienced any of the following events: renal, cardiac, cerebrovascular, death.
	Secondary endpoint	PBMC α-Gal A activity	change from baseline to month 18 (males only)

	Secondary endpoint	Plasma Lyso-Gb_3	Change from Baseline in plasma globotriaosylsphingosine (lyso-Gb3)
	Secondary endpoint	24-h urine protein	change from baseline to month 18
Database lock	Data from the 12-month OLE for Study AT1001-012 and Study AT1001-041 were locked as of 23 October 2014 and 10 October 2014, respectively, for data integration.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	modified intent to treat		
Descriptive statistics and estimate variability	Treatment group	migalastat	ERT
	Number of patients	**34**	**18**
	$eGFR_{CKD-EPI}$ (LSmean) (95% CI)	-0.40 (-2.272, 1.478)	-1.03 (-3.636, 1.575)
	$mGFR_{iohexol}$ (LSmean) (95% CI)	-4.4 (-7.651, -1.056)	-3.2 (-7.651, -1.056)
	$eGFR_{CKD-EPI}$ (mean) (95% CI)	-3.4 ± 5.5 (-9.9, -0.5)	-5.4 ± 11.7 (-5.1, -0.5)
	lyso-Gb3 (mean) (95% CI)	1.7 ± 5.5 (-0.3, 3.8)	-1.9 ± 4.9 (-0.3, 3.8)
	24-hr urine protein (mean) (95% CI)	49.2 ± 199.5 (-20.4, 188.8)	194.5 ± 690.8 (-173.6, 562.6
	24 hr albumin:creatinine ratio (mean) (95% CI)	5.8 ± 19.7 (-1.3, 12.9)	14.3 ± 40.2 (-7.9, 36.6)
	Number of patients	**13**	**5**
	LVMi – abnormal LVMi[1] (LSmean) (95% CI)	-6.6 ± 4.2 (-15.7, 2.6)	7.0 ± 3.9 (-10.7, 18.4)
	Number of patients	**18**	**7**

	PBMC α-Gal A activity (males) (mean) (95% CI)	5.4 ± 4.6 (2.7, 8.0)	-0.4 ± 1.4 (-1.8, 0.9)
Effect estimate per comparison	Primary endpoint $eGFR_{CKD-EPI}$	Comparison groups	migalastat vs ERT
		difference in means	+0.63
	Primary endpoint $mGFR_{iohexol}$	Comparison groups	migalastat vs ERT
		difference in means	-1.11
	Secondary endpoint LVMi in patients with abnormal baseline values	difference LSmeans	-10.43
		95% CI	(-28.86, 8.02)
		P-value 0.2416	
Notes	Note that not in all analysis the same number of patients was available, when different than this is indicated. **Other, specify: note that normal statistics were used. Study was not powered to demonstrated non inferiority.**		
Analysis description			
Brief pain inventory and Short health survey	Over 18 months of treatment no major changes were observed in both scores. Migalastat favored somewhat over ERT.		

#) ERT (enzyme replacement treatment; patients could either receive agalsidase α (Replagal) or agalsidase ß (Fabrazyme); dosage conform SmPC.

[1] the results correspond to 18 months data. Further long term data where provided during the assessment at 36 months and are included in the SmPC.

Male patients with classic FD (study 011 only)

Male patients with the classical presentation were defined having multi-organ system involvement and α-Gal A activity <3%. In the medical literature, the classical phenotype has been described to males with undetectable to low α-Gal A activity, elevated levels of plasma lyso-Gb3, and early onset of multi-organ system involvement (Desnick, Brady *et al.*, 2003; Wilcox, Oliveira *et al*., 2008; Rombach *et al*., 2010). The threshold of <3% was agreed upon.

Table 16: Additional Analyses in Males with Classical Disease.

		Study AT1001-011 Migalastat		Study AT1001-012 Migalastat		Study AT1001-012 ERT	
Endpoint	**Parameter**	**"Classic": Male, Multi-organ, <3% α-gal A (n=14)**	**Other (n=36)**	**"Classic": Male, Multi-organ (n=12)**	**Other (n=22)**	**"Classic": Male, Multi-organ (n=8)**	**Other (n=11)**
		Mean (SD or 95% CI)					
$eGFR_{CKD-EPI}$	Baseline	87.8 (33.6)	95.3 (19.6)	87.1 (23.3)	89.7 (19.2)	95.7 (17.1)	93.3 (22.3)
	Annualised CFB to Month 18 or 24	-0.3 (-2.8, 2.3)	-0.3 (-2.0, 1.4)	-2.4 (-4.5, -0.2)	-0.6 (-2.6, 1.5)	-1.5 (-7.8, 4.9)	-5.6 (-13.7, 2.5)
	Percent Annualised CFB to Month 18/24	-0.8 (-5.5, 4.0)	-0.3 (-2.0, 1.5)	-3.1 (-6.1, 0.0)	-0.1 (-2.8, 2.7)	-1.6 (-8.7, 5.6)	-5.8 (-15.1, 3.5)
mGFR	Baseline	78.6 (22.9)	88.2 (22.0)	78.0 (13.4)	84.6 (18.4)	82.1 (14.6)	79.8 (28.9)
	Annualised CFB to Month 18 or 24	-3.0 (-7.7, 1.6)	-1.0 (-4.4, 2.3)	-1.8 (-6.2, 2.5)	-5.9 (-10.5, -1.3)	-5.5 (-10.3, -0.6)	0.5 (-7.2, 8.2)
	Percent Annualised CFB to Month 18/24	-3.0 (-8.5, 2.5)	-0.7 (-4.5, 3.1)	-2.5 (-8.0, 2.9)	-7.0 (-12.5, -1.5)	-6.5 (-12.6, -0.4)	0.4 (-11.9, 12.6)
LVMi	Baseline	114.3 (27.3)	88.2 (32.3)	108.7 (26.4)	88.6 (17.8)	109.8 (21.6)	78.3 (17.5)
	CFB to Month 18 or 24	-16.7 (-31.1, -2.4)	-3.2 (-12.5, 6.1)	-11.8 (-20.0, -3.6)	-4.6 (-9.9, 0.8)	4.1 (-15.4, 23.5)	-7.2 (-15.9, 1.5)
	Annualised CFB to Month 18 or 24	-10.4 (-19.5, -1.4)	-1.7 (-7.1, 3.8)	-7.9 (-13.3, -2.4)	-3.1 (-6.6, 0.5)	2.7 (-10.2, 15.6)	-4.8 (-10.6, 1.0)
	Percent Annualised CFB to Month 18/24	-9.2 (-16.8, -1.5)	-1.1 (-7.1, 5.0)	-7.6 (-12.9, -2.3)	-3.3 (-7.4, 0.8)	1.8 -9.2, 12.9	-6.9 (-14.2, 0.5)
Plasma Lyso-Gb3	Baseline	99.8 (35.3)	29.3 (48.3)	14.3 (16.0)	5.9 (3.8)	36.0 (21.5)	4.8 (3.7)
	CFB to Month 18 or 24	-36.8 (-69.9, -3.7)	-7.7 (-16.6, 1.3)	3.5 (-2.6, 9.7)	0.7 (0.2, 1.3)	-5.0 (-12.2, 2.2)	0.1 (-0.5, 0.8)
	Percent CFB to Month 18 or 24	-36.0 (-67.9, -4.2)	-16.3 (-25.1, -7.6)	12.3 (-7.4, 32.1)	20.9 (10.4, 31.5)	-7.7 (-30.2, 14.8)	1.3 (-7.1, 9.7)

In study 011, 14 male patients were considered as classical Fabry patients.

Effects of migalastat on $eGFR_{CKD-EPI}$, LVMI, and lyso-Gb3 were found in both males with the classical presentation and the "other" subgroup consisting of non-classical male patients and female patients (Table 16). Due to the limited numbers of patients, no definite conclusions can be drawn. Numerically, larger effects in the classical male patients were associated with higher baseline values observed in these patients.

The GFR after 18 or 24 months of treatment in classical male patients showed a decrease of -0.3 ml/min/1.73 m^2/yr (-95%CI 2.8, 2.3). This is in the range of the deterioration of the renal function seen in healthy subjects. For the "other" subgroup (study 012), the GFR deterioration was -2.4 ±3.3 (mean±SD) after 18 months treatment.

In study 012, the ERT treated patients showed a renal deterioration of -1.5 ± 7.6. After stabilisation obtained with ERT in the literature, results are reported to be between -2.2 and -3.0 (no variation of these figures could be obtained). In untreated patients, a deterioration between -2.6 and -3.0 is reported. The publications of Schwarting (2006) and Branton (2002) were not included because these populations included patients with ESRD, thus not considered relevant. Recent literature data suggests that in these patients deterioration of renal function is not affected by ERT.

In the population of classical male patients, the LVMi after 18 or 24 months of treatment showed a decrease of -10.4 ± 11.8 g/m^2 (mean±SD).

In study 012, the LVMi decrease was -11.8 ± 12.2 after 18 months treatment. The ERT treated patients showed a deterioration of +4.1±18.5. In the literature for patients with ERT, some improvement compared to baseline is reported as between -2.2 ± 8.3 and -3.2 ± 8.2, after about 3 years of treatment. Untreated patients showed a deterioration to be between 4.1±1.0 and 8.0 (no variation reported).

Results for the classical male patients treated with migalastat were compared with those from ERT-treated and untreated patients from Phase 3 studies with agalsidase alfa and beta, as well as with ERT registries and other literature for GFR (Table 17) and for LVMi (Table 18).

Table 17: Rates of Change for Renal Function in Migalastat Phase 3 Studies and in the Literature.

Study	Treatment	n (duration)	eGFR $_{CKD-EPI}$		mGFR	
			Baseline	Annualised CFB	Baseline	Annualised CFB
			Mean (SD)			
Study 011	Migalastat	n=14 (18-24 m)	87.8 (33.6)	-0.3 (3.8)	78.6 (22.9)	-3.0 (6.0)
Study 012	Migalastat	n=12 (18 mon)	87.1 (23.25)	-2.4 (3.3)	78.0 (13.4)	-1.8 (6.8)
Study 012	ERT	n=8 (18 m)	95.7 (17.1)	-1.5 (7.6)	82.1 (14.7)	-5.5 (5.8)
Replagal Phase 3 (West 2009)	ERT	n=85 (24 mon)	-	-	84.5 (25.5)	-2.9 (8.7)
Replagal FOS (Feriozzi 2012)	ERT	n=134 (5+ yrs)	95.1 (26.4)	-2.2 (n/a)	-	-
Fabrazyme Phase 3 (Germain 2007)	ERT	n=52 (4-5 yrs)	100-140 (n/a)	-2.2 (n/a)	-	-
Fabrazyme Registry (Germain 2007)	ERT	n=151 (5 yrs)	84.1 (n/a)	-3.0 (n/a)	-	-

Replagal Phase 3 (West 2009)	Untreated	n=54 (0.5 yrs)	-	-	85.4 (29.6)	-7.0 (32.9)
Natural History (Wanner 2010)	Untreated	n=121 (5 yrs)	90.7 (n/a)	-2.6 (n/a)	-	-
Natural History (Schiffmann 2009)	Untreated	n=145 (7 yrs)	90.9 (n/a)	-3.0 (n/a)	-	-
Natural History (Schwarting 2006)	Untreated	n=6 (1 yr)	68 (27.2)	-12.7 (7.5)	-	-
Natural History (Branton 2002)	Untreated	n=14 (4 yr)	- -	-12.2 (7.5)	-	-

Notes: Literature results for male patients only; Germain 2007: annualised CFB calculated using the weighted average for proteinuria subgroups; Warnock 2012: baseline and annualised CFB calculated using weighted average for quartile subgroup; Wanner 2010: baseline and annualised CFB calculated using the weighted average for clinical event subgroups; Schiffmann 2009: annualised CFB calculated using the weighted average for ESRD subgroups and baseline calculated using the weighted average for urine protein subgroups; Schwarting 2006: calculated from raw data.

Table 18: Changes in LVMi for Classical Males in Migalastat Phase 3 Studies and in the Literature (ERT and Untreated).

Study	Treatment	(n) (duration)	LVMi (g/m^2)		
			Baseline	**CFB**	**Annualised CFB**
AT1001-011	Migalastat	(n=14) (Month 18/24)	114.3 (27.4)	-16.7 (18.6)	-10.4 (11.8)
AT1001-012	Migalastat	(n=12) (18 m)	108.7 (26.4)	-11.8 (12.2)	-7.9 (8.1)
AT1001-012	ERT	(n=8) (18 m)	109.8 (21.6)	+4.1 (18.5)	+2.7 (12.3)
Fabrazyme Registry (Germain 2013)	ERT (beta)	(n=115) (4.9 yrs)	139 (47.1)	-	+1.9 (n/a)
Replagal Phase 3 (Kampmann 2009)	ERT (alfa)	(n=9, LVH baseline) (3 yrs)	56.7 (5.1)	-3.2 (8.2)	-
Replagal Phase 3 (Kampmann 2009)	ERT (alfa)	(n=25, no LVH baseline) (3 yrs)	39.7 (6.6)	-2.2 (8.3)	-
Academic Medical Center pts (Rombach 2013)	ERT (alfa and beta)	(n=27) (5 yrs)	11/27 had LVH	-	+1.2 (0.3)
Salford Royal Hospital pts (Motwani 2012)	ERT (beta)	(n=44) (3 yrs)	123 (2)	-3 (n/a)	-
Natural History (Kampmann 2008)	Untreated	(n=39) (4.5 yrs)	56.8 (27.2)	-	+4.07 (1.03)
Natural History (Germain 2013)	Untreated	(n=48) (4.4 yrs)	137 (48.2)	-	+8.0 (n/a)

Notes: Literature results for male patients only; Germain 2013: calculated using the weighted average for age subgroups.

For study 011, the applicant performed additional analyses in male patients with classical presentation to compare GFR, LVMi, and GSRS-D results on placebo with results on migalastat (Table 19). Based on the data submitted by the applicant from the available limited number of patients that switched to migalastat after the 6 month placebo phase, improvement in mGFR, LVMi and GSRD-D was observed. However, no definite conclusion can be drawn due to the limited data.

Table 19: Change in GFR, LVMi, and GSRS-D on Placebo versus Migalastat in Study AT1001-011 Placebo Arm Patients with Classical Presentation.

Parameter	Statistic	Placebo (Baseline to Month 6)	Migalastat (Month 6 to Month 24)	Difference (Migalastat-Placebo)
mGFR ml/min/1.73m^2	**Mean (SD)**	-7.54 (11.53)	-3.72 (6.70)	3.82 (16.32)
	n	6	6	6
LVMi g/m^2	**Mean (SD)**	0.67 (7.67)	-8.81 (10.16)	-9.47 (8.77)
	n	5	5	5
GSRS-D	**Mean (SD)**	0.24 (0.46)	-0.81 (0.90)	-1.05 (0.91)
	n	7	7	7

Analysis of the consistency of effect on all disease manifestations (defined as beneficial effects on renal and cardiac function as well as in the pharmacodynamic (lyso-Gb3)) in classical male patients indicate that 62.5% showed a beneficial effect on all three parameters. Two patients lacked a beneficial response in either lyso-Gb3 or LVMi. andone patient showed deterioration on all parameters.

Elderly, gender, age

There were no effects of age, gender, baseline 24-h urine protein, or baseline renal function as evaluated by either eGFR or mGFR, on the efficacy of migalastat on renal function. Within the pivotal studies only 6 patients up to 72 years were included to date.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	6	0	0
Non Controlled Trials	0	0	0

Analysis performed across trials (pooled analyses AND meta-analysis)

The applicant performed pooled analysis for GFR and LVMi. Additional analyses were submitted from the two pivotal studies upon request from CHMP.

Renal function

The mean annualised rate of change in $eGFR_{CKD-EPI}$ in patients receiving migalastat was -0.40 (95% ± -2.272, 1.478) ml/min/1.73 m^2 in ERT-experienced patients in AT1001-012 (18 months) and -1.2 ± 14.4 (ml/min/1.73 m^2 in ERT-naïve patients in AT1001-011 after 6 months of placebo treatment, indicating stabilisation of renal function in both study populations. Similar results were obtained for $mGFR_{iohexol}$.

Additional post hoc analyses of Study AT1001-011 and the open-label extension study AT1001-041 demonstrated that migalastat stabilised renal function in more severely affected patients (Table 20 and Table 21). Results are provided for $eGFR_{CKD-EPI}$ only, as mGFR was not assessed in the open-label extension study AT1001-041.

Table 20: Annualised Rate of Change for $eGFR_{CKD-EPI}$ in patients with $eGFR_{CKD-EPI}$ <90 mL/min/1.73 m^2 or 24-hour Urine Protein ≥100 mg (Study AT1001-011)

	All patients (SD, n)	Patients with baseline GFR<90 mL/min/1.73m^2 (SD, n)	Patients with baseline 24-hr urine protein≥100mg (SD, n)
$eGFR_{CKD-EPI}$ annualised CFB (avg ~3.1 yrs)	-0.8 (3.7, n=41)	-0.1 (3.4, n=16)	-0.9 (4.1, n=32)

CFB = Change from baseline; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation; SD = Standard Deviation; | Includes ITT-amenable patients from baseline to approximately 3 years.

Table 21: Annualised Rate of Change for $eGFR_{CKD-EPI}$: Patients with Multi-organ Disease or Classic Phenotype (Study AT1001-011 and Extension Study AT1001-041)

	All Patients (SD, n)	**Patients with multi-organ disease at baseline (SD, n)**	**Patients with mutations associated with classic phenotype (SD, n)**
$eGFR_{CKD-EPI}$ annualised CFB (avg ~3.1 yrs)	-0.8 (3.7, n=41)	-0.8 (3.8, n=36)	-0.6 (4.5, n=24)

CFB = Change from baseline; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation; SD = Standard Deviation | ITT-Amenable population from Baseline to approximately 3 years.

Left ventricular mass index

Among subjects with a normal baseline LVMi, the mean annualised rate of change in LVMi was -6.6 g/m^2 (95% CI: -11.0, -2.1) at Month 18 in AT1001-012 and -7.7 mg/m^2 (95% CI: -15.4, -0.01) and Month 18/24 in AT1001-011. The corresponding changes among subjects with LVH were -8.4 g/m^2 (95% CI: -15.7, 2.6) in AT1001-012 and -18.6 g/m^2 (95% CI: -38.2, 1.0) in AT1001-011.

The applicant submitted additional data between patients with ≥2 organ failure at baseline and based on the mutation based associated with classic Fabry disease (Table 22).

Table 22: LVMi Change Migalastat-treated Patients with Multi-organ Disease at Baseline or Classic Phenotype (Studies AT1001-011 and AT1001-041).

	All patients Mean (SD, n)	**Patients with multi-organ disease at baseline Mean (SD, n)**	**Patients with mutations associated with classic phenotype Mean (SD, n)**
LVMi CFB to month 18/24 (all)	-7.7 (19.4, n=27)	-7.7 (19.4, n=27)	-10.1 (20.5, n=19)
LVMi CFB to month 30/36 (all)	-7.8 (21.5, n=24)	-9.8 (19.5, n=23)	-10.8 (15.2, n=14)
LVMi CFB to month 18/24 (LVH at BL)	-18.6 (23.5, n=8)	-18.6 (23.5, n=8)	-20.1 (27.2, n=6)
LVMi CFB to month 30/36 (LVH at BL)	-30.0 (17.5, n=4)	-30.0 (17.5, n=4)	-21.9 (4.2, n=2)

Abbreviations: SD = Standard Deviation. CFB = Change from baseline. LVMi = Left ventricular mass index. LVH = Left ventricular hypertrophy. Normal LVMi: 43 95 (female), 49-115 (male) | Includes patients in ITT-Amenable population with a baseline and post-baseline LVMi reading. | Month 6 used as baseline for placebo patients switching to migalastat; Baseline used if no month 6. | Baseline and Study visit of extension Study AT1001-041 used as month 18/24 and 30/36, respectively.

Post-hoc analysis further showed that the decreases from baseline were greater inpatients with baseline LVH (-7.1% for migalastat versus +3.2% for ERT-treated patients), and were also greater in patients in the upper half of the normal range (i.e. patients with greater but normal LVMi) compared to patients in the lower half of the normal range (i.e. patients with smaller but normal LVMi). Further, the descriptive statistics suggest a more beneficial effect in male patients compared to female, and

younger patients showed more improvement than elderly patients. However the high variability and limited numbers, prohibit any statistical difference to be demonstrated.

Supportive studies

N/A

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has performed two pivotal studies, one randomized, placebo-controlled blinded (AT1001-011) and one comparative randomized trial (AT1001-012). Scientific Advice was received on the methodology of these trials that were in general taken into account by the applicant.

All patients had a diagnosis of Fabry Disease in the pivotal studies.

The GLP-HEK assay is currently the best tool to identify patients with amenable mutations that are considered responsive to migalastat therapy. However given the positive predictive value of 95% for the HEK test, physicians should be alerted to monitor the clinical response of the patients periodically; this is reflected in SmPC section 4.4.

The applicant presented the GLA mutations for the patients in both pivotal studies. It is however known from literature that in Fabry disease that the genotype is not fully expressed leading to variable disease expression (phenotype) in patients with the same genotype. For example, the relationship between the mutation A143T and the clinical phenotype is currently under discussion.

Additional ad hoc analyses in Study 011 showed that 14 male patients had a classical phenotype.

In the placebo-controlled study, either treatment naïve or ERT experienced patients were included. In study 012 patients previously treated with intravenous ERT were either switched to oral migalastat 150 mg QOD or remained on their ERT.

Demographics between the treatment groups were more or less comparable for baseline disease characteristics as for concomitant medication. The Fabry patients in the pivotal studies were about 45-50 years, had a mean normal LVMi, mild to severe renal impairment (<90 ml/min/1.73 m^2), and most had some proteinuria (24 hr urine ≥100 mg/24 hrs).

Differences in age, residual -Gal A activity and plasma lyso-Gb3 values limit the comparability of the included patients with the patients treated with oagalsidase α and agalsidase ß as mentioned in the respective EPARs or reported in the literature.

In the placebo controlled study migalastat dose was either missed or taken more often frequently. This was not observed in the ERT comparative study. The applicant provided further clarification considered acceptable and sufficiently addressed this issue. Furthermore, in the marketing packaging, a push-out has been implemented, allowing a better compliance with the intended dosage regimen compared to clinical studies The patient will pushes-out the carton every day, including the days where no capsule is to be taken (refer to the PI for a mock-up).

Completeness of data

For study 011, the results are based on a subgroup of patients defined as amenable patients representing 75% of the randomised group of patients. It is assumed that the HEK assay used for the determination of amenability will not introduce bias in the results.

The already limited number of patients available for efficacy analysis further decreases over time with 94% of the patients being available after 6 months, 88% after one year and 82% after 18 months. Due to study design, the results for only 22 patients after 24 months are entered representing 44% of the patients.

Fourteen (14) male patients from study 011 could be considered as classical Fabry disease patients. Of the 14 male patients, 7 patients had a complete data set (i.e. all field were complete at 6 and 24 months).

In study 012, only 4 patients have been identified as being non-amenable patients; therefore the amenable subgroup represents 93% of the randomised group of patients.. In total, 91% of randomised amenable patients continued treatment after month 18. Up to month 30 of the study, only migalastat-migalastat patients were included in the submitted data set and in total only three (3) patients did not continue up to month 30.

Overall, the analysis of the original data files submitted during the assessment and discussed at the OE for both pivotal studies showed some minor deviations in patient numbers which were clarified at the completion of the assessment.

Efficacy data and additional analyses

GL-3 inclusion in the kidney interstitial capillaries

The primary endpoint in the placebo controlled study was the IC GL-3 responder analysis (responder defined as % of patients with a ≥50% reduction from baseline in the average number of GL-3 inclusions per kidney interstitial capillaries (IC)). This endpoint was not met in the ITT nor in the mITT.

A post hoc analysis in the mITT (with only amenable patients) showed a statistically significant reduction from baseline to month 6 in the average number of GL-3 inclusions per IC compared to placebo. In addition, the mean change in percentage of kidney IC with zero GL-3 inclusions was in favour of migalastat and was statistically significant.

Plasma lyso-Gb3

It has been demonstrated that migalastat, overall, reduces plasma lyso-Gb3 in patients with amenable mutations. No reduction of plasma lyso-Gb3 was observed in the patients on placebo.

Due to the fact that Lyso-Gb3 was recognised as an important secondary end point after the start of the study in the placebo controlled study (Study 011), only 31 patients out of 51 patients with an amenable mutation had available measurements of Lyso-Gb3.

In study 012, plasma lyso-Gb3 was maintained in 10/18 patients (61%) in the continued ERT group and in 11/32 patients (34%) in the migalastat group. When considering a reduction of plasma lyso-Gb3 $\leqslant$-1.0 nmol/l , being within the margins of the assay method and or biological variation, 22/32 (69%) patient remained stable in the migalastat group and 12/18 (67%) patients in the ERT arm. The results can be considered comparable in both groups.

Renal function

After 18/24 months of migalastat treatment patients showed a stable renal function -0.30 ± 0.66 mL/min/1.73 m^2/year which is in line with normal decline in renal function for healthy persons.

In the ERT comparative study, the applicant demonstrated that migalastat was comparable to ERT in maintaining stabilisation of eGFR. The primary endpoint as such was therefore considered achieved.

An additional post hoc analysis performed in patients with ≥2 organ systems involved and in patients associated with the classic Fabry mutation, showed similar results as seen for the whole population.

Further analysis showed that stabilization of renal function is observed with migalastat amenable patients independently of gender, age or seriousness of the renal insufficiency at baseline.

Cardiac parameters

In study 011, after 6 months, a comparable effect on LVMi was observed in both migalastat and placebo groups. In study 012, the effect on LVMi after 18 months, was comparable in both migalastat and ERT groups. The mean effect on LVMi was maintained in both naïve (study 011) and ERT pre-treated patients after 24, 30 and 36 months months of treatment. The magnitude of effect is related to the baseline LVMi.

The beneficial effect observed in male patients and in younger patients was more pronounced than the effect observed in females and elderly respectively.

Composite clinical endpoint

As indicated in the scientific advice by the CHMP (EMEA/CHMP/SAWP/288057/2009), the analysis of the composite clinical outcome endpoint - indicated comparable effects in kidney and heart between migalastat and ERT groups.

Male patients with classical FD

Upon request from CHMP, the applicant performed additional analyses in male patients with classical Fabry disease.

In classical male patients, after 24/30 months of treatment , the GFR showed a decrease of -0.3 ml/min/1.73 m^2/yr (95%CI -2.8, 2.3). This decrease is comparable with the deterioration of the renal function as seen in healthy subjects (<-1.0 ml/min/1.73 m^2/yr). Results between -2.2 and -3.0 (not SD available) were reported in literature after stabilisation achieved with ERT therapy. In untreated fabry male patients with classical phenotype, a deterioration of the renal function between -2.6 and -3.0 (no SD available) is reported.

In classical male patients, after 24/30 months of treatment, the LVMi values showed a decrease of -10.4 ± 11.8 g/m^2 (mean±SD). Literature reports some improvement in LVMi with changes compared to baseline observed between -2.2 ± 8.3 g/m^2 and -3.2 ± 8.2 g/m^2 after about 3 years of ERT therapy. In comparison, untreated patients showed a deterioration of LVMi values between +4.1±1.0 g/m^2 and +8.0 g/m^2 (no variation reported).

With respect to plasma lyso-Gb3 ,a reduction was observed of -36.8 nmol/l (-69.9, -3.7) after 18/24 months of migalastat treatment in males with classic FD. This is considered clinically relevant.

2.5.4. Conclusions on clinical efficacy

Available data allow to conclude that in patients amenable for migalastat a pharmacodynamic and clinical effects have been demonstrated. This effect was assessed also in a subgroup of classical male Fabry patients with an amenable mutation.

The diagnosis of FD for all patients in both pivotal studies was based on the physician expertise and local clinical guidelines.

Differences in age, residual -Gal A activity and plasma lyso-Gb3 values limit the comparability of the included patients with the patients treated with agalsidase α and agalsidase ß as mentioned in the respective EPARs or reported in the literature.

In study 011, the primary endpoint in the ITT (or the mITT population has not been met. In the ERT comparative study (study 012), the applicant demonstrated that migalastat was comparable to ERT in maintaining stabilisation of eGFR values. Comparable effects were observed on lyso-Gb3 and LVMi between ERT and migalastat treated groups.

Post-hoc analysis showed that the results observed are independent of age, gender and disease burden at baseline, except for LVMi values. For LVMi, the response to migalastat depends on the cardiac mass at baseline, with higher values at baseline resulting in a more pronounced response.

For study 012, the assay sensitivity is accepted based on results known from literature data. Tennankore *et al*. (2007) showed that statistical significant worsening occurred in eGFR, 24-hr urine protein, Mainz Severity Score Index (MSSI), and SF-36 nine (9) months after stopping ERT treatment. In another publication by Weidemann *et al.* (2014), after 12 months, statistical significant worsening was observed for eGFR, albumin-to-creatinine ratio, MSSI, pain, and gastrointestinal symptoms when patients were switch to half the normal dose of ERT treatment.

Some significant effects on gastrointestinal symptoms, in particular diarrhoea, were observed with migalastat but the clinical relevance remains uncertain at present.

Comparison of the identified classical male FD patients in study 011 with historical ERT data and comparison with literature on untreated patients, allows to conclude that in classical male patients the response pattern of migalastat on the GFR is comparable with the one observed with ERT therapy and is better than placebo. Considering the LVMi results of migalastat treated patients, they indicates the same stabilisation as reported for ERT therapy in comparison with a deterioration of the LVMi reported for untreated patients.

The applicant has clarified that the data points entered for both pivotal studies was performed adequately, though some minor deviations in patient numbers were noticed. These differences however do not impact the conclusions and the results observed in both studies are reliable. The clinical data set is considered acceptable for the purpose of assessment of efficacy and safety. The efficacy has been demonstrated for patients amenable to migalastat. Migalastat should not be used in patients with non amenable mutations. The list of mutations tested as being amenable and non amenable is provided in the SmPC. It is advised to monitor the patients to assess renal, cardiac functions and biochemical markers every 6 months.

Clinical safety

Patient exposure

The clinical development program, presented data from 386 patients/healthy volunteers which have been exposed to migalastat. Of these, 168 patients with Fabry disease have been treated with migalastat in Phase 2 and Phase 3 studies. One-hundred and nineteen (119) patients have been treated for at least 1 year. The longest patient exposure as of 10 October 2014 is 8.8 years, and is ongoing. Most patients received the proposed regimen with 150 mg capsule.

The number of patients exposed to the drug is limited both in time and number of patients. As Fabry is an orphan disease this is to be expected and acceptable.

Adverse events

Phase I studies

In the healthy volunteers studies, most reported adverse events were headache (N=12, 7.6%), dizziness (N=6, 3.8%) and abdominal pain (N=4, 4.3%). No SAEs were reported during any of the Phase 1 studies. In healthy volunteers, the reported safety profile was mild. All adverse events spontaneously resolved.

Phase II studies

In phase II studies, the most reported adverse events were headache (N=7, 20.0%), nausea (N=4, 11.4%) and abdominal pain (N=4, 11.4%). No SAEs were reported during any of the Phase 2 studies.

In phase 2 studies, the safety profile in patients was mild with all adverse events spontaneously resolvedThe most frequently reported TEAEs (≥ 10%) in patients treated with migalastat were nasopharyngitis, headache, dizziness, influenza, abdominal pain, diarrhoea, nausea, upper respiratory tract infection, urinary tract infection, and back pain.

Phase III studies

Placebo controlled study (AT1001-011)

The overall frequency of TEAEs was generally similar for migalastat and placebo (31 (91%) in the migalastat group and 30 (91%) in the placebo group). The overall percentage of patients who experienced TEAEs reported as related to study drug (i.e. definitely, probably, or possibly related) was 44% in the migalastat group and 27% in the placebo group.

The most frequently reported TEAEs (≥ 10%) in the migalastat group during Stage 1 were headache, nasopharyngitis, nausea, fatigue, pyrexia, and paresthesia (Table 23). The TEAEs with a higher frequency (≥ 10% difference) in the migalastat group compared with the placebo group, were headache and nasopharyngitis.

Table 23: Stage 1: Treatment emergent adverse events (safety population excluding patients with non-amenable mutations) with a frequency < 5%.

System Organ Class Preferred Term	Statistic	Migalastat	Placebo
Number of Patients in the Safety Population	N	34	33
Number of Treatment Emergent Adverse Events	n	204	142
Number of Patients with Treatment Emergent Adverse Events	n (%)	31 (91)	30 (91)
Cardiac Disorders			
Atrial Fibrillation	n (%)	2 (6)	0
Ear And Labyrinth Disorders			
Vertigo	n (%)	2 (6)	3 (9)
Gastrointestinal Disorders			
Nausea	n (%)	4 (12)	2 (6)
Constipation	n (%)	2 (6)	2 (6)
Diarrhoea	n (%)	3 (9)	1 (3)
Dry Mouth	n (%)	2 (6)	2 (6)
Abdominal Distension	n (%)	2 (6)	1 (3)
Vomiting	n (%)	1 (3)	2 (6)
Abdominal Pain Upper	n (%)	2 (6)	0
General Disorders And Administration Site Conditions			
Fatigue	n (%)	4 (12)	4 (12)
Pyrexia	n (%)	4 (12)	1 (3)
Asthenia	n (%)	2 (6)	1 (3)
Infections And Infestations			
Nasopharyngitis	n (%)	6 (18	2 (6)
Upper Respiratory Tract Infection	n (%)	2 (6)	3 (9)
Influenza	n (%)	0	3 (9)
Cystitis	n (%)	2 (6)	0
Urinary Tract Infection	n (%)	2 (6)	0
Injury, Poisoning And Procedural Complications			
Overdose	n (%)	2 (6)	1 (3)
Procedural Pain	n (%)	2 (6)	1 (3)

Post Procedural Complication	n (%)	2 (6)	0
Investigations			
Weight Increased	n (%)	2 (6)	1 (3)
Musculoskeletal And Connective Tissue Disorders			
Muscle Spasms	n (%)	1 (3)	3 (9)
Pain In Extremity	n (%)	0	4 (12)
Back Pain	n (%)	3 (9)	0
Myalgia	n (%)	2 (6)	1 (3)
Arthralgia	n (%)	0	2 (6)
Torticollis	n (%)	2 (6)	0
Nervous System Disorders			
Headache	n (%)	12 (35)	7 (21)
Paraesthesia	n (%)	4 (12)	4 (12)
Dizziness	n (%)	2 (6)	1 (3)
Hypoaesthesia	n (%)	2 (6)	0
Psychiatric Disorders			
Insomnia	n (%)	3 (9)	2 (6)
Anxiety	n (%)	1 (3)	1 (3)
Renal And Urinary Disorders			
Haematuria	n (%)	3 (9)	0
Respiratory, Thoracic And Mediastinal Disorders			
Oropharyngeal Pain	n (%)	3 (9)	2 (6)
Epistaxis	n (%)	3 (9)	1 (3)
Cough	n (%)	3 (9)	0

Notes: Adverse Events are coded using the MedDRA dictionary (Version 15.0).

Adverse events presented in this table are any AEs that start after first stage 1 study drug administration (treatment emergent) and before stage 2 first dose date.

Patients experiencing the same adverse event multiple times are counted only once for the corresponding preferred term. Similarly, patients experiencing multiple adverse events within the same system organ class are counted only once for that system organ class.

Adverse events are sorted alphabetically by system organ class and within each system organ class the preferred term is presented by decreasing order of total frequency.

Percentages are based on the number of patients in the Safety Population.

During Stage 2 , a lower percentage of patients reported TEAEs (all patients on migalastat) (79%), compared with Stage 1 (placebo-controlled, double-blind phase) (91%). The percentage of patients

who experienced TEAEs that were reported as related to study drug was 27% in the placebo-migalastat group and 12% in the migalastat-migalastat group.

Comparison with ERT (AT1001-012)

Compared to ERT, more AEs were reported for migalastat (14% vs 39%, respectively). SAEs were reported more in the ERT arm as compared to the migalastat arm (33% vs 19% respectively). None of the patients discontinued due to adverse events.

The most frequently reported TEAEs (≥10%) in the migalastat group were nasopharyngitis, headache, dizziness, influenza, abdominal pain, diarrhoea, nausea, upper respiratory tract infection, urinary tract infection, and back pain. Upper respiratory tract infection and back pain were more reported in the migalastat group as compared to the ERT (see Table 24: TEAEs Occurring in ≥ 10% of Patients in Either Treatment Group (Safety Population).

The term procedural pain is known in relation to invasive procedures and especially linked to children. The applicant defined the procedural pain as pain in relation to biopsies (kidney and heart).

Table 24: TEAEs Occurring in ≥ 10% of Patients in Either Treatment Group (Safety Population).

Preferred Term	Statistic	Migalastat	ERT
Number of Patients in the Safety Population	N	36	21
Number of TEAEs	n	308	166
Number of Patients 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)

AE = adverse event; ERT = enzyme replacement therapy; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Adverse events presented in this table are any AEs that started after first study drug administration (treatment emergent) and before the open-label extension period first dose date.

Patients experiencing the same AE multiple times were counted only once for the corresponding preferred term. Similarly, patients experiencing multiple AEs within the same system organ class were counted only once for that system organ class.

Adverse events are sorted by frequency in the migalastat group.

Percentages are based on the number of patients in the Safety Population.

Special populations in the phase III studies.

The limited information submitted suggests that women experience more AEs compared to men (both in frequency as discrete of AE's).

Only 3 patients in the migalastat group and 2 patients in the ERT group were older than 65 years of age, therefore no analysis for the elderly could be made.

Although the results do not indicate an increased safety risk for patients with renal impairment, the number of patients with renal impairment is too limited to draw definite conclusions .

No apparent gender or age dependent difference was observed for the percentage of patients experiencing AEs, or for the frequency of the various AEs.

In the placebo controlled study, only one patient was older than 65 years of age, therefore no analysis for the elderly could be made.

The number of patients with renal impairment is too limited to draw conclusions from. The results do not indicate an increased safety risk for patients with renal impairment.

Serious adverse events and deaths

No SAEs were reported during any of the Phase 1 studies.

In the Phase 2 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. These SAEs encompassed: TIA (n=3), acroparesthesia, (Fabry acute pain), AV-block (N=2), cardiac perforation (due to cardiac biopsy), pericardial haemorrhage (due to cardiac biopsy), arterial injury (due to cardiac biopsy), cardiac tamponade (due to cardiac biopsy), musculoskeletal chest pain, atrial fibrillation (n=3), Atrial flutter (n=1), Cardiac failure congestive (n=1), Ventricular fibrillation (n=1), Hyperthyroidism (n=1), Dyspepsia (n=1), Sensation of foreign body (n=1), Ankle fracture (n=1), Post procedural haemorrhage (n=1), Dehydration (n=1), Malnutrition (n=1), CVA (n=1), syncope (n=1), epistaxis (n=1), Pneumonia aspiration n=1).

In the Phase 3 studies, a total of 57 SAEs were reported (including during screening, on treatment and after treatment was discontinued), 2 of which were deemed related to migalastat. These 2 patients experienced fatigue and paraesthesia (one patient), and moderate proteinuria (one patient).

Two deaths were reported during the clinical program. The events were deemed unrelated to study treatment. One patient deceased due to breast cancer after 2 years treatment with migalastat. The cause of death for the second patient is unknown. This patient was treated with migalastat for more than 2 years and reported various risk factors (transient ischemic attack, obesity, type 2 diabetes mellitus, hypercholesterolemia, cardiac stent placement, triple bypass surgery, and cardiac pacemaker insertion. The patient also smoked three packs of cigarettes per day for 10 years) that might have contributed to the death of the patient.

Laboratory findings

In Phase 2 and 3 studies, no changes or trends of clinical significance were observed for any vital signs parameter. Some shifts to abnormal values occurred, but none were considered clinically significant. No dose-related trends were observed and there were also no differences between migalastat and comparator treatments (placebo or ERT). No trends of clinical significance were observed for any physical examination finding.

In individual Phase 2 and 3 studies, there were no trends of clinical significance for any ECG parameter. Some ECG shifts to abnormal values occurred in individual studies, almost all of which were assessed as not clinically significant. None of the ECG changes were assessed as treatment-related TEAEs.

Safety in special populations

*QT studies*A QT study was performed.The positive control (moxifloxacin) confirmed this study had adequate sensitivity to detect a change on the mean QTc interval of at least 5 msec. The lower bound of the 95% one-sided confidence interval of placebo-subtracted difference of QTc after administration of moxifloxacin was 9.26 msec at the 2.0 hour time point.

At therapeutic (150 mg) and supra-therapeutic (1250 mg) doses of migalastat, the cardiodynamic ECG analysis showed there was not a statistically significant increase in the placebo-subtracted change in QTcI, as defined by the primary analysis measure of an upper bound of the 95% one-sided confidence interval 10 msec. In addition, corroborative evidence was provided by confirmation of similar findings for QTcF, outlier analysis, tabulation of morphology changes, and concentration regression analysis.

Based on the results of this thorough controlled QT study, migalastat does not cause QT prolongation.

Age and gender

No apparent age effect could be observed. However, only very few patients over the age of 65 were included with no patient over the age of 75. Therefore the effect in the elderly population cannot be assessed. There are no apparent trends for an effect of gender on the safety of migalastat.

Renal function

Analysis suggests that the frequency and severity of TEAEs does not appear related to renal function.

Race and Ethnicity

A majority of the subject population in the Phase 3 studies of migalastat were Caucasian. The number of non-Caucasian subjects with Fabry disease was too small to assess potential differences in migalastat safety by race/ethnicity.

Body Mass Index

No data are available that demonstrate the effect of body mass index on the use of migalastat.

Immunological events

No immunologic events are reported during the clinical development.

Safety related to drug-drug interactions and other interactions

Based upon the available in vitro data, no interactions are expected on CYP and transporters level.

In vivo, co-administration of migalastat with agalsidase resulted in increased agalsidase activities but did not affect agalsidase protein pharmacokinetics; at the 150 mg single dose level an increase in agalsidase activity of 2.0 to 4.2-fold is observed. Agalsidase did not affect the pharmacokinetics of migalastat. This interaction is sufficiently described in section 4.5 of the SmPC.

Discontinuation due to AES

Seven out of 168 patients (4.2%) discontinued due to SAE. The 7 AE encompassed vomiting, hypertension, CVA, proteinuria, diarrhoea and vomiting, ALS, lymphoma and squamous cell carcinoma. Of these 4 were assessed to be treatment related (vomiting, hypertension, proteinuria, vomiting and diarrhoea).

2.5.5. Discussion on clinical safety

The clinical programme for Fabry disease comprised 20 studies in a total of 386 patients/healthy volunteers from ten Phase 1, six Phase 2, and four Phase 3 studies. In addition, one physician-initiated request program in one patient with Fabry disease and one investigator-initiated trial in one patient with Fabry disease have been conducted. Two of the studies are ongoing (AT1001-041, and AT1001-042).

In the 20 studies of the migalastat clinical development programme, 371 patients/healthy volunteers have been exposed to oral migalastat. Of these, 168 are patients with Fabry disease. One-hundred and nineteen (119) patients have been treated for at least 1 year. The longest patient exposure to date is 8.8 years as of 10 October 2014. Due to the limited number of patients treated for about 18 month, only limited conclusions on the short term safety can be drawn. Safety information on chronic use over 2 years is not submitted. The limited number of patient and the short term exposure are adequate for registration due to the rarity of the disease but do not allow complete identification of the safety profile. Further safety characterisation is deemed necessary in the post registration phase and will be done through the registry as detailed in the RMP.

The migalastat clinical development program included male and females patients, healthy volunteers, volunteers with renal impairment, patients with Fabry disease, and elderly patients (>65 years of age, n=6, and a range of doses and regimens (50 mg – 2000 mg). During the clinical trials exposure of three pregnant women has been noted. Appropriate wording is added in the SmPC.

Phase 1 and 2 studies demonstrated that treatment with migalastat up to 2000 mg was found to be generally safe and well tolerated.

In the phase 3 studies, the most frequently reported TEAEs (≥ 10%) in the migalastat group were headache, nasopharyngitis, nausea, fatigue, pyrexia, and paresthesia. Compared to ERT, more patients on migalastat reported headache, upper respiratory tract infection and urinary tract infection. Patients switched on ERT reported more influenza, cough and sinusitis. TEAEs reported with the use of migalastat were mostly mild or moderate in nature, and required no intervention or were readily managed in standard clinical practice.

Due to the limited number of patients, the safety profile need to be further characterised. However, no safety issue were identified from the safety database.

In both phase 3 studies, the overall frequency of treatment related AEs decreased from 44% in the initial period to 21% in the open-label extension.

In the Phase 3 studies, a total of 57 SAEs were reported, 2 of which were deemed related to migalastat. These 2 patients experienced fatigue and paraesthesia in one patient, and moderate proteinuria in the other patient. The frequency of SAE increased from 6% in the initial stage to 19% in the open label extension phase. Post hoc analysis showed that overall, the adverse events frequency is not increased over time. The observation seen after 18 months is probably linked to the study design in particular the change to an open uncontrolled design.

There were no deaths related to migalastat. There were 2 deaths unrelated to migalastat (one from breast cancer, one from unknown cause).

There were few discontinuations due to TEAEs, and most were related to underlying Fabry disease co-morbidities.

There were no clinically meaningful changes in laboratory values, physical examinations, vital signs, or ECGs.

A four-arm, single dose, placebo-controlled thorough QT study (AT1001-010) including 52 healthy patients demonstrated that migalastat at a therapeutic dose (150 mg) or supra-therapeutic dose (1250 mg) has no effect on QTc interval.

In summary, the adverse events profile appears to be mild with mild or moderate adverse events which resolve spontaneously. The most reported adverse events were headache, proteinuria, bronchitis, nasopharyngitis, nausea, fatigue, pyrexia, and paresthesia. The most common adverse reaction was headache, which was experienced by approximately 10% of patients who received Galafold.

Assessment of paediatric data on clinical safety

N/A

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.5.6. Conclusions on the clinical safety

The safety data provided in the application asbased on the adverse event profile, laboratory evaluations, physical examinations, vital signs, and ECGs, demonstrate that migalastat 150 mg QOD is generally safe and well-tolerated in the treatment for patients with Fabry disease.

The safety profile has been characterised in a limited number of patients in short term exposure. Although this considered adequate for registration, the safety profile of migalastat need to be further characterised overlong term. This will be done in a Post Authorisation Safety Study (registry) as defined in the RMP.

2.6. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	No identified risks
Important potential risks	• Lack of efficacy in case of use in patients with non-amenable mutations • Male infertility (reversible)
Missing information	• Use in pregnant or breast-feeding women • Use in older patients >74 years • Use in patients with severe renal impairment (GFR <30 mL/min/m^2) • Long term treatment (> 1 year)

Pharmacovigilance plan

Study/activity type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
Category 3: AT1001-012: A randomized, open-label study to compare the efficacy and safety of migalastat HCl and ERT in patients with Fabry disease and migalastat HCl-responsive GLA mutations, who were previously treated with ERT	Long-term safety and efficacy of migalastat	No specific safety concern; this study will provide additional long-term safety data	Ongoing	Planned Q2 2016
Category 3: AT1001-041: A phase 3 open label extension study to assess the safety and efficacy of 150 mg migalastat HCl QOD in subjects with Fabry disease who have completed Studies AT1001-011, AT1001-012 or FAB-CL-205	Long-term migalastat treatment	No specific safety concern; this study will provide additional long-term safety data	Ongoing	Planned Q2 2017
Category 3: AT1001-042: An Open-Label Extension Study to	Long-term migalastat treatment	No specific safety concern; this study will provide	Ongoing	Planned Q4 2020

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Evaluate the Long Term Safety and Efficacy of Migalastat Hydrochloride Monotherapy in Subjects with Fabry Disease		additional long-term safety data		
Category 3: Patient registry	Track clinical use	Long-term efficacy and safety of migalastat	Planned	Planned Q2 2025

An abstract protocol for the Prospective, Multi-Center, Multinational, Observational Disease Registry in Fabry Disease Patients Treated with Migalastat and Untreated Patients has been provided. The objectives of this study are to evaluate the long-term safety and effectiveness of migalastat in Fabry disease patients in real-world setting.

The study as planned is not built on the existing Fabry registry as requested but on a new parallel register. This raises several questions on the selection mechanism for recruitment of patients and a risk for substantial loss to follow-up. In addition there are uncertainties with regard to the choice of control group and with study dimension. The applicant should continue their efforts to get access to the existing register and should submit a full study protocol, as a Post-Authorisation Measure (PAM), for review by PRAC, within 6 months following CHMP positive opinion.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Lack of efficacy in case of use in patients with non-amenable mutations	Appropriate language in SmPC sections 4.1 and 5.1;	None
Male infertility (reversible)	Appropriate language in SmPC sections 4.6 and 5.3; routine pharmacovigilance	None
Use in pregnant or breast-feeding women	Appropriate language in SmPC section 4.6;	None
Use in older patients >74 years	Appropriate language in the SmPC sections 4.2 and 5.2	None
Use in patient with severe renal impairment	Appropriate language in the SmPC section 4.2 and 5.2	None
Long term treatment > 1 year	Routine pharmacovigilance	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 01 is acceptable.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. Inclusion of a link to a website in the SmPC

The applicant proposed to include a reference to a website in the SmPC which would provide a user-friendly search function for amenable and non-amenable mutations already tested. From a clinical perspective and considering the high number of mutations tested at present (more than 800), such reference in the SmPC to a website including a search tool for amenable and non-amenable mutations is considered very helpful. This link will allow healthcare professionals to search for the patient's mutation and find out whether a specific GLA mutation has been classified as amenable to treatment with migalastat or non amenable. The list of amenable and non amenable mutations currently tested is provided in the SmPC in section 5.1. Currently, the amenable mutations represent 269 mutations and the non amenable mutations represent 581 mutations out of the 850 mutations tested with the HEK GLP assay.

It is estimated that about 30-40 new mutations per year will be discovered in the next years.

The content of the above mentioned website must, however, comply at any time with the following conditions:

2) The scientific content of the website, and in particular, the list of amenable and non-amenable mutations, can only duplicate information already present in the latest approved SmPC for the medicinal product.

2) The website must not contain any information that is not compatible with the approved SmPC.

3) No promotional content should be provided in the website.

3) The CHMP review is limited to the scientific content of the website. The CHMP does not assess the compliance of the website with EU Member States' national laws governing the advertising and promotion of medicinal product.

Update of the website after initial approval

As new mutations are tested, information concerning such new mutations may not be included in the website before this information is incorporated in the latest approved SmPC for the medicinal product through the appropriate variation procedure.

In conclusion, the inclusion of a link to a website in the SmPC is exceptional but considered acceptable in this particular case provided that all of the above conditions are met. The applicant has signed a declaration to commit that the website content will reflect the latest approved SmPC for the medicinal product and will not contain information incompatible with this SmPC. The applicant also undertakes to ensure that the website will not contain promotional materials.

2.8.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.3. Additional monitoring

- Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Galafold (migalastat) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Fabry disease is a rare, progressive X-linked lysosomal storage disorder, affecting both males and females. The reduction in α-Gal A activity results in an accumulation of glycosphingolipids, including globotriaosylceramide (GL-3) and plasma globotriaosylsphingosine (lyso-Gb3) and leads to the symptoms of Fabry disease. Fabry disease encompasses a spectrum of disease severity and age at onset, and can be divided into two main phenotypes, "classic" and "late-onset". Classical Fabry disease can affect all 3 major organs (heart, kidney, central nervous system) and in end-stage disease trigger life-threatening events. In contrast, variant α-Gal A mutations may result in less aggressive clinical phenotypes, which are, leading to single organ involvement and late onset disease (Niemann *et al*., 2014) or so called "atypical" Fabry patients.

Migalastat HCl (migalastat) is an analogue of the terminal galactose of GL-3, the natural substrate of α-galactosidase A (α-Gal A). Migalastat binds to the active site of GL-3 and physically stabilizes defective α-Gal A enzymes. This enables the enzyme to pass into the lysosome where migalastat is released and activated α-Gal A reduces the substrate levels involved in Fabry disease.

Five pharmacodynamic studies in patients with Fabry disease were performed. Patients were selected for mutations based on a HEK-assay that were responsive to migalastat, thus defined as amenable mutations. The positive predictive value of the GLP HEK assay on a patient level is 95%. Further, given a specificity of 88%, about 12% of the patients will be wrongly identified. The HEK GLP assay despite its limitations in the identification of amenable and non-amenable patients is considered acceptable for the definition of amenability to migalastat therapy.

The diagnosis of FD for all patients in both pivotal studies was based on the physician expertise and local clinical guidelines.

The phase III program consisted of two pivotal studies. One open label active controlled study (012) compared oral migalastat versus intravenous enzyme replacement therapy (ERT). ERT experienced patients with an amenable mutation were either switched to oral migalastat 150 mg QOD or maintained their ERT for 18 months. The patients could participate in a 12-month open label extension. At the end of the study, the patients could participate in a long-term follow-up study currently ongoing (042).

The second pivotal study was a double blind, randomized placebo controlled study (study 011) in ERT naïve patients or in patients in whom ERT had been discontinued for at least 6 months. All patients received oral migalastat 150 mg QOD or matching placebo for 6 months. Thereafter, patients on placebo were switched to migalastat 150 mg QOD for 6 months, and patients already on migalastat continued for another 6 months. After the 12 months of the main study each patient could be enrolled in 12-months open label extension study. At the end of the study patients could participate in a long-term follow-up study (041) currently ongoing.

Increases in peripheral blood mononuclear cell (PBMC) α-Gal A activity and decreases in GL-3 observed with migalastat 150 mg QOD were not further enhanced when patients switched to higher, less frequent doses (250 and 500 mg, 3 days on/4 days off), supporting the selection of the 150 mg QOD regimen for study in Phase III trials.

In the pivotal placebo controlled study (011), patients with >50% reduction of GL-3 inclusion bodies in the interstitial capillaries of the kidney were considered responders as defined in the protocol. This responder analysis (primary endpoint) did not reach statistical significant effect neither in the ITT nor in the mITT-population. However, when excluding patients who are non-responsive to migalastat (non amenable patients), a post hoc analysis showed a statistical significant difference in the decrease of the percentage of GL-3 inclusions in patients with amenable mutations (mITT-population) compared to placebo. In addition, the mean change in percentage of kidney IC with zero GL-3 inclusions was in favour of migalastat and was statistically significant.

It has been demonstrated that migalastat, overall, reduces plasma lyso-Gb3 in patients with amenable mutations. No reduction of plasma lyso-Gb3 was observed in the patients on placebo. Indeed, after 6 months of treatment in the placebo study, lyso-Gb3 concentrations in the migalastat group decreased statistically significantly compared to placebo. Also in study 012, when considering a reduction of plasma lyso-Gb3 ≤-1.0 nmol/l , plasma lyso-Gb3 was maintained in 12/18 patients (61%) in the ERT group as compared to 22/32 patients (69%) in the migalastat group . It was also demonstrated that in the patients included with a mutation subsequently qualified as non-amenable, and were switched from ERT to migalastat an increase in lyso-Gb3 was observed.

eGFR was the primary endpoint in the ERT-comparative study and a secondary endpoint in the placebo controlled study. In the ERT comparative study, migalastat was comparable to ERT in maintaining stabilisation of eGFR. The mean annualised rate of change in $eGFR_{CKD-EPI}$ was -0.40 mL/min/1.73 m^2 (95% CI: -2.272, 1.478) in the Galafold group compared to -1.03 mL/min/1.73 m^2 (95% CI: -3.636, 1.575) in the ERT group. At 6 months, in the placebo-controlled study, changes in GFR were comparable in the placebo and migalastat treated groups. After an average of 36 months of treatment in the ERT naïve study, the mean annualised rate of change in $eGFR_{CKD-EPI}$ was -0.81 mL/min/1.73 m2 (95% CI: -2.00, 0.37) for migalastat. When combining data from both pivotal studies, it was shown that GFR stabilised after 24 to 36 months of treatment with less variability. Additionally, post-hoc analysis indicated that GFR stabilisation is independent of age, gender or renal impairment at baseline.

In the placebo study no clinical significant difference in LVMi values was observed after 6 months of treatment with migalastat compared to placebo. Long term efficacy data (24/30 months) from the extension study with migalastat showed a marginal decrease of the LVMi values in the migalastat group. In the ERT-comparative study, no statistical significant difference in reduction of LVMi was demonstrated. Notably, the mean baseline LVMi values in both pivotal studies were considered to be in the normal range for age and gender. Post hoc analyses showed that patients with ≥2 organ systems involved and patients with a classic Fabry associated mutation showed similar trends. In patients with LVH at baseline, a more pronounced effect was observed in favour of migalastat in individual cases, but variability in the response was noticed. The percent decreases from baseline were greater for patients in the upper half of the normal range (i.e. patients with greater but normal LVMi) compared to

patients in the lower half of the normal range (i.e. patients with smaller but normal LVMi). This also applied to male patients and younger patients.

24 Hour urine protein was a secondary endpoint in both the comparative and placebo-controlled study. No significant differences with migalastat were observed in both studies with an increase in 24 hr urine protein observed in both the ERT and placebo groups.

Some positive effects on the gastro-intestinal symptoms of the disease were observed in the placebo controlled study after 6 months, which were maintained up to 24 months in the follow-up studies. QoL questionnaire showed numerical improvements in the general health domain score.

In the placebo controlled study, PBMC α-Gal A activity was measured in males only. There was no significant difference for the change from baseline to 6 months of treatment in both study arms. However, post hoc analysis in male patients showed that the increase in PBMC α-Gal A activity is more pronounced in patients with higher levels of α-Gal A activity at baseline. The clinical relevance of this observation needs however to be established.

Uncertainty in the knowledge about the beneficial effects

For all included patients in the pivotal studies, the diagnosis of FD was confirmed (study 011) or was made plausible based on the disease symptoms prior ERT treatment (study 012). However in the latter study, this could not be entirely confimed for all patients.

The *in vitro* HEK assay was used to identify those patients with a genetic mutation that shows a relevant increased a-gal A activity in the presence of migalastat. Despite this increase of a-gal A activity *in vitro,* some mutations seem not to show an improvement in biochemical markers (i.e. lyso-Gb3). This justifies the need to periodically monitor the patients and to reconsider the treatment in case of insufficient response after 6 months of treatment as mentioned in the SmPC section 4.4.

During the assessment, an important proportion of data points was missing and questions were raised regarding the reliability of the data. Therefore, the original data files and CFRs were requested from the MAH and analysed. It was shown that the majority "non-assessable" data points were due to patients having discontinued the study and thus having no data available after that time. The remaining non-assessable data points were due to the fact that plasma lyso-Gb3 was added mid-study by protocol amendment where the additional consent or retained plasma samples where not available in all patients. Some slight inconsistencies were observed, however these are not considered to have impacted the overall results and conclusions.

The patients included in the pivotal studies showed large heterogeneity in genotype, phenotype and clinical presentation. Sometimes patients have been included with a phenotype (A143T) that is not associated with disease activity, for example. It is still currently under debate in the scientific community on when to treat non-classical FD patients. Given their heterogeneity, the comparability of the migalastat data with the pivotal registration trials from agalsidase α or agalsidase ß or with the data described in the literature remains limited and thus caution should be considered. The post-hoc analysis performed in 14 male patients with classical Fabry disease showed , pharmacodynamic and clinical beneficial effects. These results are considered clinically relevant and are more or less comparable with the results reported in literature for ERT. Additionally, they compared favourably in the treated migalastat arm with the results obtained in untreated patients (study 011).

Although in study 012 response in treatment with migalastat was comparable to ERT, the study had its limitations because of the absence of a placebo group and the fact that no information of the course of the disease before inclusion is available.

In total 6 patients aged ≥ 65 to 72 years and one patient aged 16 years were treated to date, therefore, there is only limited experience in these populations. This is addressed in the RMP.

Risks

Unfavourable effects

In the 20 studies of the migalastat clinical development programme, 371 patients/healthy volunteers have been exposed to oral migalastat. Of these, 168 were patients with Fabry disease. One-hundred and nineteen (119) patients have been treated for at least 1 year.

Phase 1 and 2 studies demonstrated that treatment with migalastat up to a 2000 mg single dose was found to be generally safe and well tolerated.

Most frequently reported TEAEs (≥ 10%) in the phase 3 studies in the migalastat group were headache, nasopharyngitis, nausea, fatigue, pyrexia, and paresthesia. Compared to ERT, more patients on migalastat reported headache, upper respiratory tract infection and urinary tract infection. Patients on ERT reported more influenza, cough and sinusitis. TEAEs reported with the use of migalastat were mostly mild or moderate in nature, and required no intervention or were readily managed in standard clinical practice.

In the placebo controlled study, the overall frequency of treatment related AE decreased from 44% in the initial period to 21% in the open-label extension.

In the Phase 3 studies, a total of 57 SAEs were reported, 2 of which were deemed related to migalastat. These 2 patients experienced fatigue and paraesthesia in one patient, and moderate proteinuria in the other patient.

There were no deaths related to migalastat. There were 2 deaths unrelated to migalastat (one from breast cancer, one from unknown cause).

There were few discontinuations due to TEAEs (n=7), and most were related to underlying Fabry disease co-morbidities.

There were no clinically meaningful changes in laboratory values, physical examinations, vital signs, or ECGs.

A thorough QT study demonstrated that migalastat at a therapeutic dose (150 mg) or supra-therapeutic dose (1250 mg) has no effect on QTc interval.

Uncertainty in the knowledge about the unfavourable effects

Long term safety cannot be assessed as information on chronic use over 2 years is not submitted. The limited number of patients and the relatively short term exposure with migalastat do not allow complete identification of the safety profile. Further characterisation of the safety profile is deemed necessary in the post registration phase and will be done through the registry as detailed in the RMP.

The frequency of SAE increases from 6% in the initial stage to 19% in the open label extension phase. Post hoc analysis and additional safety data showed that the adverse events frequency is not increased over time.

The increase in SAEs observed after 18 months is probably linked to the study design in particular the change to an open uncontrolled design in the extension study.

The observed male infertility in the preclinical studies was not studied in humans. No infertility was reported in clinical studies. The observation that one of the partners of a male patient became

pregnant is considered reassuring and during the clinical trials, exposure of three pregnant women has been noted.

Overall, there has been no apparent effect of gender and age on the safety profile of migalastat. However, no analyses across studies were performed.

Effects Table

Table 25: Effects Table for Migalastat capsules for treatment of Fabry disease (data cut-off: October 2014).

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
Favourable Effects							
Lyso-Gb3 in male Classic FD	change from baseline to month 6	nmol/l	-	-	-36.8 (-69.9, -3.7)	Only data for 14 classic FD males was available. Baseline 99.8 ± 35.3 nmol/L. Data based on limited number of patients.	Table 16
GFR in male Classic FD	annualised rate $GFR_{EPI-CKD}$ data baseline to month 18/24	mL/min/1.73 m^2	-2.4 ±3.3	-1.5 ± 7.6	-0.3 (2.8, 2.3)	This falls within the deterioration of the renal function seen in healthy subjects. Data based on limited number of patients.	Table 16
LVMi in male Classic FD	Annualised CFB to Month 18 or 24	g/m^2	-11.8 ± 12.2	+4.1±18.5	-	Data based on limited number of patients.	Table 16
LVMi in male Classic FD	Annualised CFB to Month 18 or 24	g/m^2	-10.4 ± 11.8	-		In literature untreated male	Table 16

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
						classic Fabry patients showed an increase in LVMi (Table 18). Data based on limited number of patients.	
annualised rate $GFR_{EPI-CKD}$	annualised change in GFR rate.	mL/min/1.73 m^2	-0.40 (-2.272, 1.478)	-1.03 (-3.636, 1.575)	-	Primary end point. This was met within the pre-specified parameters of the applicant. As renal function was already in normal range at baseline (about 90 ml/min/1.73m^2) the clinical relevance can be questioned.	Figure 7
annualised rate $GFR_{EPI-CKD}$	annualised rate $GFR_{EPI-CKD}$ pooled data baseline to	mL/min/1.73 m^2	-0.40 ± 0.93	-	-0.30 ±	As at baseline GRF was in the	

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
	month 18/24				0.66	normal range the observed effect is marginal.	
GL3 inclusion bodies in IC of kidney	GL3 inclusion bodies from baseline to month 6	amount	-0.25 ± 0.1	-	0.07 ± 0.13	secondary endpoint. Significant difference (p=0.008) between treatment and placebo could be observed.	Figure 4
24-hr urine protein	change from baseline to month 18.	mg/24h	mean 49.2 ± 199.5	mean 194.5 ± 690.8	-	24 hr urine protein test is not recommended by the CKD guideline.	
24-hr urine protein	change from baseline to month 6.	mg/24h	lsmean 53.9 ± 330.2	-	lsmean 5.0 ± 197.5	24 hr urine protein test is not recommended by the CKD guideline.	
24 hr albumin:creat	albumin: creatinine ratio change from baseline to	mg/mmol	5.8 ± 19.7	14.3 ± 40.2	-	although albumin:creatin	

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
inine ratio	month 18					ine ratio is a better predictor for proteinuria the observed result may be cofounded by concomitant ACEI/ABR/RI medication	
24 hr albumin:creatinine ratio	albumin: creatinine ratio change from baseline to month 6	mg/mmol	4.1 ± 14.6	-	-1.1 ± 11.9	*Idem*	
LVMi[b]	change from baseline to month 18	g/m^2	(m[d]) -9.4 ± 12.6	(m) 4.1 ± 18.5	-	Data was gained from the comparative open label study.	Table 9
LVMi	change from baseline to month 18/24 pooled data	g/m^2	-6.6	-	-7.7	LVMi change from baseline in both the ERT and placebo controlled study show the same trend further improvement.	
LVMi	change from baseline to	g/m^2	-8.4	4.5	-	ERT controlled	Table 9

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
abnormal values	month 18 for patients with **abnormal baseline** values		(-15.7, 2.6)	(-10.7, 18.4)		study - Subgroup analysis with limited number of patients, e.g. n=13 migalastat; n=5 ERT.	
LVMi LVH	change from baseline to month 30	g/m^2	LVMi: -3.77 ± 13.15 LVH –9.56 ± 9.33	-	-	ERT-controlled study. LVMi (95% CI -8.873, 1.328) LVH (95% CI -16.630, -3.288) The effect observed in the first 18 months could be maintained over a 30 month period.	
LVMi abnormal values	change from baseline to month 18/24 for patients **with LVH[c]** pooled data	g/m^2	-7.7 (-15.4, -0.01)	-	-18.6	Placebo controlled study. Only limited number of patients	

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
						available. (n=15) Similar trend is observed in both the ERT as the placebo controlled study.	
LVMi total population	change from baseline to month 30/36	g/m^2	-17.0 (-26.2, -7.9)	-	-	open label long term data from the placebo study.	Table 6
LVMi subpopulation **with LVH[c]**	change from baseline to month 18/24 change from baseline to month 30/36	g/m^2	- 18.6 (-38.2, 1.0) -30.0 (-57.9, -2.2)	-	-	Placebo controlled study. Only limited number of patients available: month 18/24 n=8; month 30/36 n=4	Table 6
plasma lyso-Gb3	change from baseline to month 6	nmol/l	LSmean -10.58 ± 20.2	-	0.8 ± 8.6	difference in LLS mean -11.4; (p=0.03)	Figure 5
α-GAL A	changes from baseline to month 18	nmol/h/mg	5.4 ± 4.6	-0.4 ± 1.4		value only for males, α-GAL A measurement	Table 13

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
						not useful in women.	
α-GAL A	changes from baseline to month 6	nmol/h/mg	2.4 ± 3.2	-	-0.1 ± 0.4	value only for males, α-GAL A measurement not useful in women.	
Unfavourable Effects							
%change patients with >50% reduction in GL-3 inclusion bodies	%change patients with >50% reduction in GL-3 inclusion bodies change from baseline to month 6 (responder analysis).	%	41	-	28	primary endpoint. No significant difference was seen (p=0.3). A high variability in scoring of GL-3 inclusions was observed between patients and observers. This should be explained. Similar in the mITT the endpoint was also not met.	

Effect	Short Description	Unit	Migalastat with SD	ERT	placebo	Uncertainties / Strength of evidence	References
annualised rate $GFR_{EPI-CKD}$	annualised rate $GFR_{EPI-CKD}$ baseline to month 6	ml/min/1.73 m^2	2.3 ± 17.3	-	-1.2 ± 14.4	Mean baseline values were in the normal range. Annual decline in healthy subjects is -1 mL/min/1.73 m^2/year.	
LVMi	change from baseline to month 18	g/m^2	(f[e]) -4.5 ± 10.6	(f) -7.2 ± 9.4			Table 9

LVMi	change from baseline to month 6	g/m^2	0.17 ± 7.9	-	-0.7 ± 6.7	Only double blind 6 month data is available. This might be too short to observe clinical relevant changes. This is also known from the current ERT treatment.		lyso-Gb3	change from baseline to month 18	nmol/l	1.7 ± 5.5	-1.9 ± 4.9	-	although marginal difference ERT seems to favour over migalastat	

Abbreviations: a) ERT = enzyme replacement therapy (either agalsidase α or agalsidase ß); b) LVMi = left ventricular mass index; c) LVH = Left ventricular hypertrophy; d) m = male patient; e) f = female patient;

Balance
Importance of favourable and unfavourable effects

The current treatment in Fabry disease consists of ERT and is restricted to eligible patients only (Biegstraaten *et al.*, 2015). ERT is hampered by its parenteral use, antibody formation and local side effects. Therefore, in Fabry disease, there remains an unmet medical need for additional therapies and the oral mode of administration of migalastat could be an advantage, at least for those patients defined with an amenable mutation.

Pharmacological activity was demonstrated in particular in the placebo-controlled study in male patients with classic Fabry phenotype with a statistical significant reduction of lyso-Gb3 and statistical significant reduction in the average GL-3 inclusion bodies in the interstitial capillaries of the kidney. The clinical relevance of these pharmacodynamic effects in the currently claimed population was discussed, because the primary endpoint of responder analysis (patients with >50% reduction of GL-3 inclusion bodies) did not reach a statistical significant effect in the overall study population (study 011). Treatment naive patients showed stabilisation with respect to renal and cardiac function, in the first 6 months of the 011 study (blinded part). However no differences could be demonstrated compared to placebo. Improvements in GI symptoms did occur, but their clinical relevance remains difficult to interpret due to the limited number.

The reason why the primary endpoint was not met can explained by the fact that a HEK assay has been GLP validated after enrolment of the study and some subjects where subsequently identified as non amenable patients. This has been demonstrated by a post hoc analysis in amenable patients. This post hoc analysis showed a statistical significant difference with placebo in the decrease of % GL-3 inclusions. Additionally, further analysis of the eGFR and LVMi in the classical male patients phenotype during open follow-up period indicated that 1) the stabilisation achieved with migalastat is in line with ERT treatment (based on historical comparison with agalsidase α and agalsidase β data) and 2) the results observed with migalastat are better than the results observed in untreated patients. The results observed in the male patients with classical phenotype are clinically relevant.

These results are further supported by the data from the ERT comparative study, where changes in the primary endpoint of eGFR after 18 months of migalastat treatment were considered comparable with ERT. Beneficial effects on LVMI were also observed. Of note, this study was hampered by some limitations as follows: The number of patients tested was small and the data >18 months are uncontrolled with no placebo arm and absence of information on the course of the disease before inclusion (assay sensitivity). However, the available literature data in non-classical FD patients indicate that when ERT treatment is stopped or when half the normal dose of ERT is administered, the deterioration of FD symptoms may occur already after 9 months, suggesting that in some patients treated with migalastat a true clinical effect can be concluded, considering the duration of the trial.

Post-hoc analysis showed that the results observed are independent of age, gender and disease burden at baseline, except for LVMi values. For LVMi values, the response to migalastat depends on the cardiac mass at baseline (higher values at baseline will result in a more pronounced response).

In both studies, the variability in the response was high, but data, although limited, seem to indicate that this variability would diminish over time after 24/30 months of treatment. Long term data (up to 38 months) from the placebo study indicated that stabilisation of eGFR and/or a reduction of cardiac mass was achieved in some patients treated with migalastat.

Nevertheless, the physician should closely monitor the patients on migalastat, and re-evaluate the therapy after 6 months or stop migalastat treatment as necessary. This is addressed in the SmPC.

In the ERT-controlled study, all patients were diagnosed with Fabry disease by their treating physicians and in accordance with local treatment guidelines. Patients included in the pivotal studies were not always comparable with the patients mentioned in literature who are generally considered classical Fabry patients. The discussion when to treat non-classical FD patients pharmacologically is still ongoing and under debate, compared to classical Fabry patients. Therefore the decision to treat non clinical Fabry patients should be ultimately left to the treating physician and no further restrictions in the indication is necessary apart from the amenability of the patient mutation.

The available adverse event profile, laboratory evaluations, physical examinations, vital signs and ECGs, demonstrated that migalastat 150 mg QOD is a generally safe and well-tolerated treatment for Fabry disease.

Benefit-risk balance

The diagnosis of FD for all patients in both pivotal studies was based on the physician expertise and local clinical guidelines.

The available data showed that in patients amenable for migalastat, pharmacodynamic and clinical effects have been demonstrated.

This clinical effect was assessed also in a subgroup of classical male Fabry patients with an amenable mutation.Comparison of the identified classical male FD patients in study 011 with historical ERT data and comparison with literature on untreated patients, allows to conclude that, in classical male patients, the response pattern of migalastat on the GFR is comparable with the one observed with Enzyme replacement therapy and is better than placebo.

The LVMi results of migalastat treated patients indicate the same favourable stabilisation as reported for ERT therapy compared to a deterioration in untreated patients.

Differences in age, residual -Gal A activity and plasma lyso-Gb3 values limit the comparability of the included patients with the patients treated with agalsidase α and agalsidase ß as mentioned in the respective EPARs or reported in the literature.

Migalastat 150 mg QOD has a generally safe and well-tolerated safety profile, athough patient exposure remains limited.

Discussion on the benefit-risk assessment

The applicant has clarified that the data points entered for both pivotal studies was performed adequately, though some minor deviations in patient numbers were noticed. These differences however do not impact the conclusions and the results observed in both studies are considered reliable. The clinical data set is considered acceptable for assessment of efficacy and safety. Uncertainties remain due to trial design, limited number of patients tested, variability in response and lack of long-term clinical data, but the level of evidence is considered sufficient and acceptable for such a rare disease.

The efficacy has been demonstrated for patients amenable to migalastat based on the pharmacodynamic and clinical effects observed. Migalastat should not be used in patients with non amenable mutations. The list of mutations tested as being amenable and non amenable is provided in the SmPC.

The oral administration could be an advantage in patients with Fabry disease compared to ERT. Treatment decisions will need to be made on an individual patient basis and adequate monitoring is necessary. It is advised to monitor the patients to assess renal, cardiac functions and biochemical markers every 6 months.

An acceptable safety profile has been demonstrated, it remains however limited over time based on the current data. Further safety data will be provided after marketing authorisation to further characterise the safety profile of migalastat over long term in the clinical setting.

3.1. Conclusions

The CHMP consider the overall B/R of migalastat to be positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Galafold for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that migalastat hydrochloride is qualified as a new active substance.