EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/CHMP/412211/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Galafold

International non-proprietary name: migalastat

Procedure No. EMEA/H/C/004059/II/0029

Note

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

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List of abbreviations

Term	Definition
AE	Adverse Event
ANOVA	Analysis of Variance
AT1001	Migalastat
AUC0-τ	Area under the plasma concentration-time curve over the dosing interval (i.e. 48 hours)
BW	Body Weight
CHMP	Committee for Evaluation of Human Medicinal Products
CLss/F	Apparent Oral Clearance at Steady-State concentration
CLT/F	Apparent Oral Plasma Clearance
Cmax	Maximum Observed Plasma Concentration
Cmin	Minimum Observed Plasma Concentration
CWRES	Conditional Weighted Residual
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ERT	Enzyme Replacement Therapy
FOCE-I	First-Order Conditional Estimation with Interaction
GCP	Good Clinical Practice
GL-3	Globotriaosylceramide
GLA	Gene encoding α-galactosidase A
IA	Interim analysis
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LC-MS/MS	Liquid Chromatography with tandem Mass Spectrometry
lyso-Gb3	Globotriaosylsphingosine
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
NONMEM	Non Linear Mixed Effects Model
pcVPC	Prediction-Corrected VPC
PD	Pharmacodynamics
$PEC_{surfacewater}$	Predicted Environmental Concentration in surface water
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
popPK	Population pharmacokinetics
PsN	Perl-speaks-NONMEM
PT	Preferred Term

Q/F	Apparent Distribution Clearance
QOD	Every Other Day
SAE	Serious Adverse Event
SD	Standard Deviation
SmpC	Summary of Product Characteristics
SOC	System Organ Class
T1/2	Terminal elimination half-life
TAD	Concentration-time after dose
TEAE	Treatment-Emergent Adverse Event
tmax	Time to reach Cmax
V2/F	Apparent oral Volume of Distribution of the central compartment
V3/F	Apparent oral Volume of Distribution of the peripheral compartment
VPC	Visual Predictive Checks
vPvB	Very persistent/Very bioaccumulative
Vss/F	Apparent oral volume of distribution at steady-state concentration
WT	Weight
WTCO	Allometric Weight Coefficient
α-Gal A	α-galactosidase A

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amicus Therapeutics Europe Limited submitted to the European Medicines Agency on 24 November 2020 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Galafold (migalastat) to include long-term treatment of adolescents 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC and Section 1 and 2 of the Package Leaflet are updated accordingly. A revised RMP version 4.0 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Galafold, was designated as an orphan medicinal product EU/3/06/368 on 31 May 2016. Galafold was designated as an orphan medicinal product in the following indication:

"Treatment of Fabry disease"

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0137/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0137/2019 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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Ondřej Slanař

Timetable	Actual dates
Submission date	24 November 2020
Start of procedure:	26 December 2020
CHMP Co-Rapporteur Assessment Report	19 February 2021
CHMP Rapporteur Assessment Report	22 February 2021
PRAC Rapporteur Assessment Report	22 February 2021
PRAC members comments	3 March 2021
Updated PRAC Rapporteur Assessment Report	5 March 2021
PRAC Outcome	11 March 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 March 2021
Request for supplementary information (RSI)	25 March 2021
CHMP Rapporteur Assessment Report	25 May 2021
PRAC Rapporteur Assessment Report	25 May 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	10 June 2021
CHMP members comments	14 June 2021
Updated CHMP Rapporteur Assessment Report	17 June 2021
Opinion	24 June 2021

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). It 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 1384 Fabry disease-causing GLA mutations have been identified based on data presented by the applicant. 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 paediatric 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 Fabry Disease in only a limited number of carriers.

In addition to oral Galafold for the treatment of Fabry disease, Enzyme Replacement Therapy (ERT), irrespective of the severity of the disease is also available. These ERT products (Fabrazyme, Replagal) are intravenous (IV) infusion of manufactured enzyme to be administered every 14 days and are indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).

The application is an extension of indication for Galafold (migalastat) to include long-term treatment of adolescents 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation.

2.1.1. About the product

Migalastat, a low molecular weight iminosugar, is an analogue of the terminal galactose of GL-3. Non-clinical *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 stabilises these mutant forms of α-Gal A in the endoplasmic reticulum, facilitating their proper trafficking to lysosomes where migalastat dissociation 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).

Galafold (migalastat) is currently indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in section 5.1 of the SmPC).

2.1.2. The development programme/compliance with CHMP guidance/scientific advice

The development programme is according to the paediatric investigation plan (PIP).

The present application includes the results of Study AT1001-020 (stage 1), which is a 2-stage, open-label, uncontrolled, multicenter study to evaluate the safety, Pharmacokinetics (PK), Pharmacodynamics (PD), and efficacy of migalastat treatment in paediatric subjects 12 to < 18 years of age and weighing ≥ 45 kg with Fabry disease and with amenable mutations to the gene encoding α-

galactosidase A (GLA). Stage 2 will collect efficacy data in these patients; however, as this pertains to an interim analysis, only the stage 1 data is submitted.

Stage 1 of the AT1001-020 study is a clinical measure (Study 3) defined in the agreed Paediatric Investigation Plan (PIP) for migalastat (EMEA-001194-PIP01-11-M04), to support extrapolation of efficacy from adults to the adolescent population aged 12 to 15 years.

2.1.3. General comments on compliance with GCP

Study AT1001-020 is being performed in compliance with Good Clinical Practice as claimed by the applicant, including archiving of essential documents.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

An updated environmental risk assessment has been submitted and is presented below.

2.2.1. Ecotoxicity/environmental risk assessment

The calculation of the refined Predicted Environmental Concentration in surface water ($PEC_{surfacewater}$) of the Applicant is equal to that of the initial marketing authorisation application (original submission). The extension of the indication for 12-16-year-old patients does not affect the PEC calculations; neither does it affect the persistence, bioaccumulation and toxicity (PBT) assessment. Therefore, the original conclusions that Migalastat is not subject to PBT, nor very persistent/very bioaccumulative (vPvB) and that a phase II assessment is not necessary because the refined PECsw is 0.00077 µg/L, which is below the action limit of 0.01 µg/L, are still valid.

2.2.2. Conclusion on the non-clinical aspects

Considering the above data, migalastat is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trial was performed in accordance with GCP as claimed by the MAH.

The development programme consisted of the following study:

- A Phase 3b, 2-stage, open-label, uncontrolled, multicenter study to evaluate the safety, PK, PD, and efficacy of migalastat treatment in paediatric subjects 12 to < 18 years of age and weighing ≥ 45 kg (99 pounds) with Fabry disease and with amenable GLA variants. Subjects were either naïve to enzyme replacement therapy (ERT) or had stopped ERT at least 14 days at the time of screening.

Stage 1 consisted of a treatment period of approximately 1 month (4 weeks) during which time PK assessments were conducted (at baseline and between Days 15 and 30).

To support this application, an interim clinical study report has been submitted, presenting the results of the stage 1 (1-month) safety and PK data only for subjects with Fabry disease in the 12 to < 16 years old age group who had Stage 1 plasma concentration-time data available as of the cut-off date.

2.3.2. Pharmacokinetics

Special populations

Sparse sampling for plasma migalastat concentrations to estimate exposure was done at baseline and for one 24-hour period between days 15 and 30. Patients with 1 plasma concentration-time data available as of the cut-off date were included in the interim analysis. Subjects were randomly assigned to one of the 3 3 PK sampling groups. See **Table 1**.

Table 1. Sparse sampling schedule in study AT1001-020.

PK Sampling Group[a]	Time Post-dose			
	Sample 1	Sample 2	Sample 3	Sample 4
1	1h to 1h 15min	1h 30min to 2h	5h to 5h 30min	6h 30min to 7h
2	1h to 1h 15min	2h 45min to 3h 15min	5h 15min to 5h 45min	10h 45min to 11h 15min
3	3h 15min to 3h 45min	3h 45min[b] to 4h 15min	8h 15min to 8h 45min	8h 45min[b] to 9h 15min

Plasma samples were analysed for migalastat using a validated LC-MS/MS method; this method was also used in the original MAA for the determination of migalastat.

2.3.3. PK/PD modelling

A population pharmacokinetics (popPK) model previously developed from healthy adult volunteers and adult patients with Fabry disease after oral migalastat administration. After pooling plasma concentration-time data from Phase I, II, and III studies of AT1001 administered orally in adults using a range of doses from 25 mg to 675 mg and regimens under fasting conditions, the following conclusions were made:

- A two-compartment population pharmacokinetic model with linear time-dependent absorption sufficiently characterises the pharmacokinetics of migalastat in plasma after oral administration.
- Renal function is the most important determinant of variability in migalastat exposure, with an average 3-fold range occurring for eGFR values between 30 and 120 mL/min/1.73 m^2. Subject weight is the second-largest determinant of variability in migalastat exposure, with an average < 2-fold difference for body weights between 50 and 170 kg. These average differences are not clinically relevant.
- The predicted exposures in Fabry disease remain similar to those reported for healthy volunteers (although a moderate decrease of 15% - 31% in both clearance and volume of distribution was observed in healthy volunteers compared to Fabry patients).

The dose rationale for adults (123 mg every other day (QOD)) was supported by the evaluation of several dose levels and regimens in the 4 Phase II studies (50, 150, and 250 mg QOD; 50 mg once daily; 25, 100, and 250 mg twice daily; and 250 and 500 mg x3 days and off 4 days).

The present population PK model was considered appropriate for adults; however, it does not have an allometric component with standard exponents (e.g. 0.75 for CLT/F), making paediatric predictions less feasible. Thus, the adult population PK model requires some adjustments to allow extrapolation of migalastat PK to the paediatric age sub-groups of 2 to <6, 6 to <12 and 12 to <18 years.

The popPK model of migalastat showed that subject weight (WT) and/or renal function (estimated glomerular filtration rate, eGFR) at baseline significantly impacted the apparent oral plasma clearance (CLT/F) and apparent oral volume of distribution of the central compartment (V2/F). In contrast, other covariates such as sex, age, drug formulation (solution or suspension vs 25 mg capsule vs 150 mg capsule) were not statistically/clinically significant. Since renal function gradually increases from birth and reaches adult levels by the second year of life (Rubin 1949), there are no expected age-dependent changes in eGFR in the paediatric population 2 years and older than adults. Additionally, paediatric patients with Fabry disease usually have a normal renal function or may experience renal hyperfiltration (Hopkin 2008); therefore, weight-based dosing regimens, assuming that paediatrics have a normal renal function, were planned for the simulations in paediatric Fabry patients.

NONMEM program was used to develop the popPK model of migalastat in adults using first-order conditional estimation with interaction (FOCE-I). Simulations were conducted using NONMEM to obtain plasma concentration-time; all graphical analyses were performed using R,; noncompartmental analysis and pharmacokinetic parameters summaries were conducted using Phoenix WinNonlin. Bootstrapping and visual predictive checks (VPC)s were conducted using Perl-speaks-NONMEM (PsN) R packages of popED and mrgsolve were used in the optimal sampling strategy.

The steps for population PK model optimisation were:

- Re-examine absorption models;
- Add allometric scaling components to CLT/F and Q/F with an allometric exponent equal to 0.75 and to V2/F and V3/F with an allometric exponent equal to 1.0; and
- Evaluate whether the allometric exponent should be on total CLT/F or on the non-renal clearance only.

The original linear time-dependent absorption model was chosen among the different absorption models because the conditional weighted residual (CWRES) over time plots were substantially improved, with much less bias and fluctuation throughout the profile. Because the time varying Ka model allows Ka to continuously increase, an upper limit of time-dependent absorption coefficient Ka was set up at 24 hours post-dose to provide reasonable Ka values in simulation/predictions; this was considered to be a minimal change to the original model as the drug is considered to be fairly fully absorbed within 7-10 hours, regardless of the model chosen.

The overall purpose of the model development was to come up with a model for paediatric extrapolation. The theoretical power model indices of 0.75 (for CL and Q), and 1 (for V2 and V3) were applied and evaluated. The diagnostic plots suggested that allometric scaling was only appropriate for those < 70 kg.

The final equations for CLT/F, Q/F, V2/F and V3/F were presented as follows:

- WTCO = WT/70 when WT $\leq$ 70; WTCO = 1 when WT > 70, where WTCO was the allometric weight coefficient with allometric scaling for subjects with weight $\leq$ 70 kg.
- $CL_T/F = tvCL * (RF)^{CLEGFR} * \mathbf{WTCO^{0.75}} * (1 + CLHVT)^{1-FBRY} * \exp(\text{ETA of IIV on CL/F})$
- $V_2/F = tvV_2 * \mathbf{WTCO^{1}} * (1 + V_2HVT)^{1-FBRY} * \exp(\text{ETA of IIV on } V_2/F)$

- Q/F = TVQ $*$ $\mathbf{WTCO^{0.75}}$ and V_3/F = TVV3 $*$ $\mathbf{WTCO^{1}}$, where TVQ and TVV3 were the typical value of Q/F or V_3/F, respectively.

Considering that renal function is comparable between paediatric patients 2 years and up and adults, the model was modified to apply the allometric exponent to only the non-renal clearance component. The model that successfully converged suggested only a very small portion of CLT/F was accounted for by non-renal clearance; therefore, the allometric scaling applied to this very small non-renal clearance did not really impact the overall CL_T/F. The diagnostic plots also suggested that applying the allometric exponent to overall CL_T/F for subjects < 70kg was better than applying it to the non-renal clearance. Moreover, paediatric CL_T/F values extrapolated from the non-renal model were higher than the overall CL_T/F approach, resulting in higher paediatric doses for achieving equivalent exposures with adults which was a less conservative approach. Therefore, the overall CL_T/F scaling approach is more conservative and was chosen for the final model.

The final model is shown in **Table 2**.

Table 2. Parameter estimates from the Final Optimized popPK model of migalastat (with and without bootstrap).

Parameter	NONMEM		Bootstrap	
	Estimate (%RSE); [95% CI]	IIV (%CV)	Estimate (%RSE); [95% CI]	IIV (%CV)
Typical EGFR-related estimate for those with Fabry disease, with EGFR= 90 mL/min/1.73 m^2, and with body weight >= 70 kg	18.6 (16.3%); [12.6, 24.6]	28.8%	18.5 (16.0%); [14.0, 25.4]	28.5%
Typical EGFR-related estimate for those with Fabry disease, with EGFR>120 mL/min/1.73 m^2, and with body weight >= 70 kg	20.9 (17.4%); [13.8, 28.0]		20.6 (17.3%); [15.4, 28.8]	
EGFR-related exponential index on CL/F	0.922 (5.64%); [0.820, 1.02]		0.925 (5.25%); [0.832, 1.02]	
Typical total CL/F (L/h) for those with Fabry disease, with EGFR= 90 mL/min/1.73 m^2, and with body weight >= 70 kg [a]	14.8		14.9	
Typical total CL/F (L/h) for those with Fabry disease, with EGFR>120 mL/min/1.73 m^2, and with body weight >= 70 kg [b]	16.5		16.4	
Typical V_2/F (L) for those with Fabry disease, with body weight>=70 kg	70.1 (5.29%); [62.8, 77.4]	34.5%	69.7 (4.8%); [63.8, 76.8]	33.9%
Typical Q/F (L/h) for those with body weight>=70 kg	1.00 (5.17%); [0.899, 1.10]	-	1.01 (4.59%) [0.928, 1.11]	-
Typical V_3/F (L) for those with body weight>=70 kg	27.5 (11.7%); [21.2, 33.8]	-	27.5 (11.9%); [22.7, 35.2]	-
K_a (intercept) (h^{-1})	0.256 (9.41%); [0.209, 0.303]	60.4%	0.256 (8.60%); [0.211, 0.298]	59.9%
K_a (slope)	0.284 (9.12%); [0.233, 0.335]	60.7%	0.282 (7.45%); [0.244, 0.326]	60.6%
Lag time (h)	0.175 (4.65%); [0.159, 0.191]	-	0.176 (4.52%); [0.160, 0.190]	-
WT-related exponential index on CL/F and Q/F for those with body weight<70 kg	Fixed to 0.75	-	Fixed to 0.75	-
WT-related exponential index on V2/F and V3/F for those with body weight<70 kg	Fixed to 1	-	Fixed to 1	-
Fractional Change in V_2/F in subjects without Fabry disease (decrease in V_2/F)	-0.306 (12.8%); [-0.383, -0.229]	-	-0.305 (12.3%); [-0.372, -0.227]	-
Fractional Change in total CL/F in subjects without Fabry disease (decrease in total CL/F)	-0.150 (24.9%); [-0.223, -0.077]	-	-0.151 (23.5%); [-0.223, -0.081]	-
Residual Error (%)	26.2%; [23.2%, 29.0%]	-	26.3%; [24.5%, 27.8%]	-
Residual Error (ng/mL)	2.55; [NA, 3.76]	-	2.47; [1.25, 3.51]	-

a. Derived total CL/F parameter from typical EGFR-related estimate and EGFR-related exponential index; total CL/F= THETA(1)^THETA(9), where THETA(1) is the typical EGFR-related estimate and THETA(9) is the estimate of exponential index for patients with Fabry disease, EGFR= 90 mL/min/1.73 m^2, and with body weight >= 70 kg.

b. Derived total CL/F parameter from typical EGFR-related estimate and EGFR-related exponential index; total CL/F= THETA(13)^THETA(9), where THETA(13) is the typical EGFR-related estimate and THETA(9) is the estimate of exponential index for patients with Fabry disease, EGFR > 120 mL/min/1.73 m^2, and with body weight >= 70 kg

Goodness of fit plots , and Visual Predictive Check showed acceptable performance. See

Figure 1, Figure 2 and **Figure 3**.

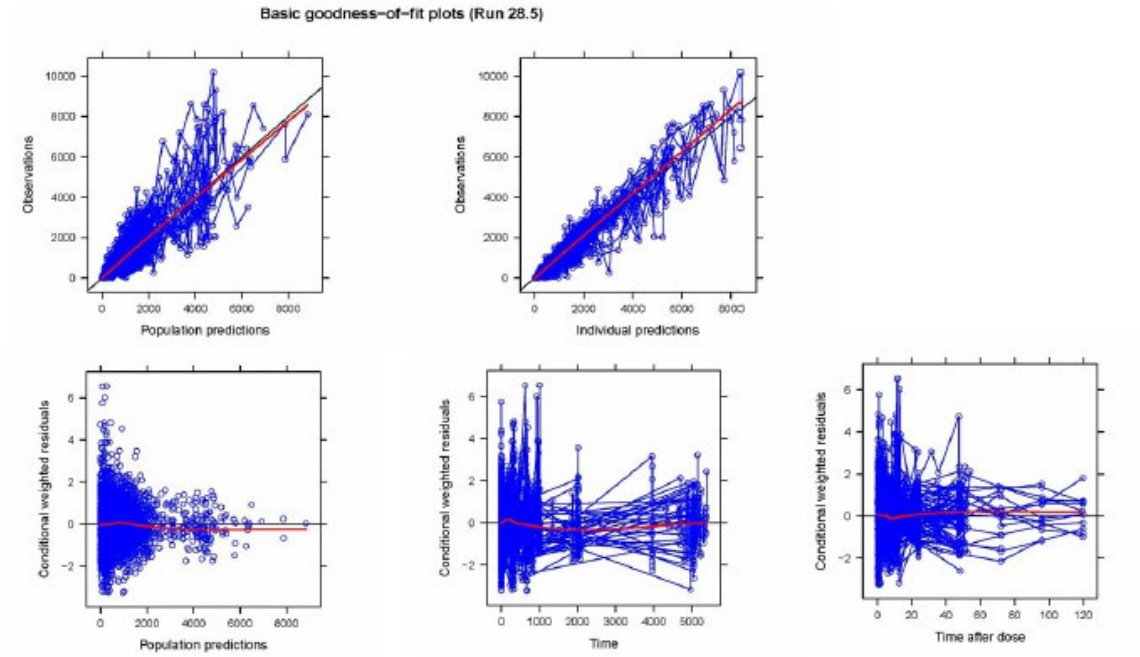

Figure 1. Goodness of Fit Plots for Final Optimised Model.

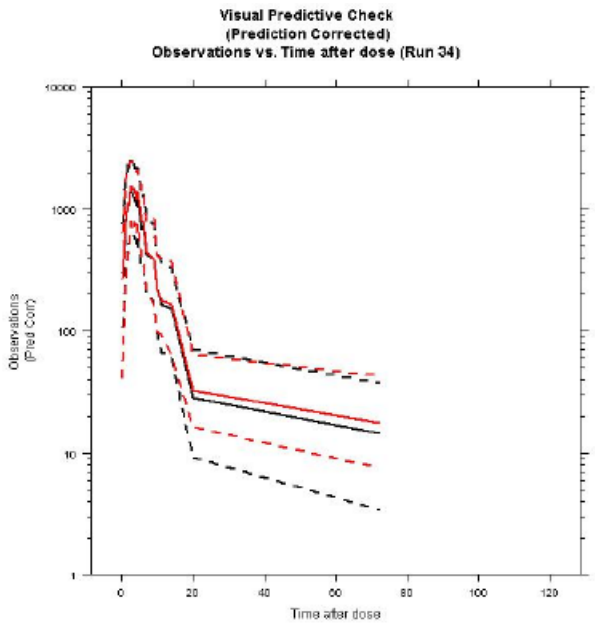

Figure 2. Prediction-Corrected VPC (pcVPC) for the concentration-time after dose (TAD) profiles of migalastat (semi-log scale).

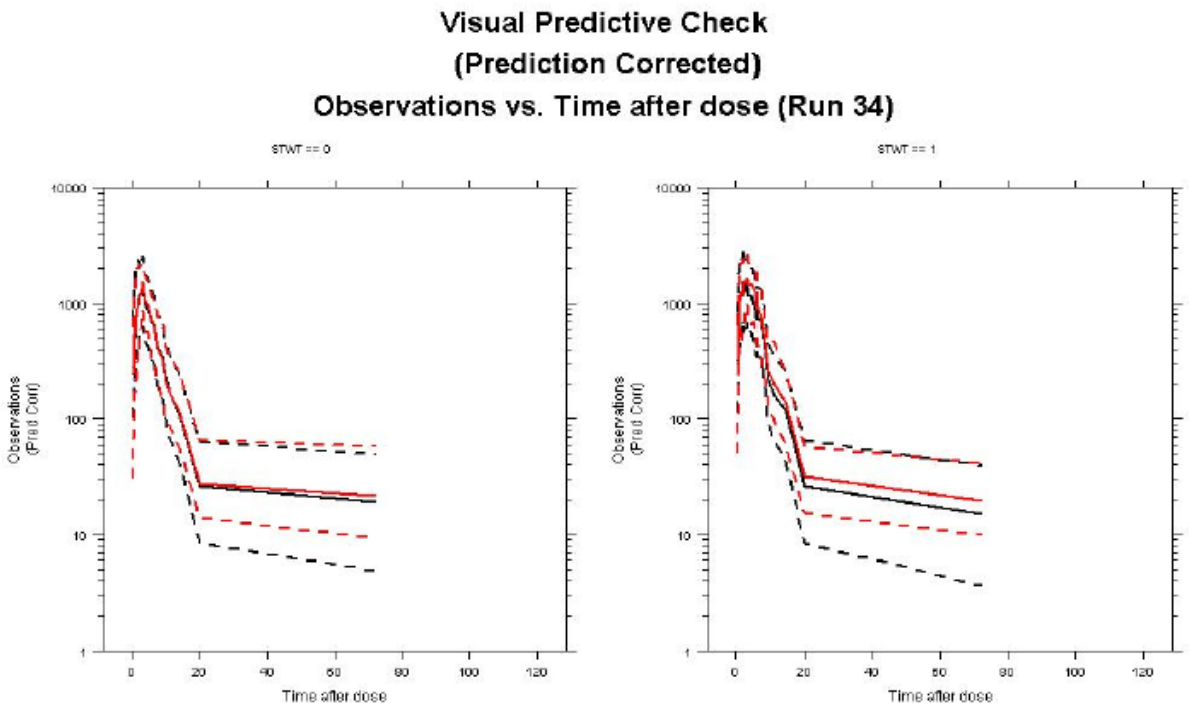

Figure 3. Prediction-Corrected VPC (pcVPC) for the concentration-time after dose (TAD) profiles of migalastat stratified by Weight (STWT=0 for WT>70 kg, STWT=1 for WT⩽70 kg) (semi-log scale).

In addition, the estimated parameters from bootstrap (see **Table 1**) were nearly identical to those estimated from the original dataset. All parameters were estimated with adequate precision. The NONMEM estimates (which assume each parameter has a normal distribution) were nearly identical to the nonparametric bootstrap estimates (which do not assume that each parameter has a normal distribution).

Model performance comparison was made for the adult population. Simulations were performed using a simulated adult dataset following 150 mg QOD doses with both model parameters and the steady-state AUCtau and Cmax were compared. The results (see **Table 3**) showed comparable results between the original model and the optimised/updated model, indicating a good model performance.

Table 3. Comparison between the original model and optimised model with simulation results for adults receiving 150 mg QOD dose.

Model	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)
	Geometric Mean (CV% of Geometric Mean)	
Original Model (N=100)	1120 (34.5%)	7200 (32.5%)
Optimized Model (N=100)	1120 (36.3%)	7580 (32.0%)

Clinical trial simulations were then conducted to predict the exposure in paediatric patients receiving the following initial various weight-based dosing regimens (comparable to about a 3 mg/kg dose):

- <15 kg receive 25 mg QOD
- 15 to <25 kg receive 50 mg QOD
- 25 to <35 kg receive 75 mg QOD
- 35 to <50 kg receive 100 mg QOD
- ≥50 kg receive 150 mg QOD

The doses were targeted to achieve a similar AUCtau at steady-state (and not Cmax or Cmin) in paediatric sub-groups to that in adults with normal renal function receiving migalastat 150 mg every other day (QOD).

To be noted: The paediatric simulations assumed the following:

- 100 subjects per group for 4 groups including 3 paediatric groups with Fabry disease (2 to <6, 6 to <12 and 12 to <18 years) and 1 adult group (Fabry disease with normal renal function), assuming 50% males and 50% females in each group.
- All children (and adults) had a normal renal function.
- Age for paediatric subjects was sampled from a uniform distribution within the age limit of each group.
- Weight for paediatric subjects was sampled from the normal distribution using the World Health Organization (WHO) weight chart for age for those less than 5.08 yrs., and from the Centers for Disease Control and Prevention (CDC) weight chart for those between 5.08 and 17.99 year old.
- The weight of the adult group was sampled from a random normal distribution (mean=75, standard deviation (SD)=15).

The results (see **Table 4**) showed that the Cmax values were comparable among groups, whereas the AUCtau (0-48 hrs) was about 25% lower in age group 2 to <6 yr olds (5570 vs 7580 h*ng/ml), and about 10% lower in age group 6 to <12 yr olds (6850 vs 7580 h*ng/ml).

Table 4. Paediatric study design with empirical dose scheme PK parameters.

Groups	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	CL/F (L/h)	QOD Dose (mg)	T_{max} (hrs)
	Geometric Mean (CV% of Geomean) [95% CI] of Geometric Mean Parameter			Frequency	Median (Min, Max)
2 to<6 yrs N=100	1030 (38.6%) [490, 2150]	5570 (37.9%) [2700, 11500]	5.56 (37.0%) [2.73, 11.3]	25 mg (N=40) 50 mg (N=60)	2 (1-4)
6 to <12 yrs N=100	1100 (37.4%) [536, 2250]	6850 (34.0%) [3550, 13200]	8.52 (38.3%) [4.09, 17.8]	50 mg (N=36) 75 mg (N=37) 100 mg (N=22) 150 mg (N=5)	3 (1-4)
12 to <18 yrs N=100	1190 (40.1%) [553, 2560]	7530 (37.5%) [3670, 15500]	14.1 (39.4%) [6.64, 29.9]	75 mg (N=2) 100 mg (N=32) 150 mg (N=66)	2 (1-4)
Adults N=100	1120 (36.3%) [556, 2250]	7580 (32.0%) [4090, 14100]	16.2 (32.0%) [8.70, 30.0]	150 (N=100)	3 (2-5)

A weight range analysis with a 5 kg increment on the simulated data was applied (see for results table PK 5). Using the AUC_{tau} geometric mean value of adult group with normal renal function receiving 150 mg QOD dose as the target (7580 h*ng/ml), dose adjustment was performed for subjects in each weight group considering dose proportionality with the equation:

$Dose_{adj,i} = Dose_{org,i} * AUC_{tau,a} / AUC_{tau,i}$,

where $Dose_{adj,i}$ is the adjusted dose for each weight group for achieving equivalent AUC exposure with adults, $Dose_{org,i}$ is the original dose used for each weight group, $AUC_{tau,a}$ is the adult group geometric mean value of 7580 h*ng/ml, and $AUC_{tau,i}$ is the geometric mean value for each weight group.

Additionally, the adjusted doses were rounded to the nearest practical dose level to ensure simplicity in formulation preparation.

Table 5. Paediatric dose adjustment per 5 kg weight range

Weight Range (kg)	Geometric Mean AUC_{tau} (h*ng/mL)	Number of Subjects	Original Dose (mg)	Adjusted Dose Calculated (mg)	Adjusted Dose Round (mg)
10-15	4481	40	25	42	40
15-20	6658	52	50	57	60
20-25	5673	43	50	67	60
25-30	7413	21	75	77	80
30-35	7230	19	75	79	80
35-40	8040	18	100	94	100
40-45	7817	18	100	97	100
45-50	5904	18	100	128	150
50+	7907	71	150	144	150

The resulted adjusted dosing scheme for paediatric groups was summarised as below:

- <15 kg receive 40 mg QOD
- 15 to <25 kg receive 60 mg QOD
- 25 to <35 kg receive 80 mg QOD
- 35 to <45 kg receive 100 mg QOD
- ≥45 kg receive 150 mg QOD

Based on the dose adjustment analysis and the new revised dosing scheme, simulations were re-run for the 3 paediatric groups (paediatric group age 2 to <6, 6 to <12 and 12 to <18 yrs), with all other assumptions and settings unchanged. The results are shown in **Table 6** and **Figure 4**.

Table 6 Predicted migalastat in paediatrics based on proposed weight-based dosing scheme.

Groups	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	CL/F (L/h)	QOD Dose (mg)	T_{max} (hrs)
	Geometric Mean (CV% of Geomean) [95% CI] of Geometric Mean Parameter			Frequency	Median (Min, Max)
2 to <6 yrs N=100	1400 (36.8%) [691, 2840]	7540 (35.7%) [3790, 15000]	5.66 (32.1%) [3.04, 10.5]	40 mg (N=37) 60 mg (N=59) 80 mg (N=4)	2 (1-4)
6 to <12 yrs N=100	1230 (36.9%) [606, 2500]	7660 (33.1%) [4040, 14500]	8.96 (38.6%) [4.28, 18.8]	60 mg (N=21) 80 mg (N=48) 100 mg (N=21) 150 mg (N=10)	3 (1-4)
12 to <18 yrs N=100	1250 (36.6%) [616, 2520]	7870 (32.1%) [4230, 14600]	14.1 (38.2%) [6.77, 29.3]	80 mg (N=3) 100 mg (N=20) 150 mg (N=77)	2 (1-4)
Adults N=100	1120 (36.3%) [556, 2250]	7580 (32.0%) [4090, 14100]	16.2 (32.0%) [8.70, 30.0]	150 (N=100)	3 (2-5)

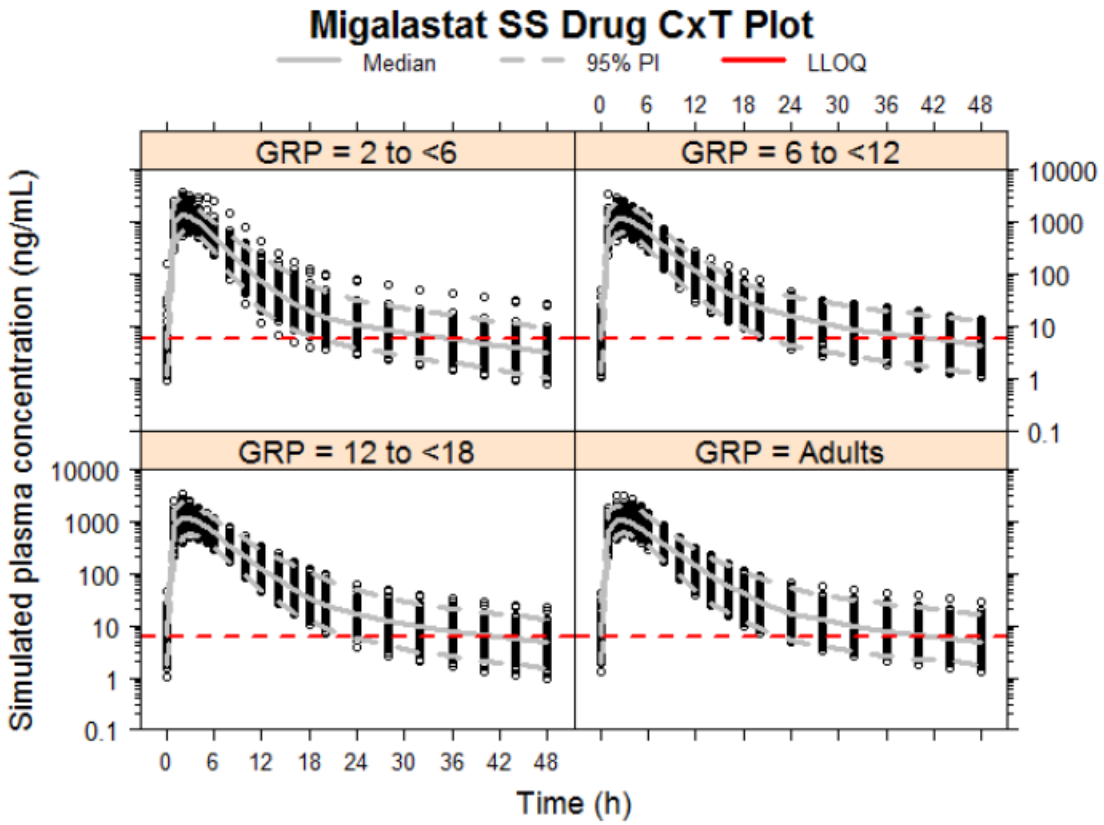

Figure 4. Plasma concentration-time data in paediatric patients receiving the proposed weight-based dosing of migalastat.

popPK data in adults and adolescents weighing ≥ 45 kg receiving the 150 mg migalastat HCL capsule q.o.d. are presented in **Table *7***.

Table 7. Simulated pharmacokinetic endpoints by age groups and adults ⩾ 45 kg.

Age Group	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC_{tau} (h*ng/mL)
12 to < 16 years	1377 (42%)	8.06 (37%)	8581 (37%)
16 to < 18 years	1275 (39%)	8.37 (38%)	8408 (37%)
12 to < 18 years	1319 (41%)	8.23 (37%)	8483 (37%)
Adults	1191 (37%)	8.13 (41%)	7958 (35%)

Abbreviations: $AUC_{0\text{-}tau}$ = plasma concentration-time curve during a dosing interval at steady state ($AUC_{0\text{-}\tau}$); C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration
Note: Data are summarized as geometric mean (CV%).

Results from the ANOVA analysis are presented in **Table 8**.

Table 8 Summary of the ANOVA on predicted pharmacokinetic parameters for subjects weighing ⩾ 45 kg.

PK Endpoint	Age Group	Point Estimate (90% CI)
$AUC_{0\text{-}tau}$	12 to < 16 years	108 (98.6, 118)
	16 to < 18 years	106 (97.1, 115)
	12 to < 18 years	107 (99.0, 115)
C_{max}	12 to < 16 years	116 (105, 127)
	16 to < 18 years	107 (97.6, 117)
	12 to < 18 years	111 (102, 120)

Abbreviations: $AUC_{0\text{-}tau}$ = plasma concentration-time curve during a dosing interval at steady state; CI = confidence interval; C_{max} = maximum observed plasma concentration

These limited pharmacokinetic data support the 150 mg migalastat HCL capsule Q.O.D. dose in adolescents weighing ≥ 45 kg.

2.3.4. Discussion on clinical pharmacology

All 9 subjects aged 12 to < 16 years and weighing ⩾ 45 kg enrolled and dosed complied with study eligible criteria and completed stage 1 of the study AT1001-020. Protocol deviations were clearly described in the dossier.

The CHMP noted that there were two deviations related to the collection of the PK samples. Nonetheless, from data listing 16.2.6.2.1 for one subject, only collection of the 2 PK samples was recorded. This was contrary to the information given in the protocol deviation form. In addition, there were missing records of the 4th PK sample collection from two subjects. The deviations, however, were not found in the list of the protocol deviations. During the procedure, the MAH adequately clarified these differences, in particular the fact that some of the missing PK data were due to amount of the samples for analysis as determined by the laboratory. This insufficient amount of the sample was not specified as protocol deviation and therefore was not included in the deviation list. The CHMP concluded that these deviations of the PK collection and analyses had only minor impact on PK assessment and Population PK modelling and simulation.

The dose administered was 123 mg every other day for subjects aged 12 to < 18 years and weighing ⩾ 45 kg. The dose regimen was the same as the adult dose and was supported by simulation results from a population pharmacokinetic model. The PopPK model in paediatric patients with Fabry disease was developed based upon PK, PD and safety data from adults with Fabry disease and normal renal function.

The population pharmacokinetics model previously developed from healthy adult volunteers, and adult patients with Fabry disease after oral administration of migalastat was adjusted to be applied in the paediatric population. Allometric scaling components to CLT/F and Q/F with an allometric exponent equal to 0.75 and to V2/F and V3/F with an allometric exponent equal to 1.0 were added to optimise the model. The updated model showed acceptable performance based upon Goodness of fit plots, Visual Predictive Check, and the estimated parameters from bootstrap.

Based upon limited data obtained from adolescent patients aged 12 – 18 years (n=9), popPK data showed that exposure in adults and adolescents weighing ⩾ 45 kg receiving the 123 mg migalastat capsule Q.O.D. were comparable. See Table *7*.

Simulations of PK parameters were conducted using the modified popPK model of migalastat to predict migalastat exposure in paediatric patients with Fabry disease. The simulated parameter of $AUC_{0-\tau}$ in adolescents who are 12 to < 16 years old and who weigh ≥ 45 kg lies within the 80-125% bioequivalence limits (compared to adults). See Table 8. For Cmax, only in the age group of 12 – 16 years, Cmax was slightly outside the 80 – 125% (90%) confidence interval (see Table 8).However, the observed Cmax levels in children (aged 6 to 12 years and ≥45 kg BW) were in line with the Cmax levels (min, max: 503, 2513 ng/ml; as observed in the pivotal study AT1001-011 in adults. AEs were mild in intensity and unrelated to treatment, except for drug interruption which could be treatment related according to the investigator. Based on these data, this finding was not considered to significantly impact on the benefit risk of the product tin this population, however the CHMP recommended to reflect this information in section 5.2 of the SmPC.

The limited pharmacokinetic data support the proposed 123 mg migalastat capsule Q.O.D. dose in adolescents weighing ≥45 kg and the results of the simulations are considered sufficiently worded in the SmPC section 5.2. Due to the capsule size and inclusion criteria of study AT1001-020, the 123 mg migalastat capsules are not suitable for patients less than 45 kg body weight and for the lower weight and age groups. The MAH intends to design and evaluate a new formulation, migalastat HCl oral formulation (sachet and/or capsules) for treatment of Fabry disease in paediatric and adolescent patients aged 2 to <18 years and with amenable GLA mutations. Thus, the CHMP recommended to include a warning for the lower weight group within the proposed age group (12 to below 16 years) in this application.

Plasma samples were analysed using the previously validated LC-MS/MS method. The final bioanalytical report will be expected later together with the clinical study report. This is acceptable since the method validation has been already assessed during original MAA and reliable method performance was demonstrated several times in previous clinical studies.

2.3.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology has been adequately documented for the new paediatric age group (12 to below 16 years) and meet the requirements to support this application.

2.4. Clinical efficacy

2.4.1. Main study

Study AT1001-020: An Open-label Study of the Safety, Pharmacokinetics, Pharmacodynamics, and Efficacy of 12-month Treatment with Migalastat in Paediatric Subjects (aged 12 to < 18 years) with Fabry Disease and Amenable GLA Variants.

Methods

Study participants

For inclusion in this study, subjects must have met all of the following criteria:

1. Male or female, diagnosed with Fabry disease aged between 12 and <18 years at baseline, and who might benefit from specific treatment for their condition, in the opinion of the investigator;

2. Confirmed, amenable GLA variant determined using the migalastat amenability assay Note: For subjects without a known amenable GLA variant, GLA genotyping must have been performed prior to Visit 2.

Note: For subjects with a GLA variant that had not yet been tested in the migalastat amenability assay, amenability testing must have been completed before Visit 2.

3. Weight of ≥45 kg (99 pounds) at screening;

4. Treatment-naïve or discontinued ERT treatment at least 14 days prior to screening 5. Had at least one complication (i.e. historical or current laboratory abnormality and/or sign/symptom) of Fabry disease;

6. Had no indication of moderate or severe renal impairment (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m2) or kidney disease requiring dialysis or transplantation at screening.

The following criteria applied for removal of Subjects from Therapy:

Subjects could discontinue study drug, withdraw from the study, or be withdrawn from the study for any reason including, but not limited to, the following reasons:

• at their own request or at the request of their parent or legally authorised representative;
• if, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being;
• occurrence of an intolerable adverse event (AE) as determined by the investigator, subject, and/or parent or legally authorised representative;
• inability to tolerate or comply with PK blood sampling procedures;
• failure of the subject to comply with the study visit schedule;
• persistent noncompliance, at the discretion of the investigator;
• pregnancy;
• inability to contact subject (i.e. subject was lost to follow-up);
• sponsor request.

Treatments

One migalastat 123 mg migalastat (= 150 mg migalastat HCL) capsule was administered with water every other day during the study.

Objectives

Stage 1

• to characterise the PK of migalastat in adolescents with Fabry disease, and to validate extrapolation of migalastat plasma exposure in adults to adolescents weighing ≥ 45 kg for the 123 mg migalastat capsule administered once every other day (QOD)

• to evaluate the safety of migalastat treatment in paediatric subjects with Fabry disease and who have variants in the gene encoding α-Gal A (GLA) amenable to treatment with migalastat

Stage 2

Primary Objective

• to evaluate the safety of migalastat treatment in paediatric subjects diagnosed with Fabry disease and who have GLA variants amenable to treatment with migalastat

Secondary Objectives

• to characterise the pharmacodynamics (PD) of migalastat in paediatric subjects diagnosed with Fabry disease and who have GLA variants amenable to treatment with migalastat

• to evaluate the efficacy of migalastat in paediatric patients diagnosed with Fabry disease and who have GLA variants amenable to treatment with migalastat

• to evaluate the relationship between exposure to migalastat and response

Outcomes/endpoints

Efficacy was not assessed for this interim analysis.

Pharmacokinetic Endpoints were as follows:

• Population PK model that describes the relationship between weight and age and migalastat pharmacokinetics in paediatric subjects (with primary PK parameter outputs listed in the following text)
• PK parameters based on simulated plasma-concentration data for migalastat after multiple-dose administration at steady-state concentration
– Cmax: maximum observed plasma concentration
– Cmin: minimum observed plasma concentration
– tmax: time to reach Cmax
– AUC_{0_tau}: area under the plasma concentration-time curve from time 0 over the dosing interval (i.e. 48 hours)
– t½: terminal elimination half-life
– CLss/F: apparent oral clearance at steady-state concentration
– Vss/F: apparent oral volume of distribution at steady-state concentration

Sample size

A sample size of at least 7 to 10 subjects per age/weight group was required for statistical comparison with adult exposure based on 2 methods described by Wang, Jadhav *et al.* 2012.

Randomisation

Not applicable

Blinding (masking)

Not applicable

Statistical methods

Analysis Populations for Interim Analysis

Safety Population

, The safety population included all subjects aged 12 to < 16 years who received at least 1 dose or a partial dose of study drug and had Stage 1 plasma concentration-time data available as of the cut-off date. All safety analyses were performed using the safety population.

Pharmacokinetic Population

The PK population included data from subjects aged 12 to < 16 years who have completed Stage 1 and who received at least 1 dose of migalastat with at least 1 quantifiable concentration. All subjects included in the Interim Analysis PK population must also have a known weight and an eGFR.

General Statistical Methods

Safety data was summarised using descriptive statistics and/or response frequencies. For numerical data, descriptive statistics included the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum. For categorical data, descriptive statistics were categorised by frequency counts and proportions (or percentages) of the number of subjects used in the analysis. The counts for the categories for 'Missing,' 'Unknown,' or 'Not applicable' were provided as appropriate, but the percentages were not provided.

For AEs, partially missing start dates were imputed to determine treatment-emergence only. No other missing data imputation was performed.

Results

Participant flow

The subject disposition at the time of the data cut-off is presented below.

Table 9 Subject disposition at the time of data cut off.

Parameter	Statistic	Overall
Number of subjects in the safety population[a]	N	9
Number of subjects in the PK population[b]	N	9
Completed subjects (Stages 1 and 2)	n (%)	2 (22.2)
Ongoing as of data cutoff	n (%)	7 (77.8)
Discontinued the study	n (%)	0
Reasons for discontinuation during treatment		NA

Abbreviations: N = total number of subjects; n = number of subjects in category indicated; NA = not applicable; PK = pharmacokinetic
Note: Percentages are based on the number of subjects in the safety population.
[a] Safety population includes all subjects aged 12 to < 16 years who receive at least 1 dose or partial dose of study drug and have Stage 1 plasma concentration-time data available as of the cutoff date.
[b] The PK population includes all data from subjects aged 12 to < 16 years who have completed Stage 1 and who received at least 1 dose of migalastat with at least 1 quantifiable concentration.
Source: Table 14.1.1

Recruitment

The first patient was enrolled in August 2018. The study is ongoing.

Conduct of the study

The original protocol of study AT1001-020 was dated 20 February 2018 and was amended four times. The most important changes were made by means of amendment 1 and 2, namely design of the study which was separated into 2 stages, changes performed in collection of PK samples as well as increase in total number of subjects enrolled into the study. Inclusion and exclusion criteria were also revised. The inclusion requirement for subjects to be off ERT treatment for 6 months was reduced to 14 days since investigator does not perceived impact on bridging of PK assessment as was seen in adult studies. An exclusion criterion of any prior or anticipated use of gene therapy was added. Two subjects were enrolled under Amendment 1; the rest of the subjects were enrolled under Amendment 3 and 4. Amendment 4 of the protocol and the final PK analyses plan dated 6 February2019 refer to multiple interim analyses. Nonetheless, a decision was made to conduct only 1 formal interim analysis. A preliminary, unpublished PK interim analysis was conducted by the vendor in order to assess model performance. Therefore, this interim analysis is referred to as Interim Report #2. PK samples were collected in all subject between Days 15 to 30 in order to capture steady-state data. All subjects comply with eligibility criteria settled in protocol amendment 4. Any impact of the changes performed in study protocol on study results is not expected.

A total of 21 protocol deviations were reported during the first month of study for the 9 subjects in the safety population. All but 1 deviation was minor, with the majority (14) related to study procedures (i.e. procedures completed when not required, vital signs measured inconsistently) and subject compliance (i.e. electronic diary completion). There were no deviations related to inclusion/exclusion criteria.

The major deviation was due to a missed procedure (i.e. Tanner staging), which was refused by the subject.

Baseline data

A total of 9 subjects, 4 females and 5 males, aged 12 to < 16 years were enrolled in Study AT1001-020, received study drug, and completed Stage 1 of the study with PK concentration data. They comprised the safety and PK populations for this interim analysis. The mean number of years since diagnosis of Fabry disease was 10.2 (± 4.12) years. Four subjects reported prior use of enzyme replacement therapy.

The median duration of migalastat exposure for the 9 subjects enrolled in Study AT1001-020 was 30 days; maximum exposure was 49 days.

Demographics and baseline characteristics are presented in Table 10 and Table 11.

Table 10: Demographics – Safety Population

Parameter	Statistic	Migalastat
Number of subjects in the safety population	N	9
Age (years)[a]	Mean (SD)	14.1 (1.17)
	Median	15.0
	Min, Max	12, 15
Sex		
Male	n (%)	5 (55.6)

Female	n (%)	4 (44.4)
Race		
White	n (%)	8 (88.9)
Black or African American	n (%)	0
Asian	n (%)	0
American Indian or Alaska Native	n (%)	0
Native Hawaiian or other Pacific Islander	n (%)	0
Other	n (%)	1 (11.1)
Ethnicity		
Hispanic or Latino	n (%)	2 (22.2)
Not Hispanic or Latino	n (%)	7 (77.8)
Height (cm)	Mean (SD)	167.09 (5.591)
	Median	168.50
	Min, Max	160.0, 175.3
Weight (kg)	Mean (SD)	67.56 (17.273)
	Median	66.50
	Min, Max	45.0, 100.6
Body Mass Index (kg/m^2)	Mean (SD)	24.25 (6.148)
	Median	24.10
	Min, Max	15.6, 33.5

Abbreviations: Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects in category
indicated; SD = standard deviation
Note: Percentages are based on the number of subjects in the safety population.
a Age = (informed consent date - date of birth + 1) / 365.25 and truncated to complete years.

Table 11: Baseline Characteristics – Safety Population

Parameter	**Statistic**	**Migalastat**
Number of subjects in the safety population	N	9
Number of years since diagnosis of Fabry disease[a]	Mean (SD)	10.15 (4.119)
	Median	11.17
	Min, Max	3.4, 15.8
Previous use of ERT n (%)		
Yes	n (%)	4 (44.4)
No	n (%)	5 (55.6)

Abbreviations: Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects in category
indicated; SD = standard deviation
a Number of years since diagnosis of Fabry disease is calculated as (informed consent date - date of diagnosis of Fabry disease + 1) / 365.25 and rounded to 1 decimal.

Medical History

The most common system organ classes for medical history in the safety population were nervous system disorders (77.8%), ear and labyrinth disorders (66.7%), gastrointestinal disorders (66.7%), and general disorders and administration site conditions, investigations, psychiatric disorders, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders (all 55.6%). The most common medical history preferred terms (all reported by 55.6% of the subjects)

were tinnitus, abdominal pain, diarrhoea, headache, and paraesthesia, most of which are consistent with Fabry disease.

Prior and Concomitant Medications

All but 1 subject reported prior use of medications. The most common previous medication was paracetamol taken by 6 (66.7%) subjects. No other medication was taken by more than 2 subjects.

The most frequently used concomitant medication was paracetamol taken by 6 (66.7%) subjects. No other concomitant medication was taken by more than 2 subjects.

Numbers analysed

Not applicable

Outcomes and estimation

Not applicable

Ancillary analyses

Not applicable

Summary of main study

Not applicable. There is no efficacy data collected in part 1 of this Phase 1/2 study. Hence, the extension of the indication from patient over 16 years of age to patients aged 12 years of age and over is solely based on pharmacokinetics/pharmacodynamics modelling. Refer to the sections 2.3.2 and 2.3.3.

2.5. Clinical safety

Introduction

To support the present application to extend the existing indication to the paediatric age range of 12- below 16 years, the safety data from the interim analysis of the ongoing study AT1001-020 are presented below.

Patient exposure

Study AT1001-020

A total of 22 subjects were enrolled.

The safety population was defined as all subjects aged 12 to < 16 years and weighing ≥ 45 kg who received at least 1 dose or partial dose of study drug, had Stage 1 plasma concentration-time data available, and completed 1 month of migalastat treatment as of the data cut-off date of 31 January 2020. As of the data cut-off, 9 subjects were enrolled in the study and completed Stage 1. Total

exposure mean (SD) was 33.0 days (± 7.55) and maximum exposure was 49 days.

From that, 2 subjects (22.2%) already completed Stage 1 and 2. The remaining 7 subjects are ongoing in the study.

Adverse events

An overall summary of TEAEs experienced by subjects in the safety population during Stage 1 is displayed in

Table 12 and **Table 13**.

Table 12: Summary of Treatment-emergent Adverse Events – Safety Population – Stage 1.

Parameter	Statistic	Migalastat
Number of subjects in the safety population	N	9
Number of TEAEs	n	6
Number of subjects with TEAEs	n (%)	5 (55.6)
Number of subjects with related TEAEs	n (%)	1 (11.1)
Number of subjects with treatment-emergent SAEs	n (%)	0
Number of subjects discontinued due to TEAEs	n (%)	0
Number of subjects with AEs leading to death	n (%)	0

Table 13: Frequency of Treatment-emergent Adverse Events Occurring in the Safety Population – Stage 1.

System Organ Class Preferred Term	Number of Subjects n (%)	Number of Events n (%)
Number of subjects with TEAEs	5 (55.6)	6
Infections and infestations	4 (44.4)	4 (66.7)
Pharyngitis	1 (11.1)	1 (16.7)
Upper respiratory tract infection	3 (33.3)	3 (50.0)
Nervous system disorders	1 (11.1)	1 (16.7)
Headache	1 (11.1)	1 (16.7)
Skin and subcutaneous tissue disorders	1 (11.1)	1 (16.7)
Drug eruption	1 (11.1)	1 (16.7)

Treatment-emergent Adverse Events by Relationship to Study Drug

One event was considered possibly related to migalastat treatment by the principal investigator. Drug eruption occurred 2 days following the start of treatment with migalastat. It was treated with a topical corticosteroid and subsequently resolved after 45 days, with no change to migalastat treatment. Subject 2308-5148, completed the study and is currently enrolled in a long-term extension study.

Serious adverse event/deaths/other significant events

During Stage 1, no treatment-emergent serious adverse events or deaths were reported in the safety Population.

Laboratory findings

During Stage 1, urinalysis (albumin, protein, specific gravity, pH, and microscopy) was the only laboratory parameter collected at Month 1 and therefore, the only laboratory parameter assessed for the Interim Analysis.

There were no clinically meaningful changes in mean values from baseline for urinalysis parameters at Month 1.

There were a few shifts from baseline to Month 1. Three subjects had pH values that went from normal at baseline to high at Month 1.

There were no potentially clinically significant abnormalities in urinalysis parameters.

Urine pregnancy tests were performed for all female subjects of childbearing potential at every visit. No female subject in the safety population had a positive pregnancy test result during Stage 1.

Discontinuation due to adverse events

During Stage 1, there were no patients in the safety population who discontinued due to an adverse event.

2.5.1. Discussion on clinical safety

Assessment of paediatric data on clinical safety

During Stage 1, there were no deaths, SAEs, or discontinuations due to an AE in the safety population. The investigators determined all TEAEs to be mild in severity. One event (drug eruption) was considered possibly related to migalastat treatment by the principal investigator. Urinalysis, vital signs, and physical findings were all non-remarkable. Overall, results indicated that 1 month of treatment with migalastat HCl 150 mg QOD was generally safe and well-tolerated in subjects aged 12 to < 16 years with Fabry disease. As it is expected, migalastat will be used for long-term treatment; long term safety data (> 1 year) in adolescents aged 12 to < 16 years are missing. Following CHMP recommendation, this information was reflected in the section 4.8 of the SmPC. Study AT1001-036 enrolls subjects who completed 12 months of migalastat treatment in Study AT1001-020, which concluded in February 2021. As of 23 September 2020, in Study AT1001-036, 7 subjects are enrolled in the phase 3b safety open-label paediatric extension of Study AT1001-020 for adolescents (as of). Duration of treatment period for this study is to be determined.

Therefore, all subjects who continue in Study AT1001-036 have long-term (i.e. > 1 year) exposure to migalastat. The MAH informed the CHMP that the study will continue at least 2 years and potentially longer unless migalastat is reimbursed for commercial use in this age group.

Following CHMP recommendation, the existing prospective, observational registry of patients with Fabry disease (Study AT1001-030) is planned to be amended to collect long-term safety data in this paediatric population (12 to below 16 years). A revised protocol is to be submitted within defined timelines in the RMP (see section 2.6).

Results were consistent with the safety profile of migalastat, with no new or unexpected safety findings observed in this population during Stage 1.

A total of 6 mild TEAEs in 5 patients, mainly consistent with the most common medical history of subjects, were reported. One AE related to migalastat (drug eruption) was recorded. However, it

didn´t require discontinuation of the study drug and resolved within the study. Of note, rash is a common ADR presented in the SmPC. No SAE or discontinuation due to adverse event was reported. Urinalysis, vital signs, and physical findings were all non-remarkable.

2.5.2. Conclusions on clinical safety

No new safety findings have been observed during stage 1 of the study. Hence treatment with migalastat 123 mg in paediatric patients aged ≥12 to 16 years of age does not lead to a different safety profile than already known.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6 with the following content:

Safety concerns

Important identified risks	None
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/1.73 m2) Long-term treatment (> 1 year) Use in the pediatric population aged 12 to < 16 years.

Abbreviation: GFR = glomerular filtration rate.

Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
AT1001-030: A prospective, observational registry of patients with Fabry disease Ongoing	Evaluate the effects of migalastat treatment on long-term safety, effectiveness, and health-related quality of life in Fabry disease patients as determined by the occurrence of all SAEs over the 5-year period.	Use in non-amenable patients; Male infertility (reversible); Use in pregnant or breast-feeding women; Use in patients with severe renal impairment (GFR < 30 mL/min/ 1.73 m2); Use in older patients > 74 years; Long-term treatment (> 1 year) Use in the pediatric population aged 12 to < 16 years.	Final report	Q2 2027 (planned)
AT1001-020: An open-label study of the safety, PK, PD, and efficacy of 12-month treatment with migalastat in pediatric subjects (aged 12 to < 18 years) with Fabry disease and amenable GLA variants Ongoing	Characterize the PK of migalastat in adolescents with Fabry disease and validate extrapolation of migalastat plasma exposure in adults to adolescents weighing ≥ 45 kg. Evaluate the safety of migalastat treatment in pediatric patients with Fabry disease who have amenable mutations.	Use in the pediatric population aged 12 to < 16 years.	Final report	Q3 2021 (planned)

Abbreviations: GFR = glomerular filtration rate; GLA = gene encoding α-galactosidase A; PD = pharmacodynamics; PK = pharmacokinetic(s); Q = quarter; SAE = serious adverse event.

Risk minimisation measures

Safety concern	Risk minimization activities	Pharmacovigilance activities
Lack of efficacy in case of use in patients with non-amenable mutations	Routine risk communication: • SmPC Sections 4.1, 4.4, and 5.1; • PL Section 1; • Amenable mutations are listed in Section 5.1; amenable and non-amenable mutations are listed on the website that is referenced in Section 5.1. Other routine risk minimization measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • AT1001-030 (patient registry).
Male infertility (reversible)	Routine risk communication: • SmPC Sections 4.6 and 5.3; • PL Section 2. Other routine risk minimization measures beyond the Product Information: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • AT1001-030 (patient registry).
• Use in pregnant or breast-feeding women	Routine risk communication: • SmPC Section 4.6; • PL Section 2; • Recommendations not to use Galafold during pregnancy or in women of childbearing potential not using contraception is included in SmPC Section 4.6 and PL Section 2; • Recommendation regarding decision to discontinue breast-feeding or to discontinue Galafold is described in SmPC Section 4.6 and PL Section 2. Other routine risk minimization measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • AT1001-030 (patient registry).
• Use in older patients > 74 years	Routine risk communication: • SmPC Sections 4.2 and 5.2. Other routine risk minimization measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities • AT1001-030 (patient registry).

Safety concern	Risk minimization activities	Pharmacovigilance activities
• Use in patients with severe renal impairment (GFR < 30 mL/min/ 1.73 m2)	Routine risk communication: • SmPC Sections 4.2, 4.4, and 5.2; • Recommendation not to use Galafold in patients with eGFR < 30 mL/min/1.73 m2 is included in SmPC Sections 4.2 and 4.4. Other routine risk minimization measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • AT1001-030 (patient registry).
• Long-term treatment (> 1 year)	Routine risk communication: • None. Other routine risk minimization measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • AT1001-030 (patient registry).
• Use in the pediatric population aged 12 to < 16 years	Routine risk communication: • SmPC Sections 4.8, 5.1, and 5.2. Other routine risk minimization measures beyond the Product Information: • Prescription only.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • AT1001-030 (patient registry) • AT1001-020.

Abbreviations: eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; PL = package leaflet; SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to non suitability of 123 mg migalastat HCL capsules for children (<12 years) weighing less than 45 kg has been added to the product information. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

With the proposed indication extension, only minimal changes have been introduced to the Package Leaflet which reflect language and a format consistent with the currently approved leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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). It 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).

3.1.2. Available therapies and unmet medical need

In addition to oral Galafold for the treatment of Fabry disease, Enzyme Replacement Therapy (ERT), irrespective of the disease's severity, is also available. It consists of an intravenous (IV) infusion of manufactured enzyme every 14 days. These ERTs are approved for use in patients aged 7 years and older.

3.1.3. Main clinical studies

The proposed extension to the indication is supported by data from Study AT1001-020, which is a 2-stage, open-label, uncontrolled, multicenter study to evaluate the safety, PK, PD, and efficacy of migalastat treatment in paediatric subjects 12 to <18 years of age and weighing ≥ 45 kg with Fabry disease and with amenable mutations to the gene encoding α-galactosidase A (GLA). Stage 2 will collect efficacy data in these patients; however, as this pertains to an interim analysis, only the stage 1 data is submitted.

Stage 1 of the AT1001-020 study is a clinical measure (Study 3) defined in the agreed Paediatric Investigation Plan (PIP) for migalastat (EMEA-001194-PIP01-11-M04), to support extrapolation of efficacy from adults to the adolescent population aged 12 to 15 years.

3.2. Favourable effects

Based upon limited data obtained from adolescent patients aged 12 – 18 years (n=9), popPK data showed that exposure in adults and adolescents weighing ≥45 kg receiving the 123 mg migalastat capsule q.o.d. was comparable.

ANOVA analysis showed predicted bioequivalence values within the 80 – 125% criteria for AUC. For C_{max} only in the aged group of 12 – 16 years, C_{max} was slight outside the 80 – 125% (90%) confidence interval.

The simulated parameter of AUC0-τ in adolescents 12 to < 16 years old and who weigh ≥ 45 kg lies within the 80-125% bioequivalence limits (compared to adults).

Cmax levels observed in the paediatric patients were in line with the Cmax levels observed in adults patients in the pivotal study AT1001-011.

3.3. Uncertainties and limitations about favourable effects

No efficacy data from stage 2 of the study has been presented. Study AT1001-020 is ongoing.

The 123 mg migalastat capsule are unsuitable for patients <45 kg body weight. For this reason, a different formulation is under development.

3.4. Unfavourable effects

No unexpected safety issues were noted.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile is based on limited number of patients (n= 9) aged 12 – 18 years.

As it is expected, migalastat will be used for long-term treatment, long term safety data (>1 year) in adolescents aged 12 to <16 years are currently missing and will be collected in the post-marketing setting.

3.6. Effects Table

Table 1. Effects Table for Galafold for the treatment of Fabry disease in patients aged ≥12 years and older (data cut-off: 31 Jan 2020).

Effect	Short description	Unit	Age group (years)	Treatment 123 mg migalastat	Uncertainties / Strength of evidence	References
Favourable Effects						
Simulated Pharmacokinetic Endpoints by Age Groups and Adults ⩾ 45 kg	AUC_{tau}	(ng/mL); geometric mean (CV%).	12 to < 16	1377 (42%)	**Unc:** only PK data is available; efficacy data (stage 2); capsules is not suitable for patients <45 kg BW	Stage 1 AT1001-020
			16 to < 18	1275 (39%)		
			12 to < 18	1319 (41%)		
			Adults	1191 (37%)		
Unfavourable Effects						
Adverse events				No unexpected safety issues were noted.	**Strength:** safety profile in paediatric patients similar to adults. **Unc**: The safety profile is based on 9 patients aged 12 – 18 years. No long term (>1 years) safety data available in	Stage 1 AT1001-020

Effect	Short description	Unit	Age group (years)	Treatment 123 mg migalastat	Uncertainties / Strength of evidence	References
					patients 12 to <16 years of age.	

Abbreviations: AUC0-τ = plasma concentration-time curve during a dosing interval at steady state (AUC0-τ); Cmax = maximum observed plasma concentration; Cmin = minimum observed plasma concentration; BW = body weight.
Notes: Data are summarised as geometric mean (CV%).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Only 9 paediatric patients aged 12 to 16 years were included in this interim analysis. This is rather limited; however, given the rarity of the disease, this is considered acceptable. Additional efficacy and safety data are expected as part of the final results of the study AT1001-020 and study AT1001-036 which enrolls subjects who completed 12 months of migalastat treatment in Study AT1001-020, for at least 2 years and potentially longer unless migalastat is reimbursed for commercial use in this age group.

No unexpected safety issues were noted. However, given the lack of long term data, the existing prospective, observational registry of patients with Fabry disease (Study AT1001-030), part of the existing risk management plan, is intended to be extended to this new paediatric population (12 to below 16 years).

3.7.2. Balance of benefits and risks

Although at this moment, no efficacy data is submitted, it is not expected that there is a difference in the mode of action of migalastat in the patients 12 to <16 years of age. The efficacy results in patients ≥16 of age and older can be extrapolated to the younger patients (12 to <16 years) based on the on the population pharmacokinetic model showed that exposure in adults and adolescents weighing ≥45 kg receiving the 123 mg migalastat capsule q.o.d. were comparable. Therefore, the extension of the indication in paediatric population aged 12 to below 16 years is acceptable.

The safety results indicated that 1 month of treatment with migalastat 123 mg QOD was generally safe and well-tolerated in patients aged 12 to <16 years with Fabry disease. Results were consistent with the known safety profile of migalastat. No new or unexpected safety findings observed in this population during Stage 1. Further long-term data will be collected through the final results of the ongoing studies AT1001-020, AT1001-036 and AT1001-030 (existing observational registry) and thus the limitation of the safety data in this new paediatric population is considered adequately addressed.

The B/R of Galafold is considered positive.

3.8. Conclusions

The overall B/R of Galafold is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Galafold (migalastat) to include long-term treatment of adolescents 12 to < 16 years with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.2 of the SmPC and Section 1 and 2 of the Package Leaflet are updated accordingly. A revised RMP version 6 has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0137/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.