13 January 2022
EMA/123203/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Galafold

International non-proprietary name: migalastat

Procedure No. EMEA/H/C/004059/II/0034

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	03 Aug 2021	03 Aug 2021	☐
☐	CHMP Rapporteur Assessment Report	06 Sep 2021	08 Sep 2021	☐
☐	PRAC Rapporteur Assessment Report	13 Sep 2021	10 Sep 2021	☐
☐	PRAC members comments	17 Sep 2021	n/a	☐
☐	CHMP members comments	20 Sep 2021	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	21 Sep 2021	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Sep 2021	23 Sep 2021	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	28 Sep 2021	28 Sep 2021	☐
☐	Start of written procedure	28 Sep 2021	28 Sep 2021	☐
☐	Request for supplementary information	30 Sep 2021	30 Sep 2021	☐
☐	Re-start of procedure	16 Nov 2021	16 Nov 2021	☐
☐	CHMP Rapporteur Assessment Report	15 Dec 2021	16 Dec 2021	☐
☐	PRAC members comments	03 Jan 2022	n/a	☐
☐	CHMP members comments	03 Jan 2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Jan 2022	n/a	☐
☐	Start of written procedure	11 Jan 2022	11 Jan 2022	☐
☒	Opinion	13 Jan 2022	13 Jan 2022	☐

Procedure resources	
Rapporteur:	Johann Lodewijk Hillege

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amicus Therapeutics Europe Limited submitted to the European Medicines Agency on 29 July 2021 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

To update sections 4.8, 5.1 and 5.2 of the SmPC based on final results from study AT1001-020 listed as category 3 in the RMP. Study AT1001-020-is a Phase 3b, 2-stage, open-label, uncontrolled, multicentre study to evaluate the safety, pharmacokinetic, pharmacodynamic and efficacy of migalastat treatment in paediatric subjects 12 to < 18 years of age and weighing ≥ 45 kg with Fabry disease and with amenable GLA variants. The updated RMP version 7.0 has also been submitted.
The final results of study AT1001-020, which is involving paediatric patients are submitted in this procedure to fulfil Article 46 of Regulation 1901/2006, as amended.
In addition, the MAH took the opportunity to introduce some minor editorial changes to the SmPC and Package Leaflet and bring the PI in line with the latest QRD template v. 10.2.

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

2. Overall conclusion and impact on the benefit/risk balance

The study design for study AT1001-020 was fully described in the recent approved variation to extend the authorised indication with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation to adolescents 12 to < 16 years (EMEA/H/C/004059/II/29) . Stage 1 of this study (PK, PK modelling) in 9 paediatric patients was the basis for approving the expansion of the indication to include paediatric patients aged 12 years and over. Stage 2 of the study describing the efficacy and safety in this population was requested as an commitment. These results are submitted for review in the present application.

The applicant presented the study results based on the overall patients included in this study. The study report comprise the results of 22 paediatric patients aged 12 to <18 years of age. Fifteen patients were aged 12 to <16 years. During the procedure, additional subgroup analyses of the data between patients aged 12 to <16 years and ≥16 to < 18 years were requested.

Based on the data it can be concluded that when treated conform the approved posology the data indicates that the paediatric patients (12 to <18 years of age; n=22) over the 1-year study period had: a stable renal function, a stable left ventricular mass index (LVMi), and a stable Plasma Globotriaosylsphingosine levels. Data in patients 12 to <16 years showed similar improvements as in the patients over 16 years of age. Given the limited number of patients included and the short treatment period of 12 months no firm conclusions can be drawn, but the results are indicative that under treatment the disease stabilises. Further, the results are in line with the results of the initial clinical studies in adolescents (aged 16 to <18 years) and adults. Results were similar for male and female subjects and for subjects who were previously ERT-experienced and ERT-naïve. With respect to the safety profile this is in line with the safety profile already known for migalastat.

The proposed SmPC updates of sections 4.8, 5.1 and 5.2 are acceptable:

Section 4.8

Adolescent population

The safety assessment in 21 adolescents (12 to <18 years of age and weighing ≥ 45 kg) is based on 1-year safety data from the open label AT1001-020 trial in which subjects received the same dosage regimen as adults (see section 5.2). No age-specific differences in adverse reactions were observed between adolescent and adult subjects. The frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults based on these data.

Section 5.1

Paediatric population

In Study AT1001-020, a 1-year, Phase 3b, open-label, uncontrolled, multicentre study, the safety, PK, pharmacodynamic (PD), and efficacy of migalastat treatment was evaluated in 21 adolescent subjects (12 to < 18 years of age and weighing ≥ 45 kg) with Fabry disease and who have amenable mutations of the gene encoding α-galactosidase A (GLA). Subjects were either naïve to enzyme replacement therapy (ERT) or had stopped ERT at least 14 days before screening. The mean number of years since diagnosis of Fabry disease was 10.2 (± 4.12) years.

At 1 year, the efficacy results in adolescents on the same dosing regimen as adults were consistent in renal, cardiac, and pharmacodynamic results as well as responses to patient-reported outcomes. The overall mean (SD) change from baseline in eGFR was -1.6 (15.4) mL/min/1.73 m2 (n=19). The overall mean (SD) change from baseline for LVMi was -3.9 (13.5) g/m2 (n=18). LVMi decreased in 10 subjects and increased in 8 subjects, but all subjects remained within normal limits at 12 months. Baseline plasma lyso-Gb3 was 12.00 ng/mL and the overall mean (SD) change from baseline in plasma lyso-Gb3 was -0.06 (32.9) (n=19). A reduction in plasma lyso-Gb3 from baseline was observed in ERT-naïve subjects (median -2.23 ng/ml, n=9) and levels remained generally stable in ERT-experienced subjects (median 0.54 ng/ml, n=10). There were no notable changes in patient reported outcomes.

Section 5.2

Paediatric population

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

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

The benefit-risk balance of Galafold, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

To update sections 4.8, 5.1 and 5.2 of the SmPC based on final results from study AT1001-020 listed as category 3 in the RMP. Study AT1001-020-is a Phase 3b, 2-stage, open-label, uncontrolled, multicentre study to evaluate the safety, pharmacokinetic, pharmacodynamic and efficacy of migalastat treatment in paediatric subjects 12 to < 18 years of age and weighing ≥ 45 kg with Fabry disease and with amenable GLA variants. The updated RMP version 7.0 has also been submitted.
The final results of study AT1001-020, which is involving paediatric patients are submitted in this procedure to fulfil Article 46 of Regulation 1901/2006, as amended.
In addition, the MAH took the opportunity to introduce some minor editorial changes to the SmPC and Package Leaflet and bring the PI in line with the latest QRD template v. 10.2.

☒ is recommended for approval.

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.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Galafold-H-C-004059-II-0034'

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The study design of study AT1001-020 was fully described in the recent approved variation (II/029; Rapporteurs' final AR circulated on 23 June 2021). Stage 1 of this study (PK, PK modelling) was the basis for approving the expansion of the indication to include paediatric patients aged 12 years and over in the indication (see FVAR II/029).

Stage 2 of the study describing the efficacy and safety in this population was requested as a commitment and is now submitted for review. With these final study results the MAH proposes to update sections 4.8, 5.1 and 5.2 of the SmPC.

Results

Conduct of the study

The original protocol AT1001-020 dated 20 Feb 2018 was amended 4 times. The first 2 patients were enrolled under Amendment 1. The remainder of the patients were enrolled under Amendment 4.

Baseline data

Demographics

Table 1 details the demographic profile and Table 2 the baseline disease characteristics of the enrolled patients.

Table 1: Demographics – Safety Population

Parameter	Statistic	Migalastat
Number of subjects in the safety population	N	22
Age (years)[a]	Mean (SD)	14.6 (1.62)
	Median	15.0
	Min, Max	12, 17
12 to < 16 years	n (%)	15 (68.2)
16 to < 18 years	n (%)	7 (31.8)
Sex		
Male	n (%)	10 (45.5)
Female	n (%)	12 (54.5)
Race		
Caucasian	n (%)	20 (90.9)
Other	n (%)	2 (9.1)
Ethnicity		
Hispanic or Latino	n (%)	2 (22.2)
Not Hispanic or Latino	n (%)	7 (77.8)
Height (cm)	Mean (SD)	166.4(7.88)
	Median	167.00
	Min, Max	146.5, 186.1
Weight (kg)	Mean (SD)	68.7 (20.80)
	Median	64.10
	Min, Max	45.0, 116.2
Body Mass Index (kg/m^2)	Mean (SD)	24.8 (7.08)
	Median	22.65

	Min, Max	15.6, 45.1

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 2: Baseline Characteristics – ITT Population

Parameter	**Statistic**	**Migalastat**
Number of subjects in the safety population	N	22
Number of years since diagnosis of Fabry disease	Mean (SD)	9.6 (4.25)
	Median	10.70
	Min, Max	1.6, 16.9
Previous use of ERT n (%)		
Yes	n (%)	11 (50.0) [a]
No	n (%)	11 (50.0)

Abbreviations: Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects in category
indicated; SD = standard deviation
a males = 4; females = 7

Medical History

The most common system organ classes for medical history in the safety population were nervous system disorders (81.0 %), gastrointestinal disorders (76.2%), general disorders and administration site conditions (71.4%), skin and subcutaneous tissue disorders (66.7%), ear and labyrinth disorders (57.1%), investigations (57.1%), and psychiatric disorders (52.4%). The most common medical history preferred terms (reported by over 50% of the subjects) were diarrhoea, abdominal pain, tinnitus, headache, paraesthesia, and hypohidrosis, which are generally consistent with Fabry disease.

Prior and Concomitant Medications

All but 1 subject reported prior use of medications. The most common previous medications were paracetamol taken by 11 subjects (52.4%) and ibuprofen taken by 8 subjects (38.1%).

The most frequently used concomitant medication was paracetamol taken by 15 (71.4 %) subjects.

Rapporteur's comments

Fifteen (15) patients aged 12 to <16 years were included in this study. The PDCO agreed that patients <18 years of age could be included as well in the study. Seven patients aged 16 to <18 years of age were included. This is agreed with

Numbers analysed

All efficacy evaluations were done in the ITT population. One of 22 patients dropped out prior dosing.

Rapporteur's comments

Given that the expansion of the indication pertains to paediatric patients aged 12 years to <16 years, the applicant is requested to submit the efficacy and safety results for this patients group - *acknowledging the numbers are small and will not allow making firm conclusions* - to confirm that the

results are comparable to the older patients (**OC**). The applicant should present the results for eGFR, LWMi, Urine Protein and urine albumin, Plasma Globotriaosylsphingosine, results should be presented for males and females in line with the presentation in this report and compared to the patients aged 16 to <18 years. With respect to the safety the applicant should compare the adverse events based on the age category.

Outcomes and estimation

Estimated Glomerular Filtration Rate

Estimated GFR (Table 3) was calculated using the modified Schwartz formula for creatinine clearance (2009).

Table 3: Estimated Glomerular Filtration Rate (mL/min x 1.73 m^2) – Intent-to-Treat Population.

Visit		Males		Females		Overall	
	Statistic	**Observed Value**	**Change from Baseline**	**Observed Value**	**Change from Baseline**	**Observed Value**	**Change from Baseline**
Baseline[a]	n	10		11		21[b]	
	Mean (SD)	113.5 (15.85)		120.3 (23.32)		117.0 (19.93)	
	Median	110.5		114.0		114.0	
	Min, Max	95, 144		77, 164		77, 164	
Month 3	n	9	9	9	9	18	18
	Mean (SD)	111.4 (15.08)	-4.1 (17.97)	121.7 (25.59)	-4.6 (18.26)	116.6 (21.05)	-4.3 (17.58)
	Median	116.0	-9.0	113.0	0.0	114.5	-4.5
	Min, Max	86, 136	-27, 18	97, 166	-24, 34	86, 166	-27, 34
Month 6	n	7	7	9	9	16	16
	Mean (SD)	115.4 (21.86)	4.4 (18.14)	115.1 (21.75)	-7.9 (10.56)	115.3 (21.06)	-2.5 (15.20)
	Median	104.0	1.0	110.0	0.0	109.0	0.5
	Min, Max	95, 146	-16, 43	95, 164	-22, 1	95, 164	-22, 45
Month 12/ET	n	10	10	9	9	19	19
	Mean (SD)	110.7 (17.19)	-2.8 (18.69)	119.9 (14.97)	-0.3 (11.70)	115.1 (16.42)	-1.6 (15.40)
	Median	110.0	-3.5	122.0	1.0	115.0	0.0
	Min, Max	86, 148	-21, 45	97, 137	-17, 24	86, 148	-21, 45
Last Observation	n	10	10	10	10	20	20
	Mean (SD)	110.7 (17.19)	-2.8 (18.69)	124.3 (19.84)	-0.3 (11.04)	117.5 (19.37)	-1.6 (14.99)
	Median	110.0	-3.5	126.0	0.5	115.0	0.0
	Min, Max	86, 148	-21, 45	97, 164	-17, 24	86, 164	-21, 45
Annualised rate of change from baseline							
	n		10		10		20
	Mean (SD)		-2.8 (18.91)		-0.3 (11.01)		-1.5 (15.11)
	Median		-3.5		0.5		0.0
	Min, Max		-21, 46		-17, 24		-21, 46

Abbreviations: eGFR = estimated glomerular filtration rate; ET = early termination; Max = maximum; Min = minimum; n = number of subjects in category indicated; SD = standard deviation
a Baseline is defined as the last non-missing assessment prior to the first dose of study drug.
b One enrolled subject did not receive study drug.
Note: eGFR is calculated using the 2009 modified Schwartz formula for creatinine clearance.

Note: Annualized rate of change from baseline of eGFR is defined as change from baseline to last visit divided by the duration from baseline to the last visit (Last assessment date – First dose date +1) and multiplied by 365.25.

Rapporteur's comments

Overall, at Month 12 (n = 19), the mean (SD) change from baseline was -1.6 (15.40) mL/min x 1.73 m^2 and the mean (SD) annualized rate of change was -1.5 (15.11) mL/min x 1.73 m^2, indicating stable renal function over the 1-year study period. Results were similar for male and female subjects and for subjects who were previously ERT-experienced and ERT-naïve.

Urine Protein and urine albumin

Table 4: Total Urine Protein (mg/L) – Intent-to-Treat Population.

Visit		Males		Females		Overall	
	Statistic	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline[a]	n	10		11		21	
	Mean (SD)	121.5 (64.88)		71.3 (34.09)		95.2 (56.00)	
	Median	104.5		64.0		85.0	
	Min, Max	50, 250		20, 120		20, 250	
Month 3	n	9	9	9	9	18	18
	Mean (SD)	294.6 (628.14)	170.7 (600.08)	123.8 (61.79)	42.0 (57.61)	209.2 (441.80)	106.4 (418.79)
	Median	70.0	-10.0	100	30.0	92.0	15.0
	Min, Max	10, 1961	-180, 1760	50, 240	-10, 170	10, 1961	-180, 1760
Month 6	n	7	7	9	9	16	16
	Mean (SD)	85.7 (62.14)	-31.4 (102.54)	111.1 (71.32)	34.4 (62.67)	100 (66.53)	5.6 (86.25)
	Median	80.0	-20.0	90.0	20.0	90.0	15.0
	Min, Max	20, 170	-230, 110	50, 290	-30, 190	20, 290	-230, 190
Month 12/ET	n	10	10	9	9	19	19
	Mean (SD)	168.6 (132.74)	47.1 (146.34)	100.8 (56.44)	23.7 (60.07)	136.5 (106.94)	36.0 (111.61)
	Median	120.0	-5.0	90.0	40.0	90.0	3.0
	Min, Max	50. 390	-190, 330	20, 190	-80, 120	20, 390	-190, 330
Last Observation	n	10	10	10	10	20	20

	Mean (SD)	168.6 (132.74)	47.1 (146.34)	100.7 (53.21)	25.3 (56.87)	134.7 (104.41)	36.2 (108.64)
	Median	120.0	-5.0	95.0	40.0	95.0	21.5
	Min, Max	50, 390	-190, 330	20, 190	-80, 120	20, 390	-190, 330

Abbreviations: eGFR = estimated glomerular filtration rate; ET = early termination; Max = maximum; Min = minimum; n = number of subjects in category indicated; SD = standard deviation
a Baseline is defined as the last non-missing assessment prior to the first dose of study drug.
b One enrolled subject did not receive study drug.
Note: eGFR is calculated using the 2009 modified Schwartz formula for creatinine clearance.
Note: Annualized rate of change from baseline of eGFR is defined as change from baseline to last visit divided by the duration from baseline to the last visit (Last assessment date – First dose date +1) and multiplied by 365.25.

initial increase in proteinuria in male subjects at Month 3 was driven by 1 subject (2308-5147) who had a spike in urine protein at Month 1 and Month 3. This subject had a history of Fabry-related microalbuminuria and Fabry-related proteinuria since 2019 and was taking pregabalin until 2 months before entering the study, which is eliminated primarily by renal excretion. Concurrently, this subject had upper and lower respiratory tract infections at these 2 time points, respectively.

Results were similar for subjects who were previously ERT-experienced and ERT-naïve.

Rapporteur's comments

There was a mean (SD) change from baseline in urine protein at Month 6 (n = 16) of 5.6 (86.25) mg/L that increased to 36.0 (111.61) mg/L at Month 12 (n = 19). The results at month 3 are driven by a male subject who had a spike in urine protein. Nevertheless, the results of urine protein were predominately stable over the 12-month study period.

As with urine protein, an initial increase in urine albumin in male subjects at Month 3 was driven by the same subject (2308-5147) who had a spike in urine albumin at Month 1 and Month 3. Other results of urine albumin were predominately stable over the 12-month study period

Results were similar for subjects who were previously ERT-experienced and ERT-naïve.

Left Ventricular Mass Index

Left ventricular mass index (LVMi) was assessed as a measure of cardiac impairment in the study subjects. At baseline and throughout the treatment period, all subjects had LVMi within normal limits (Listing 16.2.6.3). Echocardiogram results were reported by both M-mode and 2D-mode imaging. The M-mode is consistent with previous migalastat studies in adults and allows for a comparative look of the data between adolescents and adults (and thus only these results are shown).

The LVMi reported by both modes were relatively stable throughout the study. The overall mean (SD) change from baseline to Month 12 (n = 18) was -3.9 (13.53) g/m^2 as reported by M-mode. At Month 12, based on M-mode female subjects (n = 9) showed a greater decrease in mean LVMi as compared to male subjects (n = 9) (change from baseline, -7.6 [16.94] g/m^2 versus -0.2 [8.43] g/m^2, respectively) (Table 5). Based on M-mode, at Month 12 ERT-experienced subjects (n = 10) had a mean (SD) change from baseline of -6.8 (14.87) g/m^2 versus -0.3 (11.52) g/m^2 for ERT-naïve subjects (n = 8).

Table 5: Left Ventricular Mass Index (g/m^2) M-mode View – Intent-to-Treat Population.

Visit		Males		Females		Overall	
	Statistic	**Observed Value**	**Change from Baseline**	**Observed Value**	**Change from Baseline**	**Observed Value**	**Change from Baseline**
Baseline[a]	n	9		11		20	
	Mean (SD)	73.5 (11.03)		74.4 (15.84)		74.0 (13.54)	
	Median	69.63		77.21		72.81	
	Min, Max	57.8, 88.8		51.9, 99.8		51.9, 99.8	
Month 6	n	7	6	9	9	16	15
	Mean (SD)	79.3 (19.74)	1.1 (10.51)	67.4 (12.88)	-7.3 (7.79)	72.6 (16.77)	-3.9 (9.60)
	Median	79.57	0.71	65.42	-10.97	73.55	-8.09
	Min, Max	56.3, 112.1	-10.8, 16.8	51.1, 88.4	-15.1, 7.1	51.1, 112.1	-15.1, 16.8
Month 12/ET	n	10	9	9	9	19	18
	Mean (SD)	73.1 (14.60)	-0.2 (8.43)	67.6 (3.71)	-7.6 (16.94)	70.5 (10.99)	-3.9 (13.53)
	Median	69.50	2.58	67.52	-11.76	68.32	-4.28
	Min, Max	53.4, 105.0	-13.8, 9.6	62.3, 73.2	-29.9, 15.3	53.4, 105.0	-29.9, 15.3
Last Observation	n	10	9	10	10	20	19
	Mean (SD)	73.1 (14.60)	-0.2 (8.43)	65.9 (6.27)	-8.2 (16.06)	69.5 (11.54)	-4.4 (13.31)
	Median	69.50	2.58	67.31	-12.40	68.18	-5.96
	Min, Max	53.4, 105.0	-13.8, 9.6	51.1, 73.2	-29.9, 15.3	51.1, 105.0	-29.9, 15.3

Abbreviations: ET = early termination; Max = maximum; Min = minimum; n = number of subjects in category indicated; SD = standard deviation
a Baseline is defined as the last non-missing assessment prior to the first dose of study drug.

Rapporteur's comments

Based on the results on LVMi it can be concluded that this remained fairly stable throughout the 12 months treatment period. This is considered relatively short to expect large changes in LVMi, and thus no firm conclusion can be drawn.

Plasma Globotriaosylsphingosine

The PD parameter observed in this study was plasma lyso-Gb3. There was an increase at Month 6 for male subjects that resulted in an overall mean change (SD) from baseline of 5.7 (30.72) ng/mL at this timepoint (n = 14). Results were stable at all other collection time points. The overall mean (SD) change from baseline to Month 12 (n = 19) was -0.1 (32.89) ng/mL.

Table 6: Summary of Observed and Change from Baseline Lyso-Gb3 (ng/mL) in Plasma by Sex and Overall.

	Male N=10		Female N=11		Overall N=21	
Visit Statistics	Observed Values	Change from Baseline	Observed Values	Change from Baseline	Observed Values	Change from Baseline
Baseline [1]						
n	10		11		21	
Mean (SD)	22.3061 (28.07040)		2.5981 (2.31917)		11.9829 (21.42407)	
Median	8.6850		1.1800		4.4900	
Min, Max	0.731, 78.800		0.422, 5.970		0.422, 78.800	
Month 3						
n	8	8	8	8	16	16
Mean (SD)	24.5154 (33.87145)	-0.4923 (35.90748)	2.7446 (2.45234)	0.3925 (0.19371)	13.6300 (25.77969)	-0.0499 (24.53409)
Median	11.6500	0.7760	1.4600	0.4320	3.7600	0.4320
Min, Max	0.983, 102.000	-56.300, 71.800	0.611, 6.650	0.160, 0.680	0.611, 102.000	-56.300, 71.800
Month 6						
n	7	6	9	8	16	14
Mean (SD)	28.3723 (48.93460)	13.0742 (48.36599)	2.6406 (2.10528)	0.1723 (0.43917)	13.8982 (33.67505)	5.7016 (30.72009)
Median	9.7500	0.9825	1.7100	0.2875	3.5900	0.2875
Min, Max	0.956, 137.000	-35.700, 106.800	0.508, 6.440	-0.830, 0.530	0.508, 137.000	-35.700, 106.800
Month 12/ET						
n	10	10	9	9	19	19
Mean (SD)	22.1615 (44.23608)	-0.1446 (46.50793)	3.0734 (1.96444)	0.0359 (0.61889)	13.1198 (32.80264)	-0.0591 (32.88879)
Median	7.5250	-1.0830	3.2200	0.2630	3.7000	0.1800
Min, Max	0.795, 146.000	-65.400, 115.800	0.745, 6.180	-1.190, 0.710	0.745, 146.000	-65.400, 115.800

Lyso-Gb3 = Globotriaosylsphingosine; ET = Early Termination.
[1] Baseline is defined as the last non-missing assessment prior to the first dose of study drug.

Rapporteur's comments

Based on the overall results it can be concluded that treatment kept lyso-Gb3 at a stable level. Given the limited number of patients no firm conclusion can be drawn, especially as the results are driven by the 10 male patients who had higher baseline values. It is known that male Fabry patients have higher baseline values.

Patient Reported Outcomes

Patient reported outcomes (PROs) were assessed by subject responses in the subject e-diary (comprised of the FABPRO and BSS), PGI-C, FPHPQ, and PedsQL questionnaires. In general over the 12-month study period, there were small or no changes in the FABPRO-GI and pain scores and in patient-reported outcomes of FPHPQ, PGI-C, or PedsQL. Only the results of the PGI-C are presented here as the results of the measures pointed in the same direction.

Patient's Global Impression of Change

Diarrhoea

Overall, at Month 12 (n = 19), the subjects' perception of improvement was favourable with 12 (54.5%) subjects indicating an improvement in their diarrhoea and 7 (31.8%) subjects indicating no change. No subjects reported a worsening of diarrhoea.

Overall Pain

At Month 12 (n = 19), 10 subjects (45.5%) indicated an improvement in their overall pain and 8 subjects (36.4%) indicated no change. One subject (4.5%) reported a worsening of pain. The overall mean (SD) improvement was 2.9 (1.29). Female subjects (n = 9) reported slightly less improvement (3.3 [1.00]) than male subjects (n = 10; 2.5 [1.43]).

Tummy Pain

At Month 12 (n = 19), 10 subjects (45.5%) indicated an improvement in their overall tummy pain and 8 subjects (36.4%) indicated no change. One subject (4.5%) reported a worsening of tummy pain. The overall mean (SD) improvement at Month 12 was 3.0 (1.25). Consistent with the FABPRO-GI tummy pain results, the subject reporting a worsening of tummy pain was female. Subjects who were ERT-naïve (n = 9) prior to the study reported slightly better tummy pain results than subjects who were ERT-experienced (n = 10). At Month 12, ERT-experienced subjects reported tummy pain improvement as 3.4 (1.07) versus 2.6 (1.33) for ERT-naïve subjects.

Daily Living

At Month 12 (n = 19), 10 subjects (45.5%) indicated an improvement in their overall activities of daily living (e.g. eating, sleeping, school attendance, playing) and 8 subjects (36.4%) indicated no change. One subject (4.5%) reported a worsening of daily activity. The overall mean (SD) improvement at Month 12 was 3.0 (1.20). Female subjects (n = 9) reported slightly less improvement (3.3 [1.00]) than male subjects (n = 10; 2.7 [1.34]).

Rapporteur's comments

Over the 12-month study period, there were small or no changes in the FABPRO-GI and pain scores and in patient-reported outcomes of FPHPQ, PGI-C, or PedsQL Based on the PGI-C patients reported improvement in diarrhoea, modest improvement in pain severity score and overall pain. This may be due to the relatively young patient group where disease progression has not too advanced.

Ancillary analyses

Not applicable.

Patient exposure

All 9 subjects in the safety population had completed Stage 1 (1 month) of treatment. The extent of exposure is displayed in Table **7**7.

Table 7: Total Exposure – Safety Population.

Parameter	**Statistic**	**Migalastat**
Number of subjects in the safety population	N	21
Total exposure (days)	Mean (SD)	342.5 (80.84)
	Median	362.0
	Min, Max	0, 380

Abbreviations: Max = maximum; Min = minimum; N = total number of subjects; SD = standard deviation Note: The duration of study exposure (days) is defined as (end date of last dosing administration – start date of first dosing administration). The duration of study exposure (months) is defined as (end date of last dosing administration – start date of first dosing administration)/30, rounded to one decimal place.

Adverse events

An overall summary of TEAEs experienced by subjects in the safety population is displayed in Table 8.

Table 8: Summary of Treatment-emergent Adverse Events – Safety Population.

Parameter	Statistic	Migalastat
Number of subjects in the safety population	N(%)	20 (95.2)
Number of TEAEs	n	89
Number of subjects with:		
Mild TEAEs	n (%)	13 (61.9)
Moderate TEAEs	n (%)	5 (23.8)
Severe TEAEs	n (%)	2 (9.5)
Number of subjects with related TEAEs	n (%)	5 (23.8)
Number of subjects with treatment-emergent SAEs	n (%)	1 (4.8)
Number of subjects discontinued due to TEAEs	n (%)	0
Number of subjects with AEs leading to death	n (%)	0

Abbreviations: N = total number of subjects; n = number of subjects in category indicated; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Note: Treatment-emergent adverse events include adverse events that begin after the first dose of study drug until 30 days after the last dose.
Note: Treatment-related TEAEs are defined as TEAEs that have an investigator-defined relationship to study drug of "Definite," "Probable," or "Possible."

Note: Percentages are based on the number of subjects in the safety population.

Table 9: Frequency of Treatment-emergent Adverse Events Occurring in the Safety Population.

System Organ Class Preferred Term	Number (%) of Subjects	Number (%) of Events
Number of subjects with TEAEs	20 (95.2)	89
Gastrointestinal disorders	5 (23.8)	7
Infections and infestations	16 (76.2)	32
Influenza	3 (14.3)	4
Nasopharyngitis	3 (14.3)	4
Upper respiratory tract infection	6 (28.6)	8
Injury, poisoning, and procedural complications	3 (14.3)	3
Investigations	3 (14.3)	6
Musculoskeletal and connective tissue disorders	4 (19.0)	6
Back pain	3 (14.3)	4
Nervous system disorders	5 (23.8)	9
Headache	3 (14.3)	4
Psychiatric disorders	3 (14.3)	6
Respiratory, thoracic, and mediastinal disorders	3 (14.3)	4

Skin and subcutaneous tissue disorders	3 (14.3)	4

Abbreviations: TEAE = treatment-emergent adverse event
Note: Adverse events are coded using MedDRA version 21.0.
Note: Treatment-emergent adverse events include adverse events that begin after the first dose of study drug until 30 days after the last dose. Subjects are counted only once within each system organ class (SOC) and preferred term
(PT). TEAEs are presented alphabetically by SOC and PT.
Note: Percentages are based on the number of subjects in the safety population.

Rapporteur's comments

Most subjects reported mild TEAEs. Five subjects reported 13 moderate TEAEs and 3 severe TEAEs were reported by 2 subjects. Severe events of paraesthesia and H1N1 influenza were reported by 1 subject and 1 subject reported severe depression. None of the severe events were attributed to study drug by the investigator and no action was taken with the study drug. This seems plausible.

Treatment-emergent Adverse Events by Relationship to Study Drug

Five subjects reported TEAEs that were considered either possibly, probably, or definitely related to study drug by the investigator. Table 10 displays all related TEAEs by SOC and PT. All events resolved.

Table 10: Treatment-emergent Adverse Events Related to Study Drug – Safety Population.

System Organ Class **Preferred Term**	**Number of Subjects (N = 21)** **n (%)**	**Number of Events** **n (%)**
Number of subjects with related TEAEs	5 (23.8)	11
Gastrointestinal disorders	1 (4.8)	2
Abdominal pain upper	1 (4.8)	1
Vomiting	1 (4.8)	1
Investigations	1 (4.8)	4
Alanine aminotransferase increased	1 (4.8)	1
Aspartate aminotransferase increased	1 (4.8)	1
Blood creatine phosphokinase increased	1 (4.8)	1
Blood lactate dehydrogenase increased	1 (4.8)	1
Musculoskeletal and connective tissue disorders	1 (4.8)	1
Pain in extremity	1 (4.8)	1
Nervous system disorders	2 (9.5)	3
Headache	2 (9.5)	2
Paraesthesia	1 (4.8)	1
Skin and subcutaneous tissue disorders	1 (4.8)	1
Drug eruption	1 (4.8)	1

Abbreviations: N = total number of subjects; n = number of subjects in category indicated; TEAE = treatment-emergent adverse event
Note: Adverse events are coded using MedDRA version 21.0.
Note: Treatment-emergent adverse events include adverse events that begin after the first dose of study drug until

30 days after the last dose. Subjects are counted only once within each system organ class (SOC) and preferred term
(PT). TEAEs are presented alphabetically by SOC and PT.
Note: Treatment-related AEs are defined as TEAEs that have an investigator-defined relationship to study drug of "Definite," "Probable," or "Possible."

Note: Percentages are based on the number of subjects in the safety population.

Rapporteur's comments

Eleven events of potential drug related TEAEs were reported in 5 subjects. Based on the listing these were reported in 2 patients aged 16 years and 2 patient aged 15 years and 1 patient aged 14 years.

The applicant is requested to include the AES Alanine aminotransferase increased, Aspartate aminotransferase increased and Blood lactate dehydrogenase increased as these are currently not included in SmPC section 4.8 (**OC**).

Serious adverse event/deaths/other significant events

No deaths were reported in the safety Population.

Other Serious Adverse Events

One female subject in the safety population experienced an SAE.

Rapporteur's comments

One event of SAE was reported (e.g. suicidal ideation) due to worsening depression. The event was not considered related to study drug by the investigator. This conclusion can be agreed with.

Safety related to drug-drug interactions and other interactions

Discontinuation due to adverse events

There were no patients in the safety population who discontinued due to an adverse event.

Rapporteur's comments

No comments.

Clinical Laboratory Evaluation

Haematology

Haematology parameters remained stable throughout the study period with mean changes fluctuating within normal limits. Results were similar for male and female subjects as well as subjects who were ERT-naïve and ERT-experienced prior to the study.

Shifts from Baseline

Shifts from baseline in haematology parameters were rare with a total of 6 reports of excursions from normal at baseline to high at Month 12 occurred in eosinophils, erythrocytes, monocytes, and

neutrophils. There were 2 shifts from normal at baseline to low at Month 12 in leukocytes and lymphocytes. A total of 12 shifts occurred from either low or high at baseline to normal at Month 12.

Results were similar for male and female subjects and subjects who previously were ERT-naïve or ERT-experienced.

Potentially Clinically Significant Results

Abnormal, potentially clinically significant (PCS) results were reported for 2 subjects (2001-5114 and 2308-5146) who had low leukocyte counts at Month 12. A low leukocyte count was also reported at baseline for Subject 2308-5146 and at Month 6 for Subject 2001-5115. Abnormal, PCS erythrocytes were reported for Subject 2001-5114 at Month 6 and for Subject 2308-5148 at baseline.

Serum Chemistry

There were no significant mean changes from baseline to Month 12 for any chemistry analyte. Results were similar for male and female subjects as well as subjects who were ERT-naïve and ERT-experienced prior to the study.

Shifts from Baseline

Shifts from baseline in chemistry analytes were infrequent. A total of 16 reports of excursions from normal at baseline to high at Month 12 occurred in alanine aminotransferase, creatine kinase, creatinine, lactate dehydrogenase (LDH), phosphate, potassium, sodium, and urate. There was 1 shift from normal at baseline to low at Month 12 in creatinine. A total of 21 shifts occurred from either low or high at baseline to normal at Month 12.

Results were similar for male and female subjects and subjects who previously were ERT-naïve or ERT-experienced .

Potentially Clinically Significant Results

Abnormal, PCS results occurred sporadically throughout the study at various time points and were related to pre-existing conditions including Fabry disease or represent acute medical conditions. At Month 12, PCS results were reported for 2 subjects who had high gamma glutamyl transferase at multiple study visits in addition to Month 12, 1 subject who had high LDH at Month 12, and 1 subject who had high phosphate at Month 12. Given the random occurrence of these excursions in laboratory values, which occurred at all time points during the study including baseline, these are not considered clinically meaningful outside of their association with Fabry disease and the subjects' baseline disease status.

Rapporteur's comments

Haematology parameters remained stable throughout the study period with mean changes fluctuating within normal limits. There were no significant mean changes from baseline to Month 12 for any chemistry analyte.

Results were similar for male and female subjects as well as subjects who were ERT-naïve and ERT-experienced prior to the study.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs

Vital signs remained stable throughout the study period with normal fluctuations. The results were similar for male and female subjects as well as subjects who previously were ERT-naïve or ERT-experienced.

Potentially clinically significant measurements were seen sporadically in diastolic blood pressure, systolic blood pressure, heart rate, and weight. It should be noted that all of the PCS weight changes observed at Month 12 involved weight gains, which may be expected in an adolescent population. There was a PCS weight loss reported for 1 subject (2001-5114) at all postbaseline interim study visits, which was not seen by Month 12.

Results were similar for male and female subjects and for subjects who previously were ERT-naïve or ERT-experienced.

Electrocardiograms

There were no significant changes in ECGs throughout the study period with similar results seen for male and female subjects and for subjects who previously were ERT-naïve or ERT-experienced. There were no PCS findings either overall or for any of the subgroups.

Physical Examinations

Complete physical examinations were conducted at screening, baseline, and Months 3, 6, and 12. Brief physical exams were conducted at intervening visits between Days 15 and 30 and at Months 1 and 9.

Overall, physical findings were nonremarkable with few findings noted. Results were similar for male and female subjects and for subjects who previously were ERT-naïve or ERT-experienced.

Clinically significant findings were noted sporadically throughout the study with most observations related to acute illnesses (i.e. wheezing, pharyngeal erythema, rhinitis, etc).

Tanner Staging

There were no remarkable changes in sexual maturation throughout the study. Results were similar for male and female subjects and for subjects who previously were ERT-naïve or ERT-experienced.

Rapporteur's comments

Vital signs remained stable throughout the study period with normal fluctuations and physical findings were non-remarkable. There were no significant changes in ECGs throughout the study period with similar results seen for male and female subjects. There were no remarkable changes in sexual maturation throughout the study.

Results were similar for male and female subjects as well as subjects who were ERT-naïve and ERT-experienced prior to the study.

6. Risk management plan

The MAH submitted an updated RMP (version 7.0) with this application.

The amendments mainly concern inclusion of AT1001-020 final data and changes relevant to study completion. Furthermore, the Applicant has taken this regulatory opportunity to update the due dates for completion and provision of the final study report for category 3 study AT1001-030 (A Prospective, Observational Registry of Patients with Fabry Disease) in the RMP.

The proposed RMP changes were the following:

- To include AT1001-020 final data and changes relevant to study completion.

- To update the due dates for completion and provision of the final study report for category 3 study AT1001-030 (A Prospective, Observational Registry of Patients with Fabry Disease) in the RMP.

Part I. Product overview is proposed to be updated to include information on the paediatric indication (assessed within the finalised variation II/29).

Part II. Safety specification is proposed to be updated in:
- *Module SIII (Clinical trial exposure)* with data from the finalised AT1001-020 study.
- *Module SIV (Populations not studied in clinical trials)* with minor information applicable for the AT1001-020 study.
- *Module SVII (Identified and potential risks)* with outcome data from the AT1001-020 study

No changes have been proposed to the summary of safety concerns.

Table Summary of 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 m^2) Long-term treatment (> 1 year) Use in the pediatric population aged 12 to < 16 years.

Part III. Pharmacovigilance Plan is proposed to be updated to remove the AT1001-020 study. Moreover, the final study report for category 3 study AT1001-030 has been proposed to be updated with a due date of Q2 2029 instead of Q2 2027.

Table Summary of ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 – Required additional pharmacovigilance activities				

Table Summary of ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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 m^2); • 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~~ **2029** (planned)

Part V. Risk minimisation measures is proposed to be updated in Table V.1 (Description of routine risk minimisation measures by safety concern) with minor changes related to references to sections in the SmPC regarding the missing information "use in paediatric population aged 12 to <16 years". No additional risk minimisation measures are in place.

Part VI. Summary of the RMP is proposed to be updated to be in line with the proposed changes in the other sections of the RMP.

Assessor's comments

The proposed changes are endorsed.

7. Changes to the Product Information

As a result of this variation, section(s) 4.8, 5.1 and 5.2 of the SmPC are being updated to include the study result of the final study AT1001-020. The Package Leaflet (PL) is updated accordingly.

8. Request for supplementary information

8.1. Major objections

N/A

8.2. Other concerns

1. The applicant presented the study results based on the overall patients included. However, given that the expansion of the indication pertains to paediatric patients aged 12 years to <16 years, the applicant is requested to submit the efficacy and safety results for this patients group - acknowledging the numbers are small and will not allow making firm conclusions - to confirm that the results are comparable to the older patients. The applicant should present the results for eGFR, LWMi, Urine Protein and urine albumin, Plasma Globotriaosylsphingosine; results should be presented for males and females in line with the presentation in this report and compared to the patients aged 16 to <18 years. With respect to the safety, the applicant should compare the adverse events based on the age category (e.g. 12 -<16 and 16 to <18 years of age).
2. The applicant is requested to include the AES Alanine aminotransferase increased, Aspartate aminotransferase increased and Blood lactate dehydrogenase increased as these are currently not included in SmPC section 4.8.
3. The applicant is requested to update the SmPC section 5.1 in line with CHMP Rapporteur's comments.

9. Assessment of the responses to the request for supplementary information

9.1. Major objections

N/A

9.2. Other concerns

1. The applicant presented the study results based on the overall patients included. However, given that the expansion of the indication pertains to paediatric patients aged 12 years to <16 years, the applicant is requested to submit the efficacy and safety results for this patients group - acknowledging the numbers are small and will not allow making firm conclusions - to confirm that the results are comparable to the older patients. The applicant should present the results for eGFR, LWMi, Urine Protein and urine albumin, Plasma Globotriaosylsphingosine; results should be presented for males and females in line with the presentation in this report and compared to the

patients aged 16 to <18 years. With respect to the safety, the applicant should compare the adverse events based on the age category (e.g. 12 -<16 and 16 to <18 years of age).

Summary of Applicant's response

A total of 22 subjects aged 12 to <18 years were enrolled in Study AT1001-020 and 21 subjects took at least 1 dose of study drug (safety population). Of these, 15 subjects were aged 12 to < 16 years and 7 subjects were aged 16 to < 18 years (Table 11).

Table 11: Subject Disposition by Age Subgroup

Parameter	**Statistic**	**12 - < 16 years (N = 14)**	**16 - < 18 years (N = 7)**
Number of subjects in the ITT population[a]	N	15	7
Number of subjects not dosed	N	1	0
Number of subjects in the safety population[b]	N	14	7
Number of subjects in the PK population[c]	N	13	7
Completed subjects (Stages 1 and 2)	n (%)	12 (80.0)	7 (100)
Discontinued the study	n (%)	3 (20.0)	0
Reasons for discontinuation during treatment			
Withdrawal by subject	n (%)	1 (6.7)	0
Withdrawal by parent or legally-authorized representative	n (%)	1 (6.7)	0
Lost to follow-up	n (%)	1 (6.7)	0

Abbreviations: CSR = clinical study report; N = total number of subjects; n = number of subjects in category indicated; PK = pharmacokinetic; ITT = intent-to-treat
[a] Intent-to-treat included all enrolled subjects
[b] Safety population included all subjects who received at least 1 dose or partial dose of study drug.
[c] The PK population included all subjects with at least 1 quantifiable concentration and a known weight and eGFR

Changes from baseline for the efficacy assessments of estimated glomerular filtration rate (eGFR), left ventricular mass index (LVMi), urine protein, urine albumin, and plasma globotriaosylsphinogosine (lyso-Gb3) conducted during the treatment period indicated a stability of response for renal, cardiac, and pharmacodynamic (PD) parameters and were comparable between the 2 age subgroups.

Table 12: Estimated Glomerular Filtration Rate by Age Subgroup – Intent-to-treat Population.

Visit		Males				Females				Overall			
		12 to < 16 years		16 to < 18 years		12 to < 16 years		16 to < 18 years		12 to < 16 years		16 to < 18 years	
	Statistic	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline[a]	n	6		4		8		3		14		7	
	Mean (SD)	122.8 (13.56)		99.5 (3.42)		119.6 (25.66)		122.0 (20.22)		121.0 (20.69)		109.1 (16.94)	
	Median	119.5		100		113.0		130.0		117.0		101.0	
	Min, Max	106, 144		95, 103		77, 164		99, 137		77, 164		95, 137	
Month 12/ET	n	6	6	4	4	6	6	3	3	12	12	7	7
	Mean (SD)	112.7 (7.92)	-10.2 (9.02)	107.8 (27.62)	8.3 (25.32)	118.7 (14.09)	-0.7 (14.79)	122.3 (19.66)	0.3 (0.58)	115.7 (11.34)	-5.4 (12.69)	114.0 (23.90)	4.9 (18.40)
	Median	114.5	-9.5	98.5	0.5	118.5	1.0	130.0	0.0	115.0	-3.5	102.0	0.0
	Min, Max	101, 123	-21, 0	86, 148	-13, 45	97, 134	-17, 24	100, 137	0, 1	97, 134	-21, 24	86, 148	-13, 45
Annualized rate of change from baseline													
	n		6		4		7		3		13		7
	Mean (SD)		-10.3 (9.16)		8.4 (25.61)		-0.5 (13.47)		0.3 (0.58)		-5.0 (12.29)		4.9 (18.61)
	Median		-9.5		0.5		1.0		0.0		-2.0		0.0
	Min, Max		-21, 0		-13, 46		-17, 24		0, 1		-21, 24		-13, 46

Fifty treatment-emergent adverse events (TEAEs) were observed in 14 subjects for the 12 to < 16 years age subgroup; and 39 TEAEs across 7 subjects for the 16 to < 18 years age subgroup. The most frequently reported TEAE in the 12 to < 16 years age subgroup was upper respiratory tract infection (35.7%), followed by influenza, nasopharyngitis, back pain, headaches, and rash (14.3% each) (Table 13).

Five subjects reported TEAEs that were considered either possibly, probably, or definitely related to study drug by the investigator. Of these events, 3 events were in 3 subjects aged 12 to < 16 years (pain in extremity, headache, and drug eruption) and 8 events were in 2 subjects aged 16 to < 18 years (1 subject reporting events of abdominal pain, vomiting, headache, and paraesthesia, and 1 subject reporting concurrent events of alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, blood creatinine phosphokinase [CPK] increased, blood lactate dehydrogenase [LDH] increased, headache) (Module 2.5, Appendix 1, Table 14.3.1.4 and Appendix 2, Table 14.3.1.4).

Most subjects reported mild TEAEs and there were no treatment-related serious AEs in either age group. The data appears to be comparable to the older population.

Table 13: Frequency of Treatment-emergent Adverse Events Occurring in ≥ 2 Subjects.

System Organ Class **Preferred Term**	**12 - < 16 years**		**16 - < 18 years**	
	Number of Subjects (N = 14) n (%)	**Number of Events n (%)**	**Number of Subjects (N = 7) n (%)**	**Number of Events n (%)**
Number of subjects with TEAEs	13 (92.9)	50	7 (100)	39
Ear and labyrinth disorders	0	0	2 (28.6)	2
Gastrointestinal disorders	2 (14.3)	3	3 (42.9)	4
Infections and infestations	9 (64.3)	16	7 (100)	16
Influenza	2 (14.3)	3	1 (14.3)	1
Nasopharyngitis	2 (14.3)	2	1 (14.3)	2
Pharyngitis streptococcal	0	0	2 (28.6)	2
Upper respiratory tract infection	5 (35.7)	6	1 (14.3)	2
Injury, poisoning and procedural complications	2 (14.3)	2	1 (14.3)	1
Investigations	2 (14.3)	2	1 (14.3)	4
Musculoskeletal and connective tissue disorders	3 (21.4)	5	1 (14.3)	1
Back pain	2 (14.3)	3	1 (14.3)	1
Nervous system disorders	4 (28.6)	7	1 (14.3)	2
Headache	2 (14.3)	3	1 (14.3)	1
Psychiatric disorders	2 (14.3)	4	1 (14.3)	2
Respiratory, thoracic and mediastinal disorders	3 (21.4)	4	0	0
Skin and subcutaneous tissue disorders	3 (21.4)	4	0	0
Rash	2 (14.3)	2	0	0

Abbreviations: N = total number of subjects; n = number of subjects in category indicated; TEAE = treatment-emergent adverse event

Note: Adverse events were coded using MedDRA version 21.0.
Note: Treatment-emergent adverse events included adverse events that began after the first dose of study drug until
30 days after the last dose. Subjects were counted only once within each system organ class (SOC) and preferred term (PT). TEAEs are presented alphabetically by SOC and PT.
Note: Percentages were based on the number of subjects in the safety population.

Rapporteur's comments

As requested the applicant submitted the subgroup analyses on the efficacy data. As expected the numbers are very small. So no firm conclusions can be drawn. Of the 15 children aged 12 to <16 years, 8 were treatment naïve. Data on eGRF indicates that in both the treatment naïve as the ERT experienced group similar result in reduction were obtained after 12 month of treatment; treatment naïve change from baseline (mean, SD) -3.2 (15.5), ERT-experienced -7.7 (10.2) mL/min. For left ventricular mass index (LVMi), urine protein, urine albumin, and plasma globotriaosylsphinogosine (lyso-Gb3) also small changes from baseline to EOT were observed. These are indicative for stabilisation. Results between the patients 12 to <16 years are in line with the results of the patients ≥16 to <18 years of age, and to patients over 18 years of age.

For patients aged 12 to <16 years, the most frequently reported SOCs (i.e., 20% of the subjects or more) were infections and infestation (64.3%), nervous systems disorder (28.6%), musculoskeletal and connective tissue disorders, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous disorders (21.4% each). The most frequently reported TEAE was upper respiratory tract infection (35.7%), followed by influenza, nasopharyngitis, back pain, headaches, and rash (14.3% each).

For patients aged 16 to <18 years, the most frequently reported SOCs (i.e., 20% of the subjects or more) were infections and infestations (100%), and gastrointestinal disorders (42.9%). The most frequently reported TEAE was pharyngitis streptococcal (28.6%). All other TEAEs were reported in 1 subject only.

Conclusion: Issue resolved

2. The applicant is requested to include the AES Alanine aminotransferase increased, Aspartate aminotransferase increased and Blood lactate dehydrogenase increased as these are currently not included in SmPC section 4.8.

Summary of Applicant's response

The TEAEs of ALT increased, AST increased, and blood LDH increased were reported in a single subject. The Applicant considers that the enzyme elevations may have been a sequelae of the concurrent ear infection and resultant tissue damage, rather than causally related to Galafold exposure.

In order to determine if such enzyme elevations have been observed previously following exposure to Galafold, the Applicant conducted a broader search of the global safety database to assess any similar cases retrieved by using the high level term (HLT) of 'Liver function analyses,' 'Hepatic enzymes and function abnormalities,' and 'Tissue enzyme analyses NEC' (including all blood lactate dehydrogenase preferred term (PT)/low level terms (LLT) followed by filtering for relevant cases representative of ALT/AST and LDH elevation. Four (4) non-serious reports of abnormal liver function enzymes were retrieved during this search. Two (2) cases from HLT of 'Liver function analyses' and 3 cases from HLT of 'Tissue enzyme analyses' were excluded from this table as the events were not related to the topic in discussion. The HLT of 'Hepatic enzymes and function abnormalities' didn't retrieve any cases. No other reports of abnormal blood LDH results were identified.

Rapporteur's comments

The applicant elaborate that the TEAEs of ALT increased, AST increased, and blood LDH increased were reported in a single subject who experienced the AEs of elevation of ALT, AST, CPK, and LDH on the same day, approximately 3 months after starting treatment with Galafold. These events were all mild in nature and the subject recovered from them 22 days after the day of event onset. No action was taken towards Galafold treatment. Four (4) non-serious reports of abnormal liver function enzymes were retrieved when these events were investigated in the applicant data. No other reports of abnormal blood LDH results were identified.

Based on these cases, the applicant did not include AES Alanine aminotransferase increased, Aspartate aminotransferase increased and Blood lactate dehydrogenase increased which is considered agreed with.

Conclusion: Issue resolved

3. The applicant is requested to update the SmPC section 5.1 in line with CHMP Rapporteur's comments.

Summary of Applicant's response

The Applicant agrees to add the following text to Section 5.1 in the paediatric population subsection of the SmPC. The updated SmPC is provided with this response.

At 1 year, the efficacy results in adolescents on the same dosing regimen as adults were consistent in renal, cardiac, and pharmacodynamic results as well as responses to patient-reported outcomes.

Rapporteur's comments

The Applicant updated SmPC section 5.1 as requested, see also attached SmPC.

Conclusion: Issue resolved

10. Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 13 January 2022.