EU-RISK MANAGEMENT PLAN FOR MYOZYME® (ALGLUCOSIDASE ALFA)

Data Lock Point (DLP)	30-SEP-2022
RMP Version number	Version 11.0
Date of final sign-off	09-NOV-2023

[redacted]

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Risk management plan is updated to introduce the risk management strategy for home infusion related risk. RMP updated to v11.0 to address [redacted] comments received on RMP v10.1 [redacted]
Summary of significant changes in this RMP	**Safety specification:** Part II Module SVII and SVIII: Added new important potential risk "Medication errors in the home infusion setting". **Risk minimization plan:** Part V: Added new aRMM: Home infusion guide for HCP and Home infusion guide for Patient/Caregiver including an infusion diary. **Annexes:** Annex 6 and 8 are updated. Annex 6: Added key elements of home infusion guide for HCP and Home infusion guide for patient/caregiver including infusion diary. Annex 8: Updated to reflect the current changes in the RMP.

aRMM: Additional Risk Minimization Measure; HCP: Healthcare Professional; [redacted] RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	10.1
Approved with procedure	EMEA/H/C/000636/II/0095
Date of approval (opinion date)	26-Oct-2023

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	[redacted] [a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

[redacted]

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ABBREVIATIONS

ACEI:	Angiotensin-Converting Enzyme Inhibitor
ADA:	Anti-Drug Antibody
ADR:	Adverse Drug Reaction
AMD:	Acid Maltase Deficiency
aRMM:	Additional Risk Minimization Measure
ATC:	Anatomical Therapeutic Chemical
CHO:	Chinese Hamster Ovary
CI:	Confidence Interval
COVID-19:	Coronavirus Disease-2019
CRIM:	Cross-Reactive Immunologic Material
DLP:	Data Lock Point
DPH:	Diphenhydramine
EAP:	Expanded Access Program
EEA:	European Economic Area
EMC:	Erasmus Medical Center
EPAR:	European Public Assessment Report
ERT:	Enzyme Replacement Therapy
EU:	European Union
FDA:	Food and Drug Administration
GAA:	Acid Alpha-Glucosidase
GCP:	Good Clinical Practices
GPE:	Global Pharmacovigilance and Epidemiology
GSD-II:	Glycogen Storage Disease Type II
HCP:	Healthcare Professional
HSAT:	High Sustained Antibody Titre
IAR:	Infusion Associated Reaction
ICAP:	International Charitable Access Program
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
INN:	International Nonproprietary Name
IO:	Infantile-Onset
IOPD:	Infantile-Onset Pompe Disease
ITI:	Immune Tolerance Induction
IV:	Intravenous
LO:	Late-Onset
LOPD:	Late-Onset Pompe Disease
LV:	Left Ventricular
MAH:	Marketing Authorization Holder
Max:	Maximum
MedDRA:	Medical Dictionary for Regulatory Activities
Min:	Minimum
n:	Number of Patient

[redacted]

N:	Total Number of Patient
NA:	Not Applicable
ND:	Not Determined
NOAEL:	No-Observed-Adverse-Effect-Level
PASS:	Post-Authorization Safety Study
PBRER:	Periodic Benefit-Risk Evaluation Report
PL:	Package Leaflet
PSUR:	Periodic Safety Update Report
PTC:	Product Technical Complaint
QOW:	Every Other Week
QPPV:	Qualified Person Responsible for Pharmacovigilance
QW:	Every Week
rhGAA:	Recombinant Human Acid Alfa-Glucosidase
RMP:	Risk Management Plan
SD:	Standard Deviation
SmPC:	Summary of Product Characteristics
UK:	United Kingdom
US:	United States

[redacted]

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Alglucosidase alfa
Pharmacotherapeutic group(s) (ATC Code)	A16AB07
Marketing Authorization Holder	Sanofi B.V. Paasheuvelweg 25 1105 BP Amsterdam The Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	MYOZYME
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Alglucosidase alfa is a hydrolase enzyme.
	Summary of mode action: Alglucosidase alfa is an exo acting hydrolase that catalyzes the hydrolysis of α 1,4 and α 1,6 glucosidic linkages of glycogen.
	Important information about its composition: Alglucosidase alfa is produced by recombinant deoxyribonucleic acid technology using CHO cell culture and is identical in amino acid sequence to a commonly occurring human form of GAA.
Hyperlink to the product information	https://www.ema.europa.eu/en/documents/product-information/myozyme-epar-product-information_en.pdf
Indication(s) in the EEA	Current: Alglucosidase alfa is indicated for long-term ERT in patients with a confirmed diagnosis of Pompe disease (acid α glucosidase deficiency). Alglucosidase alfa is indicated in adults and pediatric patients of all ages.
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dosage regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks as an IV infusion. Infusions should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/hr and be gradually increased by 2 mg/kg/hr every 30 minutes if there are no signs of IARs until a maximum rate of 7 mg/kg/hr is reached.
	Proposed: Not applicable

[redacted]

Pharmaceutical form(s) and strength(s)	Current: Powder for concentrate for solution for infusion, 50 mg. White to off white powder for concentrate for solution for infusion. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5.0 mg/mL alglucosidase alfa. MYOZYME 50 mg vials are supplied as a sterile, non-pyrogenic, white to off white lyophilized cake or powder. MYOZYME is supplied in single use, clear Type I glass 20 mL (cc) vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic flip off cap.
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	No

ATC: Anatomical Therapeutic Chemical; CHO: Chinese Hamster Ovary; EEA: European Economic Area; ERT: Enzyme Replacement Therapy; EU: European Union; GAA: Acid Alpha-Glucosidase; IAR: Infusion Associated Reaction; INN: International Nonproprietary Name; IV: Intravenous; RMP: Risk Management Plan.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Alglucosidase alfa is indicated for long-term ERT in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). Alglucosidase alfa is indicated in adults and pediatric patients of all ages.

Pompe disease is a rare metabolic muscle disease inherited in an autosomal recessive fashion. Pompe disease is caused by a deficiency of *GAA*, which is needed for degradation of lysosomal glycogen. The estimated global incidence of Pompe disease is 1:40 000. Other names for Pompe disease include glycogen storage disease type II (GSD-II), acid maltase deficiency (AMD) and glycogenosis type II.

The prevalence figure can be calculated from the maximum birth incidence of 11.6 per 100 000 and the number of live births according to the following formula:

Prevalence (P) = incidence (I) x mean duration or patient life expectancy (D).

Due to disease progression and in agreement with literature, the average ages of death were 1, 15-20 and 45-60 for infantile, juvenile and adult-onset phenotypes respectively. To avoid under reporting the prevalence of Pompe disease, the highest literature-reported birth incidence combined with reported mortality rates were used to estimate the total maximum prevalence of Pompe disease. The calculated maximum prevalence of Pompe disease is 6.0:100 000 (or 0.6:10 000).

Historically, patients with Pompe disease have been classified into different subtypes such as classic infantile-onset (IO), non-typical IO, childhood-, juvenile-, and adult-onset, based on age at onset of symptoms, extent of organ involvement and rate of progression to death. However, it is difficult to reliably classify patients into such categories using any particular clinical, biochemical or genetic criteria as the manifestations of Pompe disease encompasses a spectrum of presentation, ranging from a rapidly progressive IO form to a more slowly progressive late-onset (LO) form, with considerable variability and overlap between these extremes. (1)(2)(3) What is consistent across all presentations is the underlying deficiency of lysosomal *GAA* resulting in progressive tissue damage, and ultimately death, if left untreated. Alglucosidase alfa is indicated for long-term ERT in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). Alglucosidase alfa is indicated in adults and pediatric patients of all ages.

Acid alpha glucosidase deficiency is mainly dictated by the variation of mutations in the two *GAA* alleles, and the extent of this deficiency correlates inversely with the disease severity. The lower the amount of the residual *GAA*, the earlier a person will develop the disease and the worse the prognosis. (4)(5)(6)(7)

The epidemiology of the disease is summarized in the following table.

[redacted]

Table 6 - Epidemiology of the (untreated) target disease

Indication	Pompe disease
Incidence	The incidence of Pompe disease appears to vary in different ethnic groups. Estimates of the frequency of IOPD in the Caucasian population range from 1:100 000 to 1:200 000. (2) The incidence of IOPD may be the highest among patients of African descent (estimated 1:14 000) and among Chinese (estimated 1:40 000 to 1:50 000). (2) The calculated incidence of all Pompe disease phenotypes is estimated to be 1:40 000 births. (8)(9) The incidence estimate for LOPD is 1 per 57 000 births. A recent published study estimated the prevalence of LOPD to be 3.9 per 1 000 000 in Belgium. (10)
Prevalence	With the recent availability of a highly sensitive and specific screening process for Pompe disease (11), numerous studies have investigated the prevalence of Pompe disease among high-risk populations as well as the birth prevalence in newborn screening programs and pilot studies. Nordic countries exhibit some of the lowest prevalence of Pompe disease among the general population (1 in 224 000 or lower) as well as high risk individuals with undetermined muscle diseases. (12)(13)(14) On the opposite side of the spectrum, the socially and geographically isolated African-American Maroon population of French Guiana living along the Maroni river have an estimated birth prevalence of 1 in 2000 due to the founder effect of two specific genetic mutations. The estimated rate is 50 times higher than anywhere in the world, and limited to IO cases. (15) Newborn screening indicates that Pompe disease may be more prevalent than previously estimated with prevalence closer to 1 in 20 000 live births or even more common in the US, Europe, Mexico, and Taiwan, and at least half of which are expected to manifest as LO disease. (16)(17)(18)(19) For instance, in a recent screening study in the US, the incidence of IOPD + LOPD was 1:16 095. (20)
Demographics of the population in the authorized/proposed indication	Demographics of patients with Pompe disease can be derived from the Pompe Registry. As of 01-May-2020, a total of 2254 patients were enrolled in the Pompe Registry. A summary of patient ages at enrolment and baseline, as well as current age, gender, and ethnicity, as well as a figure of the age at enrolment in the Pompe Registry, are presented below (source: Pompe Registry May-2020 data download):

Table 6a - Pompe Registry Demographics, May-2020

Parameter	Statistic	All Patients Enrolled	IOPD	LOPD
Total Number of patients	N	2254	390	1640
Age at Enrollment (year)	n	2254	390	1640
	Mean (SD)	32.5 (24.19)	2.2 (2.58)	41.5 (20.47)
	Median (25^{th}, 75^{th})	36.1 (5.2, 53.2)	1.3 (0.6, 2.8)	44.1 (27.9, 57.5)
	Min, Max	0.0, 83.7	0.0, 16.3	0.1, 83.7
Age at last follow-up (year)	n	2249	390	1640
	Mean (SD)	36.3 (24.91)	5.2 (4.65)	45.9 (20.67)

[redacted]

Indication	Pompe disease

	Median (25th, 75th)	40.1 (9.7, 57.1)	3.7 (1.5, 7.6)	49.6 (31.7, 61.9)
	Min, Max	-0.4, 87.2	0.0, 27.7	0.3, 87.2
Gender				
Male	n (%)	1123 (49.8)	193 (49.5)	820 (50.0)
Female	n (%)	1131 (50.2)	197 (50.5)	820 (50.0)
Race[a]				
American Indian or Alaska Native	n (%)	7 (0.3)	3 (0.8)	4 (0.2)
Asian	n (%)	147 (6.5)	55 (14.1)	84 (5.1)
Black	n (%)	89 (3.9)	53 (13.6)	31 (1.9)
Native Hawaiian or other Pacific Islander	n (%)	4 (0.2)	2 (0.5)	2(0.1)
White	n (%)	1387 (61.5)	166 (42.6)	1154 (70.4)
Latin American	n (%)	17 (0.8)	4 (1.0)	11 (0.7)
Not reported/ Unknown	n (%)	632 (28.0)	123 (31.5)	366 (22.3)

Program Name: Y:\Registry\Pompe\Programs\Data Requests\2020\PDR_200605_01_RMP_NeoGAA\Programs\Output\TDEMO.sas (Download Date: 01-May-2020)
Note: Infantile-onset Pompe disease patients were defined as those with age of symptom onset ≤12 months and cardiac enlargement/myopathy determined from echocardiography or chest X-ray. Late-onset Pompe disease patients were defined as patinets withs symptom onset ≤12 months of age without cardiac enlargement/myopathy, or with symptopm onset >12 months of age.
a For race, the patient can check all races that apply.
IOPD: Infantile-Onset Pompe disease; LOPD: Late-Onset Pompe Disease; n: Number of Patient; N: Total Number of Patient; SD: Standard Deviation.

Risk factors for the disease

The incidence of Pompe disease appears to vary in different ethnic groups. The frequency of rapidly progressive disease is at least 1:100 000 to 1:200 000 in the Caucasian population, 1:14 000 among African-Americans, and 1:40 000 to 1:50 000 among Chinese. The frequency of later onset disease in Caucasians may be as high as 1:60 000. (2)

Main existing treatment options	Among the available approaches to treat Pompe disease, ERT based on rhGAA is the only treatment that specifically targets the underlying enzymatic cause of the disease by replacing the enzyme that is deficient. Alglucosidase alfa and avalglucosidase alfa, at 20 mg/kg body weight/qow are the only approved products in the market. In addition, symptomatic treatment can be provided through a multidisciplinary team including eg, a metabolic disease specialist, a cardiologist, pulmonologist, neurologist/neuromuscular specialist, orthopedist, physical therapist, speech therapist, geneticist, and/or metabolic dietician.
Natural history of the indicated condition in the untreated population including mortality and morbidity	At the most severe end of the disease spectrum is the rapidly progressive, IO form, in which patients present with signs and symptoms of Pompe disease within the first 12 months of life. A massive deposition of glycogen in the heart and skeletal muscle results in rapidly progressive cardiomyopathy and generalized muscle weakness with hypotonia. Motor development is often completely arrested, or if motor development milestones are achieved, they are subsequently lost. Death from cardiac and/or respiratory failure occurs before most patients reach 1 year of

Indication	Pompe disease
	age. Patients presenting with this typical disease course have been described in the literature as having "classic" IOPD. (2)(3) A subset of patients with IOPD characterized by a slightly later age at onset of symptoms (but before 12 months of age) and slower progression of cardiomyopathy has been described by Slonim and colleagues. (21) These "non-typical" patients may survive beyond their first birthday, but often develop respiratory failure between 1 and 2 years of age. In general, patients with IOPD (both classic and non-typical) have little or no residual *GAA* activity due to *GAA* gene mutations which severely impair protein function or preclude its expression altogether. (2)(3) At the other end of the disease spectrum, patients with LO Pompe disease manifest signs and symptoms anywhere from early childhood through the sixth decade of life and experience slower progression in skeletal and respiratory involvement. The heart is typically spared, or if it is affected, it is generally secondary to respiratory involvement. (2)(22)(23) Patients usually present with myopathy, predominantly of the proximal muscles in the trunk and pelvic and shoulder girdles, and a variable progression of respiratory involvement. Initial myopathic symptoms can be very subtle and may include difficulty combing the hair, rising from a chair, climbing stairs, or rising from a squat. However, over time there is increasing involvement of lower, truncal, and upper body muscles, and most patients ultimately become wheelchair bound. Initial respiratory symptoms may be related to sleep apnea and include somnolence and morning headache. As the disease progresses, orthopnoea, and/or exertional dyspnoea develop. Many patients eventually require non-invasive or invasive ventilation and ultimately progress to respiratory failure, the leading cause of death in these patients. (2)(24)(25)(26)
Important co-morbidities	**Important co-morbidities found in the target population:** Identified safety risks related to underlying Pompe disease include cardiac arrhythmias during general anesthesia induction, hearing loss, fractures, increase risk of infection and complications associated with brain aneurysm and other arteriopathies. Long-term survivors of IOPD exhibit sustained improvements in cardiac parameters and gross motor function as a result of ERT. Residual muscle weakness, hearing loss, risk for arrhythmias, hypernasal speech, dysphagia with risk for aspiration, and osteopenia are common. Initially, LOPD was characterized by proximal limb-girdle myopathy and substantial respiratory involvement. This spectrum includes bulbar muscle involvement manifesting as lingual weakness with dysarthria and dysphagia, osteoporosis, scoliosis, rigid spine syndrome, sleep apnea and sleep disordered breathing, small-fiber neuropathy, sensorineural hearing loss, cerebral and intracranial aneurysms, cardiac hypertrophy, abnormal cardiac rhythm, impaired gastric function and gastrointestinal motility, lower urinary tract and anal sphincter involvement, pain, and fatigue. (27)(28) **Concomitant medication(s) in the target population:** In addition to ERT, because Pompe disease is a multisystem disorder, it is best managed by a multidisciplinary team led by an experienced physician. Optimally, the team should include a metabolic disease specialist in addition to the specialist dictated by the patient's signs and symptoms, possibly a cardiologist, pulmonologist, neurologist/neuromuscular specialist, orthopedist, physical therapist, speech therapist, geneticist, and/or metabolic dietician, among others. Cardiovascular: In the presence of LV outflow tract obstruction, the use of digoxin, other inotropes, diuretics and afterload reducing agents such as ACEI may exacerbate the LV outflow tract obstruction. Respiratory: Liberal use of bronchodilators is recommended in conjunction with airway clearance techniques and assisted coughing maneuvers to maximize the

Indication	Pompe disease
	patient's pulmonary toilet care. Supplementary O2 can be used to treat hypoxia, and noninvasive positive pressure ventilation could be used in case of hypo-ventilation. Gastrointestinal and Dietary: Maintaining good nutrition with attention to macro and micronutrients is important in the management of all patients with Pompe disease. Exercise and Rehabilitation: It is recommended to perform submaximal, functional and aerobic exercise, to avoid excessive, resistive and eccentric exercise, to avoid overwork weakness, and to avoid disuse atrophy.

ACEI: Angiotensin-Converting Enzyme Inhibitor; ERT: Enzyme Replacement Therapy; GAA: Acid Alfa-Glucosidase; IO: Infantile-Onset; IOPD: Infantile-Onset Pompe Disease; LO: Late-Onset; LOPD: Late-Onset Pompe Disease; LV: Left Ventricular; Max: Maximum; Min: Minimum; n: Number of Patient; N: Total Number of Patient; QOW: Every Other Week; rhGAA: Recombinant Human Acid Alfa-Glucosidase; SD: Standard Deviation; US: United States.

RISK MANAGEMENT PLAN - PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A number of non-clinical safety studies were conducted to evaluate the safety pharmacology/toxicology profile of alglucosidase alfa for use as ERT in patients with Pompe disease. The toxicology program conducted with alglucosidase alfa includes several single-dose, repeat-dose, and reproductive and developmental toxicity studies. Non-clinical evaluation with in vivo models of Pompe disease has shown alglucosidase alfa is able to reverse biochemical and histopathological manifestations of the disease. Toxicological evaluation in mice, rats, rabbits, dogs, and monkeys suggest an acceptable safety profile for human use.

The key non-clinical safety findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Key findings identified from single or repeat-dose toxicity studies Alglucosidase alfa was well tolerated in single-dose toxicity studies conducted in rats and dogs at doses of 1, 10, and 100 mg/kg. Only tremors were observed 60 minutes post dose in some dogs at 10 and 100 mg/kg. No adverse effects were observed in mice when alglucosidase alfa was administered intravenously once weekly for 4 weeks up to 100 mg/kg. Two 4-week toxicity studies were conducted in rats at doses of 0, 1, 10 and 100 mg/kg/week, and 0, 1, 5, 10 and 50 mg/kg/week, administered once weekly. Hypersensitivity reactions were observed in several rats, even after pretreatment with DPH. In addition, sporadic incidences of elevated liver enzymes and microscopic lesions in the stomach were observed. These findings were not dose or sex specific and while notable, are not considered related to the treatment but rather due to a secondary effect associated with hypersensitivity. Two studies were conducted in monkeys receiving 13 doses up to 100 mg/kg alglucosidase alfa or 7 doses at 200 mg/kg alglucosidase alfa once every other week The results showed a dose response with respect to the levels of rhGAA recovered in the liver and levels above background were still detectable at various time points post dose; however, no concurrent alteration in liver function tests or histopathology changes were observed. • Reproductive/developmental toxicity studies A fertility and early embryonic development study was conducted in mice at doses of 0, 10, 20, or 40 mg/kg every other day for a minimum of 9 weeks to males and 2 weeks to females prior to cohabitation.	Hypersensitivity reactions have been documented in human clinical trials and during post marketing surveillance. These reactions have been added to the important identified risk of infusion-associated reactions including hypersensitivity and anaphylactic reactions and are included in the product label. They are also monitored by routine pharmacovigilance assessment. Although accumulation of rhGAA in the liver of the monkeys infused with 100 mg/kg and 200 mg/kg once every other week of alglucosidase alfa and sporadic elevations of liver enzymes in rodents were observed, similar elevations in liver enzymes attributed to rhGAA administration have only rarely been observed in the clinical setting. Based upon these findings, patients treated with rhGAA chronic dosing in the clinical setting should be monitored for liver enzymes prior to treatment initiation and periodically thereafter. Based on the rationale developed above, the MAH is not retaining this risk as relevant to human. In addition, this is supported by post-authorization experience. The results of the analysis from the patient disease registry revealed that no adverse events of hepatic insufficiency attributable to alglucosidase alfa have been reported to GPE. Use of alglucosidase alfa in pregnant women is considered missing information: reproductive toxicity at a maternal toxic dose was shown in rabbits but no congenital malformations were reported. The relevance to human is unknown. This

Key Safety Findings	Relevance to human usage
Diphenhydramine (5 mg/kg) was administered to males and females after the 4th and 6th dose, respectively. There was no test article-related effect reported on mating and fertility and the NOAEL was 40 mg/kg every other day. No adverse findings were observed in an embryo-fetal developmental toxicity study in mice. Alglucosidase alfa was administered at 0, 10, 20 or 40 mg/kg/day to rabbits from gestational day 7 through 19 DPH (10 mg/kg) was administered starting on the 5th day of dosing. Adverse clinical observations, significant decrease in feed and water consumption, significant loss of body weight were observed in all groups following alglucosidase alfa and/or DPH alone administration. Cases of abortion and early delivery were also observed (considered secondary to maternal toxicity). The maternal NOAEL including pre-treatment with DPH is <10 mg/kg/day. The developmental NOAEL is >40 mg/kg/day. A pre- and post-natal development study was conducted in female mice at 0, 0 (DPH alone), 10, 20, or 40 mg/kg administered intravenously once every other day from Days 6 through 22 of presumed gestation or Day 20 postpartum. Diphenhydramine (5mg/kg) was administered beginning with the 5th dose. No effect on the F0 generation was observed up to 40 mg/kg every other day. The NOAEL for the F0 and F1 generations was 40 mg/kg every other day. There was an increase in pup deaths in the 40 mg/kg every other day maternal dosage group during the last week of the lactation period. There were no other effects on any parameter evaluated including clinical observations or body weight gain in F1 generation pups. Furthermore, no effect on sexual maturation, learning or memory, or the ability to produce another generation occurred for the F1 generation mice. • Genotoxicity No studies have been conducted to evaluate the mutagenic potential of alglucosidase alfa. • Carcinogenicity No studies have been conducted to evaluate the carcinogenic potential of alglucosidase alfa.	justifies addressing the use of alglucosidase alfa in pregnant women as a missing information in this RMP, to ensure adequate caution in the SmPC. No reproductive/development related risk has been detected from postmarketing experience to date.
Safety pharmacology Cardiovascular and respiratory parameters were examined in dogs and monkeys with no results reported that indicated potential safety pharmacological effects.	Not applicable.

Key Safety Findings	Relevance to human usage
Other toxicity-related information or data A 6-month IV toxicity study was conducted in juvenile mice with alglucosidase alfa administration starting 21 days after birth. Standard toxicity endpoints, in addition to physical development and behavior, were evaluated. Doses of 0, 0 (DPH alone), 10, 20, and 50 mg/kg of alglucosidase alfa were administered every other week for 26 weeks. There were no test article-related effects, and the NOAEL was considered to be 50 mg/kg every other week.	Not applicable.

DPH: Diphenhydramine; GPE: Global Pharmacovigilance and Epidemiology; IV: Intravenous; MAH: Marketing Authorization Holder; NOAEL: No-Observed-Adverse-Effect-Level; rhGAA: Recombinant Human Acid Alfa-Glucosidase; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Animal models studied in the non-clinical setting provided sufficient information for MAH to estimate the occurrence of certain safety risks. However, based on limitations of the animal models, a complete prediction of the risks in the clinical setting is not always possible.

Based on non-clinical studies use in pregnant women is considered missing information for alglucosidase alfa.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

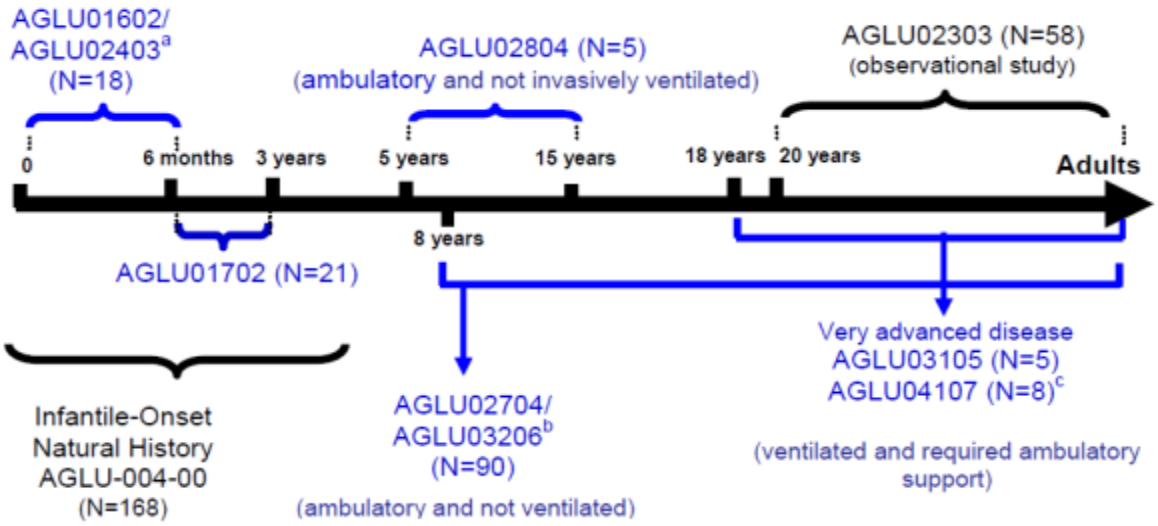
The variability of Pompe disease in terms of age at onset, rate of progression, severity, and pattern of systemic involvement has rendered the selection of a homogeneous clinical study population and an appropriate clinical endpoint challenging.

[redacted]

All patients with Pompe disease currently receiving ERT are either being treated with alglucosidase alfa or avalglucosidase alfa.

Despite the challenges of conducting clinical studies in patients with Pompe disease due to the rare nature of the disease and the young age of many of the patients, the MAH has treated patients with alglucosidase alfa across the entire Pompe disease spectrum under various clinical studies and expanded access program (EAPs) (see Figure 1).

Figure 1 - Alglucosidase alfa Treatment Initiatives Across the Pompe Disease Spectrum (Age Range at Initiation of Treatment)



Note: Figure shows patient age range at treatment initiation for alglucosidase alfa studies conducted in patients who were naïve to ERT at study onset.
N = number of patients providing efficacy data for the present dossier (except for Natural History Study AGLU-004-00 and observational study AGLU02303, both of which were non-treatment studies).
a Upon completion of AGLU01602, patients could participate in open-label extension study AGLU02403.
b Upon completion of AGLU02704, patients could participate in open-label extension study AGLU03206.
c Study AGLU04107 included 3 patients from study AGLU03105 and 5 new patients.
ERT: Enzyme Replacement Therapy.

[redacted]

The difficulty in performing clinical studies in rare diseases, particularly in children, should be acknowledged. Patient identification and recruitment have been challenging, and the limited drug supply largely determined the number of patients that could be enrolled in early clinical studies. Additionally, the use of placebo in clinical studies evaluating patients with the rapidly progressive and uniformly fatal IO form would be unethical and there are no active comparator products.

To address the lack of suitable comparator drugs and the unethical use of a placebo in clinical studies evaluating patients with the rapidly progressive and uniformly fatal IO form of the disease, the MAH created matching historical control or reference groups for the pivotal AGLU01602/AGLU02403 and AGLU01702 studies by applying screening criteria based on the eligibility criteria for the 2 treatment studies to the 168 untreated patients with IOPD in the Natural History Study (AGLU-004-00). For the critical endpoints of survival, invasive ventilator-free survival (ie, survival free of invasive ventilation) and any ventilator-free survival (ie, survival free of invasive and non-invasive ventilation), results for alglucosidase alfa-treated patients in AGLU01602/AGLU02403 are compared to overall survival in an appropriate historical control group (invasive ventilation was defined as any ventilator support applied via an endotracheal tube or tracheostomy; non-invasive ventilation was defined as ventilator support applied without invasion of the airway). Similarly, 52- and 104-week survival in AGLU01702 patients is compared with estimated survival in an appropriate historical reference group. For all other endpoints, efficacy and safety findings following treatment are compared to those obtained at Baseline or results are expressed relative to normative data.

The clinical programme for patients with LO Pompe disease has proven no less complicated. Again, the lack of alternative therapies means there is no active comparator. In addition, patients have been enrolled at varying stages of disease progression from those in the earlier stages who are still ambulatory to those with advanced disease who are wheelchair-bound and require ventilatory assistance, and this heterogeneity often precludes the use of uniform assessments across studies. Further, patients with very advanced LO disease may have reached a “point of no return” prior to the start of therapy (ie, muscle damage has already occurred to such an extent as to render it resistant to treatment with ERT), and these patients are a challenging population in whom to demonstrate clinical efficacy of alglucosidase alfa. However, it should be emphasized that Pompe disease is universally progressive in nature and therefore any reversal or stabilization of disease during treatment is likely to be due to therapy itself, and not due to spontaneous resolution of the disease or normal growth and development.

The clinical studies that provided efficacy and safety data for approval are summarized in Table 8 below, classified by IO and LO disease. These studies include 2 pivotal studies in 39 patients with IOPD (AGLU01602 and its open-label extension AGLU02403, and AGLU01702) and 1 pivotal randomized, double-blind, placebo-controlled study in 90 patients with LO Pompe disease (AGLU02704 and its open-label extension AGLU03206). In addition to these pivotal studies, several other clinical studies and (per-patient) EAPs with alglucosidase alfa have been conducted in patients with IO or LO Pompe disease.

[redacted]

Table 8 - Pivotal Clinical Studies Providing Efficacy and Safety Data for Alglucosidase alfa in the Treatment of Infantile-Onset and Late-Onset Pompe Disease

Study Number	Study Design	Study Dates	Planned Dose Range & Frequency	No. of Patients Providing Data on Alglucosidase alfa Efficacy/Safety
		NATURAL HISTORY STUDY1		
AGLU-004-00	Natural History Study	Feb-2002 - Nov-2002	NA	0/0[a]
		INFANTILE-ONSET STUDIES		
AGLU01602	Randomized, Open-label, Multicentre, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic, Dose-Ranging Study	26-May-2003 - 15-Jun-2005	20 or 40 mg/kg qow	18/18
AGLU02403 (extension of AGLU01602)	Open-label, Multicenter, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Dose-Ranging, Continuation Study	15-Jun-2005 - 15-Jun-2006	20 or 40 mg/kg qow	16/16[b]
AGLU01702	Open-label, Multicentre, Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study	19-Feb-2003 - 14-Jul-2006	20 or 40 mg/kg qow[c]	21/21
		LATE-ONSET STUDIES		
AGLU02704	Randomized, Double-Blind, Multicenter, Multinational, Placebo-Controlled Safety, Efficacy, and Pharmacokinetic Study	07-Sep-2005 - 28-Sep-2007	20 mg/kg qow	60/60
AGLU03206 (extension of AGLU02704)	Open-label, Multicenter, Multinational Safety and Efficacy Continuation Study	07-Sep-2005 - 17-Oct-2008	20 mg/kg qow	90/86[d]

a AGLU-004-00 was not an alglucosidase alfa treatment study, but a retrospective chart review study of 168 untreated patients with IOPD. Historical control or reference groups for the pivotal studies AGLU01602/AGLU02403 and AGLU01702 were derived from this study.

b Of the 18 patients in AGLU01602, 16 continued in extension study AGLU02403. One patient [redacted] died while in AGLU01602, and 1 patient [redacted] continued to receive treatment with alglucosidase alfa via the international EAP at a centre near the patient's home.

c After at least 26 weeks of alglucosidase alfa therapy, patients could be evaluated to determine whether they met at least 1 of the criteria for augmentation to a maximum dose of 40 mg/kg qow.

[redacted]

Study Number	Study Design	Study Dates	Planned Dose Range & Frequency	No. of Patients Providing Data on Alglucosidase alfa Efficacy/Safety

d In double-blind, randomized study AGLU02704, 60 patients received alglucosidase alfa and 30 patients received placebo. In open label extension study AGLU03206, all patients who were on placebo in AGLU02704 were switched to active treatment with alglucosidase alfa. A total of 81 of the 90 patients who enrolled in the double-blind, placebo-controlled study continued on to the open-label extension study. However, the population used for the efficacy analyses in AGLU03206 included all randomized patients in AGLU02704 (n = 90). The safety population in AGLU03206 included all patients randomized to alglucosidase alfa treatment in AGLU02704 who received at least 1 infusion of alglucosidase alfa in AGLU02704 and all patients randomized to placebo treatment in AGLU02704 who received at least 1 infusion of alglucosidase alfa in extension AGLU03206 (n=86). Data collected during the placebo treatment period in AGLU02704 were not used in the safety analyses.

EAP: Expanded Access Program; IOPD: Infantile-Onset Pompe Disease; NA: Not Applicable; QOW: Every Other Week.

CLINICAL TRIAL EXPOSURE

Clinical trial exposure is based on the number of patients on alglucosidase alfa participating in the MAH sponsored clinical trials. At the time of the approval in EU there were about 277 patients being treated with alglucosidase alfa via clinical trials and EAPs.

Patients with IO and LO Pompe disease have received treatment with alglucosidase alfa under one or more of 22 completed good clinical practices (GCP) clinical studies. Table 9 below provides a summary of these studies. Studies AGLU03807 and AGLU03707 are the trials that explored the use of Immune Tolerance Induction (ITI) in IOPD patients.

[redacted]

Table 9 - Summary of Completed Good Clinical Practice Studies with Alglucosidase Alfa Included in this RMP

Protocol Number and Study Description	Study Design	Number of Centres (Location)	Alglucosidase Alfa Dosage Regimen	Duration of Treatment	Number of Patients (Gender) [Race]	Chronological Age at First Infusion of Alglucosidase Alfa Mean ± SD (Range)
COMPLETED INFANTILE-ONSET GCP STUDIES						
AGLU01602[a] Pivotal Infantile-Onset Study in Patients <6 Months (Adjusted for Gestation)	Randomized Open-label	Multicentre (US, EU, Taiwan, Israel)	20 mg/kg qow 40 mg/kg qow	Up to 106 weeks	18[b] (11 male, 7 female) [7 Caucasian, 4 Black, 2 Hispanic, 3 Asian, 2 Other]	5.1 ± 1.96 months (1.2-7.3 months)
AGLU02403[a] Pivotal Infantile-Onset Extension Study	Randomized Open-label Patients rolled over from AGLU01602	Multicentre (US, EU, Taiwan, Israel)	20 mg/kg qow 40 mg/kg qow	Up to 51 weeks (until US market approval)	16[c] (11 male, 5 female) [6 Caucasian, 4 Black, 2 Hispanic, 2 Asian, 2 Other]	5.1 ± 1.962 months (1.2-7.3 months)
AGLU01702[a] Infantile-Onset Study in Patients Between 3 and 44 Months	Non-randomized Open-label	Multicentre (US, EU, Israel)	20 mg/kg qow[d] 40 mg/kg qow[d]	Up to 168 weeks	21 (10 male, 11 female) [15 Caucasian, 3 Black, 2 Asian, 1 Other]	15.7 ± 10.96 months (3.7-43.1 months)
AGLU02203[a] US Expanded Access Infantile-Onset Study	Open-label Expanded Access	Multicentre (US)	20 mg/kg qow	Up to 132 weeks	33 (22 male, 11 female) [19 Caucasian, 4 Black, 3 Hispanic, 4 Asian, 3 Other]	44.5 ± 0.76 months (0.5 months-16.3 years)
AGLU1205-02[e] Infantile-Onset Follow-Up Study	Non-randomized Open-label Patient previously received Pharming rhGAA and Synpac rhGAA	Single centre (Germany)	20 mg/kg qw and 40 mg/kg qw[f]	139 weeks[f]	[redacted] [Other]	ND (41.0 months)[e]
AGLU02003 Infantile-Onset Extension Study	Non-randomized Open-label Patients previously received Synpac rhGAA	Multicentre (US, France, South Africa)	10 mg/kg qw or 20 mg/kg qw or 20 mg/kg qow or 40 mg/kg qow	Up to 170 weeks	7 (5 male, 2 female) [5 Caucasian, 1 Asian, 1 Other]	3.4 ± 1.7 years (2.0-6.3 years)

[redacted]

Protocol Number and Study Description	Study Design	Number of Centres (Location)	Alglucosidase Alfa Dosage Regimen	Duration of Treatment	Number of Patients (Gender) [Race]	Chronological Age at First Infusion of Alglucosidase Alfa Mean ± SD (Range)
AGLU03807 An Exploratory Study of the Safety and Efficacy of Prophylactic Immunomodulatory Treatment in MYOZYME-naive CRIM (-) Patients with Infantile-Onset Pompe Disease	Exploratory, Open-label, Comparative study	Multicentre (US)	20 mg/kg qow or 20 mg/kg qw	18 months and up to 2 years of age if enrolled at age <6 months	4 (1 male, 3 female) [2 black, 1 Caucasian/black, 1 Caucasian/Hispanic]	5.4 months; 6.1 months; 6.3 months; 2.1 months Mean: 4.975 months
AGLU03707[g] An Exploratory Study of the Safety and Efficacy of Immune Tolerance Induction (ITI) in Patients with Pompe Disease Who Have Previously Received MYOZYME	Exploratory, Open-label, Comparative study	Multicentre (US, Israel)	20 mg/kg qow	18 months and up to 2 years of age if enrolled at age <6 months	4 (2 male, 2 female) [2 Caucasian, 1 Caucasian/Black, 1 Caucasian/Hispanic]	12 months; 14 months; 24 months; 33 months Mean: 20.75 months
AGLU03606 A long-term study to evaluate growth and development outcomes in patients with infantile-onset Pompe disease who are receiving MYOZYME (alglucosidase alfa)	Open Label-Patients to receive commercial alglucosidase alfa	Multicentre (US)	20 mg/kg qow	-	12 (5 male, 7 female) [7 Caucasian, 5 Black]	-
				Subtotal	116 (67 male, 49 female) [61 Caucasian, 22 Black, 7 Hispanic, 12 Asian, 2 Caucasian/Black, 2 Caucasian/Hispanic 10 Other]	

Protocol Number and Study Description	Study Design	Number of Centres (Location)	Alglucosidase Alfa Dosage Regimen	Duration of Treatment	Number of Patients (Gender) [Race]	Chronological Age at First Infusion of Alglucosidase Alfa Mean ± SD (Range)
COMPLETED LATE-ONSET GCP STUDIES						
AGLU02704[h] Late-Onset Placebo-Controlled Study (LOTS)	Randomized Double-blind Placebo-controlled	Multicentre (US, EU, Canada, Australia)	20 mg/kg qow	Up to 78 weeks	Alglucosidase alfa: 60 (34 male, 26 female) [57 Caucasian, 1 Hispanic, 1 Asian, 1 Other] Placebo: 30 (11 male, 19 female) [27 Caucasian, 1 Hispanic, 1 Asian, 1 Other]	Alglucosidase alfa: 45.3 ± 12.37 (15.9-70.0) Placebo: 42.6 ± 11.63 (10.1, 68.4)
AGLU03206[h] Open label Extension study of the Late-Onset Placebo-Controlled Study (LOTS)	Open-label Extension of AGLU02704	Multicentrer (US, EU, Canada, Australia)	20 mg/kg qow	Minimal 26 weeks (for a total of 104 weeks including study AGLU02704)	81 patients entered LOTS Extension Alglucosidase alfa/Alglucosidase alfa: 55 patients (32 male, 23 female) [52 Caucasian, 1 Hispanic, 1 Asian, 1 Other] Placebo/Alglucosidase alfa:26 patients (11 male, 15 female) [24 Caucasian,1 Hispanic, 1 Other]	Alglucosidase alfa/Alglucosidase alfa: 45.3 (15.9-70.0) Placebo/Alglucosidase alfa:46.8 (29.1-69.9)
AGLU02804[h] Late-Onset Open-Label Study	Non-randomized Open-label	Single centre (Netherlands)	20 mg/kg qow	Up to 74 weeks (until study termination or reimbursement of rhGAA)	5 (3 male, 2 female) [5 Caucasian]	ND (5.9-15.2 years)[i]

Protocol Number and Study Description	Study Design	Number of Centres (Location)	Alglucosidase Alfa Dosage Regimen	Duration of Treatment	Number of Patients (Gender) [Race]	Chronological Age at First Infusion of Alglucosidase Alfa Mean ± SD (Range)
AGLU02603[h] US Late-Onset Expanded Access Study	Non-randomized Open-label	Multicentre (US)	20 mg/kg qow	Up to 82 weeks	9 (4 male, 5 female) [7 Caucasian, 1 Hispanic, 1 Other]	45.6 ± 16.0 years (17.6-71.1 years)
AGLU03105[h] Advanced Late-Onset Study	Non-randomized Open-label	Single centre (France)	20 mg/kg qow	52 weeks	5 (2 males, 3 females) [4 Caucasian; 1 Black]	ND (28-62 years)[i]
AGLU02103[e] Late-Onset Single Patient Extension Study	Non-randomized Open-label Patient previously received Pharming rhGAA and Synpac rhGAA	Single centre (US)	30 mg/kg qow and 60 mg/kg qow	168 weeks	[redacted]	ND (20.2 years)
AGLU03907 Alglucosidase Alfa Temporary Access Program	Non-randomized Open-label	Multicentre (US)	20 mg/kg qow	Up to 169 weeks (until program termination)	216 (107 males, 109 females) [202 Caucasian; 10 Black, 2 Asian, 2 Other]	49.2 ± 12.9 years (18.1-79 years)
AGLU04107 Severe Late-Onset Study	Observational	Single centre (France)	20 mg/kg qow	24 months	8[j] (4 males, 4 females) [8 Caucasians]	54.0 ± 12.5 years (30-73 years)
AGLU07310 A Phase 4 Prospective Exploratory Muscle Biopsy, Biomarker, and Imaging Assessment Study in Patients with LO Pompe Disease Treated with Alglucosidase Alfa	Exploratory, Open-label	Multicentre (US, Netherlands, Germany, UK)	20 mg/kg qow	24 Weeks	16 (7 male, 9 female) [16 Caucasian]	ND (24.5-70.7 years)
				Sub total	Alglucosidase alfa only: 320 (161 male, 159 female) [300 Caucasian,	

Protocol Number and Study Description	Study Design	Number of Centres (Location)	Alglucosidase Alfa Dosage Regimen	Duration of Treatment	Number of Patients (Gender) [Race]	Chronological Age at First Infusion of Alglucosidase Alfa Mean ± SD (Range)
					11 Black, 2 Hispanic, 3 Asian, 4 Other] Placebo/Alglucosidase alfa: 26 (11 male, 15 female) [24 Caucasian, 1 Hispanic, 1 Other]	
COMPLETED INFANTILE-/LATE-ONSET GCP STUDIES						
AGLU03306[k] Dose/Dose Interval Study	Randomized Open-label	Multicentre (US, Canada, Australia)	20 mg/kg qw and 40 mg/kg qow	Up to 114 weeks (until study termination)	13 (8 males, 5 females) [12 Caucasian, 1 Asian]	19.8 ± 21.3 years (1.8-60.1 years)
AGLU07510 A Phase 3/4, Prospective, Multinational, Open-label, Noninferiority Study of Alglucosidase Alfa Manufactured at the 160 L and 4000 L Scales in Treatment Naive Patients with IOPD	Non-randomized, Open Label, Parallel Assignment, Safety and Efficacy Study	Multicentre (US, Turkey, Russia, Germany, Taiwan, Saudi Arabia)	20 mg/kg qow	52 weeks	4 (4 male) [2 black, 1 white, 1 multiple]	ND (0.3 to 0.9 years)
AGLU09411 A Phase 4, Open-Label, Prospective Study In Patients With Pompe Disease To Evaluate the Efficacy and Safety of Alglucosidase alfa Produced at the 4000 L Scale	Open Label, Single Assignment, Safety Study	Multicentre (US)	20 mg/kg qow	52 weeks	113 (60 male, 53 female) [71 Caucasian, 26 black, 7 Asian, 2 not reported, 7 multiple]	1.7 ± 2.68 years

Protocol Number and Study Description	Study Design	Number of Centres (Location)	Alglucosidase Alfa Dosage Regimen	Duration of Treatment	Number of Patients (Gender) [Race]	Chronological Age at First Infusion of Alglucosidase Alfa Mean ± SD (Range)
AGLU07710/ MSC12790 A Phase 3/4 prospective study to characterize the pharmacokinetics of alglucosidase alfa in patients with Pompe disease	Non-randomized, Open Label, Single Assignment, Pharmacokinetics Study	Multicentre (US, India, Russia, Bulgaria, Ukraine, UK)	One Single infusion of 20 mg/kg	1 day (One single infusion that lasts approximately 4 hours, with at least 2 hours of observation period following infusion)	20 (13 male, 7 female) [4 Asian, 14 Caucasian, 2 Multiple]	23.4 ± 20.86 years (0.6-57.1 years)
				Sub total	150 (85 male, 65 female) [98 Caucasian, 28 Black, 12 Asian, 10 Multiple, 2 not reported]	

a Study included in IO pooled analysis.

b Based on the AGLU01602 As Treated population at Baseline.

c Of the 18 patients treated in AGLU01602, 16 patients continued to receive alglucosidase alfa under AGLU02403, 1 patient continued to receive alglucosidase alfa under International EAP, and the remaining patient died while under treatment in AGLU01602.

d After a minimum of 26 weeks of treatment at the 20 mg/kg qow dose, patients could have their dose increased to 40 mg/kg qow if specific clinical criteria were met and with the approval of the Sponsor. Eight patients were approved for dose augmentation and received at least 1 infusion at 40 mg/kg qow.

e All patients had received Pharming rhGAA and/or Synpac rhGAA prior to initiating treatment with MYOZYME.

f The single patient in this study initially received alglucosidase alfa 20 mg/kg (25 weeks) and thereafter transitioned to alglucosidase alfa 40 mg/kg (114 weeks).

g All patients enrolled have completed. The database has been locked and an interim report has been prepared.

h Study included in late-onset pooled analysis.

i Age at first infusion was not determined; therefore, age at time of informed consent is provided.

j Study AGLU04107 included 3 patients from study AGLU03105 and 5 new patients.

k Patients included 9 IO patients and 4 late-onset patients.

CRIM: Cross Reactive Immunologic Material; EAP: Expanded Access Program; EU: European Union; QOW: Every Other Week; QW: Every Week; GCP: Good Clinical Practices; IO: Infantile Onset; IOPD:Infantile-Onset Pompe Disease; ITI: Immune Tolerance Induction; LO: Late-Onset; ND: Not Determined; rhGAA: Recombinant Human Acid Alfa-Glucosidase; RMP: Risk Management Plan; SD: Standard Deviation; UK: United Kingdom; US: United States.

For the purposes of summarizing IO and LO treatment exposure in clinical studies, patient's naive to rhGAA ERT prior to the first infusion of alglucosidase alfa were pooled. For the IO population, exposure data from studies AGLU01602/AGLU02403, AGLU01702, and AGLU02203 involving 72 patients were pooled. For the late-onset population, exposure data from studies AGLU02603, AGLU02704, AGLU02804, and AGLU03105 involving 79 patients were pooled. Table 10 below summarizes exposure to alglucosidase alfa for patients in each pooled analysis population as well as combined. Of the 151 patients, 142 patients received a dose of 20 mg/kg qow alglucosidase alfa and 17 patients (all IO patients) received a dose of 40 mg/kg qow alglucosidase alfa. The patient numbers for each dose group are inclusive of eight IO patients who received both doses of alglucosidase alfa. Median exposure was lower in the 20 mg/kg dose group (38.5 weeks; 78.0 infusions) compared with the 40 mg/kg dose group (52.0 weeks; 104.0 infusions), which was influenced in part by the short duration of exposure for many patients treated under the US expanded access studies, in IO (AGLU02203) and LO patients (AGLU02603), in which all patients received a dose of 20 mg/kg.

Table 10 - Summary of Exposure to Alglucosidase Alfa for the Three Pooled Analysis Populations: Infantile-Onset, Late-Onset, and Infantile-Onset and Late-Onset Combined

Category	Statistic	Pooled Analyses		
		Infantile-Onset (N = 72)[a]	Late-Onset (N = 79)[b]	Infantile-Onset and Late-Onset (N = 151)[a,b]
Number of infusions per patient	Mean ± SD	44.0 ± 25.5	34.5 ± 9.6	39.1 ± 19.4
	Median	48.5	39.0	39.0
Time on treatment per patient (weeks)[c]	Min, Max	1, 85	2, 42	1, 85
	Mean ± SD	87.0 ± 51.2	68.7 ± 19.7	77.4 ± 39.1
	Median	95.9	78.1	78.1
	Min, Max	0.1, 168.3	1.9, 82.4	0.1, 168.3

a Includes AGLU01602/02403, AGLU01702, and AGLU02203.
b Includes AGLU02704, AGLU02804, AGLU02603, and AGLU03105.
c Calculated in weeks as (date of last infusion - date of first infusion + 1)/7
Max: Maximum; Min: Minimum; SD: Standard Deviation.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 11 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients who are pregnant or lactating	Limited information is available in pregnant or lactating women	Yes	NA
Patients who have renal insufficiency	Limited information is available in patient with renal insufficiency	Yes	NA
Patients who have hepatic insufficiency	Limited information is available in patient with hepatic insufficiency	Yes	NA

NA: Not Applicable.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Ability to detect adverse reactions	Limitation of trial programme	Discussions of implications for target population
Which are common	Two hundred seventy seven (277) patients being treated with alglucosidase alfa via clinical trials and EAP at the time of approval in the EU. As of 28-Sep-2022, 634 patients were exposed to alglucosidase alfa.	Pompe is a rare disease with an estimated incidence of 1:40 000. The ADRs with a frequency greater than 1 in 277 could be detected if there were no background incidence. Only common and very common events are able to be identified during clinical program. With increased exposure in postmarketing setting, uncommon events will be identified such as immune-mediated reactions.
Due to prolonged exposure	NA	NA
Due to cumulative effects	NA	NA
Which have a long latency	Malignancies and atherosclerotic cardiovascular disease often have a long latency.	Postmarketing surveillance may provide insight into these theoretical ADRs.

ADR: Adverse Drug Reaction; DLP: Data Lock Point; EAP: Expanded Access Program; EU: European Union; NA: Not applicable.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Pompe disease is a rare disease, with an estimated global incidence at birth of all phenotypes of 1:40 000. (8)(9) Alglucosidase alfa received orphan drug designation in the US and Europe as well as several other countries. As a consequence of the rarity and fatal nature of Pompe disease, the number of patients treated has been limited and long-term safety data are limited. A Pompe registry has been established in order to enhance understanding of the variability, progression and natural history of the key manifestations of both IO and LO Pompe disease as well as to collect additional information on special populations of interest (eg, patients with renal or hepatic insufficiency, pregnant or lactating women).

Table 12 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breastfeeding women	There are no adequate, well-controlled studies of alglucosidase alfa in pregnant women. Only rare reports of pregnancy in patients receiving alglucosidase alfa have been received, therefore, there is a limited amount of data in this sub-group of patients. A study in rabbits has shown the potential for maternal toxicity of alglucosidase alfa due to decreased feed consumption. Women of childbearing potential will be encouraged to enroll in the Pompe Registry.
Patients with relevant comorbidities • Patients with hepatic or renal impairment	Alglucosidase alfa was not studied in patients with renal or hepatic insufficiency.
Other • Pediatric use	The safety and efficacy of alglucosidase alfa have been primarily evaluated in children with ages ranging from infancy to adolescence. Long-term data in Pompe patients less than 1 year in age at initiation of treatment was collected as part of study AGLU03606 assessing the growth and development of patients treated with alglucosidase alfa over a 10 year period and the study has been completed see Table 9.
• Geriatric use	Clinical studies of alglucosidase alfa included subjects as old as 70 years at initiation of treatment.

- **Pregnant or breastfeeding women**

Pregnancy

There is a limited amount of data from the use of alglucosidase alfa in pregnant women. MYOZYME should not be used during pregnancy unless the clinical condition of the woman requires treatment with alglucosidase alfa.

Studies in animals have shown reproductive toxicity.

[redacted]

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity. No significant adverse findings on embryofoetal development were observed in a mouse and a rabbit embryofoetal study and no significant adverse findings were observed in a mouse fertility and early embryonic development study. In the rabbit embryofoetal development study, following administration of MYOZYME (10-40 mg/kg/day) with co-administration of DPH, a treatment-related increase in the incidence of abortions and early delivery was observed. This effect was partly attributable to maternal toxicity, as a significant decrease in feed consumption and body weight gain was observed.

A pre- and post-natal development study was conducted in female mice at doses up to 40 mg/kg alglucosidase alfa administered intravenously once every other day on days 6 through 22 of presumed gestation or day 20 postpartum. Diphenhydramine (5 mg/kg) was administered intraperitoneally beginning with the 5^{th} dose. There were no adverse effects on the F0 generation. An increase in pup deaths occurred in the 40 mg/kg/day group during the last week of the lactation period. However, the relationship of these deaths to treatment is unclear as no other effects were observed on any parameter evaluated including clinical observations or body weight gain in F1 generation pups. Furthermore, no effect on sexual maturation, learning or memory, or fertility occurred for the F1 generation mice. The NOAEL for the F0 and F1 generations was 40 mg/kg/day.

Breastfeeding

Limited data suggest that alglucosidase alfa is excreted in breast milk in very low concentrations. No clinical effect is expected in a breastfed infant due to low breast milk transfer and poor bioavailability. Breastfeeding during treatment with MYOZYME may therefore be considered. As a precautionary measure, breastfeeding interruption for the first 24 hours after treatment may be considered.

As limited data are available concerning the use of alglucosidase alfa in pregnant or breastfeeding women, the use of alglucosidase alfa in pregnant or breastfeeding women is considered as missing information. Women of childbearing potential and women who choose to nurse while continuing alglucosidase alfa therapy will be requested to participate in the Pompe Registry. As part of the Pompe Registry, sub-registries evaluating the effect of alglucosidase alfa on pregnancy and lactation have been established. The pregnant women in the registry will be encouraged to join the Pregnancy sub-registry. The women in the registry who want to nurse while on treatment with alglucosidase alfa are encouraged to join in the Lactation sub-registry

- **Patients with renal or hepatic impairment**

The safety of alglucosidase alfa in patients with renal or hepatic impairment has not been evaluated. Based upon its route of metabolism (peptide hydrolysis) and experience with other ERTs, it is not anticipated that renal or hepatic impairment will impact its use. For the same reasons, a change in the recommended dose is not anticipated in these sub-populations.

Due to limited data, use in patients with renal or hepatic impairment is considered as missing information. Healthcare providers are encouraged to enroll patients in the Pompe Registry where information on patients with renal and hepatic insufficiency will be analyzed annually and results submitted to regulatory authorities.

[redacted]

[redacted]

- **Geriatric use**

It is not expected that geriatric patients will respond differently to alglucosidase alfa treatment when compared to younger patients. Based upon the route of metabolism of alglucosidase alfa (peptide hydrolysis) and experience with other ERTs, the MAH does not anticipate that renal or hepatic impairment in the geriatric population will impact the safety and efficacy of alglucosidase alfa. However, clinical studies completed to date did not include a sufficient number of subjects aged 65 years and older in order to evaluate the safety and efficacy of alglucosidase alfa in this population. Due to limited data, use in elderly patients is considered as missing information.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

In the postmarketing setting, the total number of patients treated with alglucosidase alfa was calculated from sales figures received from the MAH regional offices, on the basis of direct interaction with prescribing physicians.

SV.1.2 Exposure

MYOZYME (alglucosidase alfa) received authorization in the EU on 29 March 2006 and in the US on 28 April 2006. Alglucosidase alfa is authorized in 88 countries worldwide. In addition, patients received commercial alglucosidase alfa via an International Charitable Access Program (ICAP), therefore, the number of patients treated each month also includes ICAP.

An internal sales database has been used as the source for exposure data retrieval.

Due to the rarity of Pompe disease, the MAH has access to the actual patient exposure on a monthly basis.

The number of patients on treatment in any given month is an estimate based on our country office's local knowledge of the country's health care environment. The office provides its estimate to our global team on an aggregate basis received from the patient support programs, field liaisons or sales team in accordance with local laws, and never includes in its report data that could allow identification of individual patients; therefore, presentation of patient exposure by age, sex, and indication is not possible. The monthly exposure data allows for systematic and consistent exposure calculations over time which most reliably reflect exposure.

Patients treated with alglucosidase alfa often receive treatment over multiple months. Therefore, when determining the cumulative number of patients exposed during the reporting period, the cumulative exposure is chosen to be the month with the most patients treated. Cumulative patient exposure to alglucosidase alfa since product launch through 30 September 2022 was estimated to be 3564 patients (greatest monthly patient exposure in the cumulative experience). Of note, these figures are net patient per month figures: if a patient dies or stops treatment, this patient is deducted from the reporting; if a naive patient starts therapy or a former patient restarts therapy, this patient is added to the reporting.

The estimated cumulative patient commercial and charitable exposure per periodic safety update report (PSUR)/periodic benefit-risk evaluation report (PBRER) reporting period since international birth date is presented in Table 13

Table 13 - Cumulative commercial and charitable patient exposure by PBRER reporting period

PBRER Reporting period	Greatest patient exposure during the reporting period
29-Mar-2006 to 28-Sep-2006	330
29-Sep-2006 to 28-Mar-2007	584
29-Mar-2007 to 28-Sep-2007	696
29-Sep-2007 to 28-Mar-2008	723
29-Mar-2008 to 28-Sep-2008	838
29-Sep-2008 to 28-Sep-2009	926
29-Sep-2009 to 28-Sep-2010	1325
29-Sep-2010 to 28-Sep-2011	1632
29-Sep-2011 to 28-Sep-2012	1829
29-Sep-2012 to 28-Sep-2013	2004
29-Sep-2013 to 28-Sep-2014	2154
29-Sep-2014 to 28-Sep-2015	2445
29-Sep-2015 to 28-Sep-2016	2661
29-Sep-2016 to 28-Sep-2017	2852
29-Sep-2017 to 28-Sep-2018	3013
29-Sep-2018 to 28-Sep-2019	3176
29-Sep-2019 to 28-Sep-2021	3564
29-Sep-2021 to 28-Sep-2022	3543

PBRER: Periodic Benefit-Risk Evaluation Report.

RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

The legal status of alglucosidase alfa will control who will dispense, prepare and/or administer the drug; dispensation, preparation and administration is restricted to appropriate HCPs, including pharmacists and physicians. The administration of alglucosidase alfa will take place in a hospital or clinical setting under the close supervision of a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases to minimize potential errors during the preparation and administration of the drug. The product label includes specific language concerning preparation and administration of alglucosidase alfa.

Potential for misuse of alglucosidase alfa for illegal purposes is considered low as this product is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use, such as known pharmacological addictive effects.

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

Not applicable

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

From RMP version 10 onwards, the three important identified risks, “Infusion associated reactions including hypersensitivity and anaphylactic reactions”, “Immunogenicity: anti-rhGAA Immunoglobulin G (IgG) antibodies”, and “Immunogenicity: anti-rhGAA Immunoglobulin E (IgE) antibodies” are combined to a single important identified risk - “Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies”. This is to include IgE or IgG mediated mechanisms causing the infusion associated reactions including hypersensitivity/anaphylactic reactions.

Important identified risk “Immunogenicity: inhibitory antibodies to rhGAA” is renamed to “Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)” indicating the clinical impact as a consequence to the occurrence of these antibodies.

[redacted], the MAH was requested to consider whether existing data might support safe administration of alglucosidase alfa in the home infusion setting and discuss the appropriateness of label amendments and aRMMs to provide guidance to HCPs and patients in this regard (along with the submission of a RMP update). As for the other ERTs for which home infusion is possible, there is a possible risk of medication errors in the home infusion setting due to insufficient understanding of the instructions for use of the product (eg, dose calculation, reconstitution, administration). Hence, the MAH proposes to include “Medication errors in the home infusion setting” as an important potential risk.

[redacted]

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Identified safety risks of alglucosidase alfa treatment include development of infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies; immune mediated reactions; and immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies). Each of these identified alglucosidase alfa-related safety risks, the additional potential risk of medication errors in the home infusion setting and the missing information, are discussed in the sections below.

SVII.3.1 Presentation of important identified risks and important potential risks

Table 14 - Identified risk: Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies

Identified Risk	**Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies**
Potential mechanism	Alglucosidase alfa is a biological medicinal product produced in a CHO production system. Potential mechanisms for infusion associated reactions including hypersensitivity/anaphylactic reactions include: • IgE mediated • IgG mediated with complement activation • Cytokine release but the mechanism is unclear • Nonspecific immunogenic mechanism which is not understood to date • Direct stimulation of mast cells by drug with release of histamine • Related to higher infusion rate, ie, protein load Possible factors associated with the induction of rhGAA IgG Antibody: Foreignness of rhGAA (recognized as non-self protein), chemical complexity, route, frequency, and dose of administration. Induction of the antibody response involved the following steps: • Immune recognition-antigen associated with major histocompatibility complex molecule is recognized as non-self by the immunocompetent cells. • Stimulation of B-lymphocyte response by complex interactions between T, B and accessory cells. • Continuing proliferation and differentiation of B cells into plasma cells by several cytokines. • Plasma cells produce antibody specific to rhGAA.
Evidence source(s) and strength of evidence	Clinical trial, postmarketing surveillance, literature.
Characterization of the risk	**Frequency with 95% CI** Infusion associated reactions occurred in approximately 50% of patients treated with alglucosidase alfa in two IO clinical studies for 52 weeks. In an 18 month, randomized, double-blind, placebo-controlled clinical study of LO patients, approximately 28% of patients in the alglucosidase alfa treatment group experienced IARs. The occurrence of IARs is not unexpected given the clinical presentation of immunogenic responses to recombinant human proteins. (29) In clinical trials with alglucosidase alfa, approximately 3% of patients experienced severe or significant hypersensitivity reactions, including life-threatening anaphylactic shock and cardiac arrest. In the LO treatment

Identified Risk	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	study (AGLU2704), three serious hypersensitivity reactions in the alglucosidase alfa treatment group occurred, in two of these patients reactions were IgE mediated. It is not possible to reliably estimate the frequency of the infusion associated reactions reported in the post-marketing, expanded access programs and non-controlled clinical studies as these events are reported voluntarily from a population of uncertain size. In clinical studies, the majority (approximately 90%) of IO and LO Pompe patients developed IgG antibodies to alglucosidase alfa, generally within 3 months of initiation of treatment. Similar proportions of patients treated in the commercial setting have developed anti-rhGAA IgG antibodies. Patients treated with alglucosidase alfa in clinical studies or the commercial setting have tested positive for alglucosidase alfa-specific IgE antibodies, some of whom experienced anaphylactic reactions. Testing was typically performed for IARs, especially moderate to severe or recurrent reactions. Skin testing, a more sensitive measure for detection of IgE antibodies, was also performed for some patients. **Severity and nature of risk** Infusion associated reactions occur at any time during, and mostly up to 2 hours after the infusion of alglucosidase alfa, and are more likely to occur with higher infusion rates. The majority of reactions were assessed as mild or moderate; some reactions were assessed as severe. Severe infusion reactions reported in more than 1 patient included pyrexia, decreased oxygen saturation, tachycardia, cyanosis and hypotension. A single event of angioedema of severe intensity has been reported. In postmarketing settings: IARs assessed as severe included anaphylactic shock, cardiac arrest, bradycardia, tachycardia, cyanosis, chest pain, respiratory arrest, apnoea, respiratory distress, bronchospasm, tachypnoea, hypoxia, stridor, dyspnoea, cough, wheezing, abdominal pain, pyrexia, chills, erythema, rash, headache, tremor, agitation, hypertension, hypotension, vasoconstriction, pallor, face oedema, peripheral coldness, and hyperhidrosis. Reactions generally occurred shortly after initiation of the infusion. Patients presented with a constellation of signs and symptoms, primarily respiratory, cardiovascular, oedematous, and/or cutaneous in nature. Reactions included bronchospasm, wheezing, respiratory arrest, respiratory distress, apnoea, stridor, dyspnoea, decrease in oxygen saturation, brief episodes of cardiac arrest, hypotension, bradycardia, tachycardia, cyanosis, vasoconstriction, flushing, chest pain, chest discomfort, throat tightness, angioedema, pharyngeal oedema, face oedema, peripheral oedema, urticaria, and rash. Recurrent reactions consisting of flu-like illness or a combination of events such as fever, chills, myalgia, arthralgia, pain, or fatigue occurring post-infusion a few hours to 2 days following the infusion and lasting usually for a few days, have also been observed in some patients treated with alglucosidase alfa (predominantly in LO Pompe patients). The majority of patients were successfully re-challenged with alglucosidase alfa using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and have continued to receive treatment under close clinical supervision. In clinical studies, the majority of patients (approximately 90%) developed IgG antibodies to rhGAA typically within 3 months of treatment. A tendency was observed for IO patients treated with a higher dose (40 mg/kg) to develop higher titres of IgG antibodies. There was no consistent relationship between time to seroconversion and onset of IARs. Infantile-onset patients who develop high antibody titres appear to be at higher risk for developing more frequent IARs. In the LO study there was no apparent association between higher IgG titres and occurrence of IARs. A limited number of the IgG positive patients evaluated tested positive for inhibitory effects on in vitro testing. The probability of developing HSATs and poor outcome appears higher among CRIM

Identified Risk	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	negative patients than among CRIM positive patients (patients in whom endogenous *GAA* protein was detected by Western blot analysis). However, high and sustained antibody titres also occur in some CRIM positive patients. The cause of a poor clinical outcome in some of these patients is thought to be multifactorial. In clinical studies of IO and LO Pompe patients, a trend toward decreasing IgG antibody titres over time was observed in the majority of patients. In the LO treatment extension study (AGLU03206), 60% of patients in the alglucosidase alfa treatment group showed trends toward decreasing titres while on treatment. Patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for the occurrence of IARs and/or anaphylactic reactions when alglucosidase alfa is readministered. Therefore, these patients should be monitored more closely during administration of alglucosidase alfa. Some IgE positive patients were successfully rechallenged with alglucosidase alfa using a slower infusion rate at lower initial doses (or desensitization procedures) and have continued to receive alglucosidase alfa under close clinical supervision. **Seriousness/outcomes** Infusion associated reactions which were reported in more than one patient in clinical studies and the EAP included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnoea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face oedema, feeling hot, headache, hyperhidrosis, lacrimation increased, livedo reticularis, nausea, periorbital oedema, restlessness, wheezing, non-cardiac chest pain, angioedema, and supraventricular tachycardia. The infusion associated reactions reported additionally in the commercial setting included conjunctivitis, abdominal pain, dyspepsia, dysphagia, palmar erythema, transient skin discolouration, blister, peripheral coldness and infusion site reactions including pain, swelling, induration, extravasation and erythema. (30) All these infusion associated reactions in clinical & commercial settings were reported as serious except for decreased oxygen saturation, increased blood pressure & rigors. The most serious adverse reactions reported with alglucosidase alfa were anaphylactic reactions, and cardiac arrest. In the commercial setting, significant hypersensitivity reactions have been reported in both IO and LO patients treated with alglucosidase alfa. Some patients experienced life threatening anaphylactic reactions, including anaphylactic shock, some of which were IgE-mediated. In the clinical development program for alglucosidase alfa, development of anti-rhGAA IgG antibodies was monitored using an enzyme-linked immunosorbent assay with results confirmed by radioimmunoprecipitation assay. In clinical studies, the majority of IO and LO Pompe patients developed IgG antibodies to alglucosidase alfa, generally within 3 months of initiation of treatment. Similar proportions of patients treated in the commercial setting have developed anti-rhGAA IgG antibodies. Time to first detection of IgG antibodies in commercially treated patients has been similar to that observed in clinical studies. The development of antibodies against recombinant protein is well recognized and has been demonstrated with other ERT. (29) A small number of alglucosidase alfa treated patients in clinical trials and postmarketing setting who were evaluated, tested positive for presence of alglucosidase alfa-specific IgE antibodies. Some of these patients experienced anaphylaxis. Patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for the occurrence of infusion reactions and/or anaphylactic reactions. Therefore, these patients should be monitored more closely during administration of alglucosidase alfa.

Identified Risk	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	Background incidence/prevalence Infusion associated reactions including hypersensitivity and development of anti-rhGAA IgG or anti-rhGAA IgE antibodies are specific to the biologic product and do not occur in patients with Pompe disease who are not intravenously exposed to the product. **Impact on individual patient** The majority of IARs were mild to moderate and resolved spontaneously with infusion rate reduction, infusion interruption or administration of antihistamines and/or corticosteroids. Some reactions were severe. The most serious adverse reactions reported with alglucosidase alfa were anaphylactic reactions, or cardiac arrest. Some patients experienced severe or life-threatening anaphylactic reactions, anaphylactic shock, and cardiac arrest including anaphylactic shock, some of which were IgE-mediated. These reactions were generally managed with temporary interruption and/or discontinuation of infusion and administration of antihistamines, corticosteroids, IV fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reaction and cardiac arrest, epinephrine and/or cardiopulmonary resuscitation were also administered. The majority of patients continued to receive treatment with alglucosidase alfa, under close clinical supervision.
Risk factors and risk groups	Infantile-onset patients who develop high antibody titres appear to be at higher risk for developing more frequent IARs and hypersensitivity. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody titres. Patients with an acute illness (eg, acute febrile illness, such as pneumonia or sepsis, or wheezing/bronchospasm) at the time of alglucosidase alfa infusion appear to be at greater risk for IARs. Patients with advanced Pompe disease or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. Patients treated with higher doses of alglucosidase alfa (>20 mg/kg) tended to develop a more robust IgG antibody response and experience more IARs. Patients who have experienced infusion reactions may be at increased risk of IARs when alglucosidase alfa is readministered. Additionally, IgE positive patients are at increased risk of developing IARs upon readministering the drug. In the LO study, there was no apparent association between higher IgG antibody titres and occurrence of IARs. It is recommended that patients be monitored for IgG antibody formation periodically. Baseline serum sample collection prior to the first infusion is encouraged. For IOPD patients, regular monitoring during first year of treatment (example: every 3 months) is suggested and subsequent monitoring dependent on clinical outcomes and antibody titre levels. For LOPD patients, antibody development should be assessed within 6 months and subsequent monitoring as clinically warranted based on safety and efficacy considerations. The probability of developing HSATs and poor outcome appears higher among CRIM-negative patients (patients in whom no endogenous *GAA* protein was detected by western blot analysis) than among CRIM-positive patients (patients in whom endogenous *GAA* protein was detected by western blot analysis). However, high and sustained antibody titres also occur in some CRIM-positive patients. The cause of a poor clinical outcome in some of these patients is thought to be multifactorial. It is unknown who will develop immediate hypersensitivity reactions (IgE positive) to alglucosidase alfa.
Preventability	Some patients received pretreatment with antihistamines, antipyretics, and/or steroids as a result of IARs. Infusion associated reactions may occur in patients after receiving pretreatment with antipyretics, antihistamines, or steroids. If an IAR occurs, regardless

Identified Risk	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	of pretreatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of antihistamines and/or antipyretics may ameliorate the symptoms. To prevent complications, immediate discontinuation of the administration of alglucosidase alfa should be considered when severe infusion reactions occur, and appropriate medical treatment should be initiated. Because of the potential for severe hypersensitivity reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when alglucosidase alfa is administered. Patients who have experienced IARs (and in particular anaphylactic reactions) should be treated with caution when readministered alglucosidase alfa. Careful consideration should be given to the patient's clinical status prior to administration of alglucosidase alfa. Prophylactic treatment with antihistamines prior to the infusions is recommended to reduce the frequency and or severity of IARs. Patients with moderate to severe and recurrent IARs should be evaluated for alglucosidase alfa specific IgE antibodies, and skin testing is recommended for patients who experienced significant hypersensitivity reactions.
Impact on the benefit-risk balance of the product	The majority of IARs were mild to moderate and resolved spontaneously with infusion rate reduction, infusion interruption or administration of antihistamines and/or corticosteroids. Some reactions were severe. The most serious adverse reactions reported with alglucosidase alfa were anaphylactic reactions, or cardiac arrest. Some patients experienced severe or life-threatening anaphylactic reactions, anaphylactic shock, and cardiac arrest including anaphylactic shock, some of which were IgE-mediated. These reactions were generally managed with temporary interruption and/or discontinuation of infusion and administration of antihistamines, corticosteroids, IV fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reaction and cardiac arrest, epinephrine and/or cardiopulmonary resuscitation were also administered. The majority of patients continued to receive treatment with alglucosidase alfa, under close clinical supervision to prevent disease progression. The benefit-risk balance of ERT with alglucosidase alfa remains positive for mild IARs. Due to the negative impact of severe, serious and life-threatening IARs on the benefit-risk balance of ERT with alglucosidase alfa, permanent discontinuation of ERT with alglucosidase alfa may be required.
Public health impact	Given the extremely small number of Pompe patients, IARs and development of antibodies in relation to alglucosidase alfa treatment has a negligible public health impact.

CHO: Chinese Hamster Ovary; CI: Confidence Interval; CRIM: Cross-Reactive Immunologic Material; EAP: Expanded Access Program; ERT: Enzyme Replacement Therapy; GAA: Acid Alpha Glucosidase; HSAT: High Sustained Antibody Titre; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IO: Infantile-Onset; IOPD: Infantile-Onset Pompe Disease; IV: Intravenous; LO: Late-Onset; LOPD: Late-Onset Pompe Disease; rhGAA: Recombinant Human Acid Alfa-Glucosidase.

Table 15 - Identified risk: Immune mediated reactions

Identified Risk	Immune mediated reactions
Potential mechanism	Background (pathophysiology) Immune complex disease is a local or systemic disease caused by the formation of circulating immune complexes and their deposition in tissues or in vascular endothelium. (31)(32) In most cases this will be an inconsequential process of events in

Identified Risk	Immune mediated reactions
	our bodies. Circulating immune complexes are usually cleared by phagocytic system. In some cases where the massive formation of circulating immune complexes is present and the clearance capacity of the phagocytic system is exceeded, the deposition of these immune complexes in tissues will trigger the inflammation reactions. Small immune complexes formed in antigen excess are easily filtered from the circulation by macrophages without triggering further inflammation. In the next phase of slight antigen excess, intermediate sized immune complexes form. These intermediate sized immune complexes are large enough to active complement and small enough to cross the endothelial barrier leading to tissue inflammation (skin, myocardium, joints, and kidney). Immune mediated syndromes may result in a heterogeneous array of clinical signs and symptoms such as glomerulonephritis, haematuria, proteinuria, papular rash, purpura like eruptions, arthritis, serositis, and vasculitis. Reactions are self-limited and usually develop within 7 to 10 days of antigen injection, starting with some constitutional flu like symptoms of fever, myalgia, arthralgia, and rash. Clinical recovery is usually apparent after 7 to 28 days, as intermediate sized immune complexes are cleared by the reticuloendothelial system. Free antigen continues to clear from the blood, leading to antibody excess, and the formation of large immune complexes, which are quickly removed by circulating macrophages. Finally, the antigen is no longer detectable, and the level of circulating antibodies continues to rise.
Evidence source(s) and strength of evidence	Nonclinical trials, clinical trial, postmarketing surveillance, literature.
Characterization of the risk	**Frequency with 95% CI** Uncommon reports (<1/100 to ≥1/1000) of severe cutaneous and systemic immune mediated reactions have been reported in a small number of patients treated with alglucosidase alfa. These reactions occurred several weeks to 3 years after initiation of alglucosidase alfa infusions. Severe cutaneous reactions, possibly immune mediated, have been reported with alglucosidase alfa including ulcerative and necrotizing skin lesions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Systemic immune mediated reactions, including possible type III immune mediated reactions have been observed with alglucosidase alfa. Nephrotic syndrome was observed in a few Pompe patients treated with alglucosidase alfa and who had high IgG antibody titres. In these patients' renal biopsy showed immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis among patients with high IgG antibody titres. **Severity and nature of risk** Immune-mediated syndromes may result in a heterogeneous array of clinical signs and symptoms such as glomerulonephritis, haematuria, proteinuria, papular rash, purpura-like eruptions, arthritis, serositis, and vasculitis. Reactions are self-limited and usually develop within 7 to 10 days of antigen injection, starting with some constitutional flu like symptoms of fever, myalgia, arthralgia, and rash. Clinical recovery is usually apparent after 7 to 28 days, as intermediate-sized immune complexes are cleared by the reticuloendothelial system. **Seriousness/outcomes** Immune complex disease is a local or systemic disease caused by the formation of circulating immune complexes and their deposition in tissues or in vascular endothelium). To identify any potential immune complex mediated reactions to alglucosidase alfa in the Global safety database, all adverse events reported in patients treated with alglucosidase alfa cumulatively through RMP DLP were examined to identify events that might be mediated by immune complex deposition, with particular emphasis on renal disorders, skin disorders, and arthralgias and other arthropathies. Case reports with the

Identified Risk	Immune mediated reactions
	MedDRA Preferred Terms of nephrotic syndrome, glomerulonephritis, glomerulonephritis membranous, proteinuria, Haematuria, arthralgia, arthritis, arthropathy, myalgia, serum sickness, Type III immune complex mediated reactions, myocarditis, serositis, lymphadenopathy, influenza like illness, skin lesion, skin necrosis and additionally standardized MedDRA queries of severe cutaneous adverse reactions and vasculitis were included. A medical review of these cases which included all relevant medical history and available immunogenicity data was performed by Global Pharmacovigilance to determine whether the events were consistent with an immune-mediated syndrome. Following alglucosidase alfa treatment in clinical trials or commercial settings, twelve patients on alglucosidase alfa and 1 patient on Synpac rhGAA (33) experienced reactions suggestive of immune mediated reactions described as nephrotic syndrome and membranous nephropathy (1 patient); nephrotic syndrome, glomerulonephritis membranous and proteinuria (1 patient); nephrotic syndrome & proteinuria (1 patient), glomerulonephritis membranous and proteinuria (2 patients), nephritis and proteinuria (1 patient), serum sickness, joint swelling and arthralgia (1 patient); proteinuria and/or hematuria (2 patients); type III immune complex mediated reaction (1 patient); inflammatory arthropathy, fever, lymphadenopathy and increased sedimentation rate (1 patient), and skin necrosis (1 patient) and the IO patient on Synpac rhGAA experienced nephrotic syndrome. Six of the 13 patients were IO patients including 3 CRIM negative patients. Age range was 7 months to 9 years; 4 male and 2 female. Six of the 13 patients were adult patients (2 were described as an IO) and one was adolescent, 4 males, and 3 females. Age range was 22 to 51 years. Therapy duration prior to events onset ranged from a few weeks to 3 years. IgG antibody titres ranged from 1600 to 3 276 800 with median titre of 102 400. C1q binding assay was positive in 4 patients at 1 or more time points (including baseline in one patient), negative in 2 patients and not tested in 3 patients. Of the 9 patients, 4 patients discontinued treatment due to decreased response to treatment or infusion reactions. Three of the four patients that discontinued subsequently died: 1 due to cardiac arrest assessed as unrelated, 1 due to skin necrosis assessed as unrelated, and the third patient died due to multiorgan failure, and the causality was not provided. In 6 patients, including the patient on Synpac rhGAA, the reactions resolved with temporary interruption of therapy, reducing the dose of biweekly infusions or use of corticosteroids and patients continued to receive therapy. **Background incidence/prevalence** Development of immune complex disease to rhGAA is an antigen antibody reaction that occurs as a result of exposure to specific antigen or biologic product and does not occur in patients with Pompe disease who are not intravenously exposed to the product. **Impact on individual patient** Immune mediated syndromes may result in a heterogeneous array of clinical signs and symptoms such as glomerulonephritis, haematuria, proteinuria, papular rash, purpura like eruptions, arthritis, serositis, and vasculitis. Reactions are self-limited and usually develop within 7 to 10 days of antigen injection. Clinical recovery is usually apparent after 7 to 28 days. Some patients have been successfully rechallenged with alglucosidase alfa and continued to receive alglucosidase alfa under close clinical supervision.
Risk factors and risk groups	Unknown
Preventability	Patients should be monitored for the development of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa. It is recommended to perform periodic urinalysis among patients with high IgG antibody titres to monitor for proteinuria.

Identified Risk	Immune mediated reactions
	Temporary interruption of treatment until resolution and/or reducing the dose of alglucosidase alfa as well as corticosteroids was used in some patients. These measures were successful in resolving some of the immune-mediated reactions.
Impact on the benefit-risk balance of the product	Most patients with these reactions (5/9) are IOPD, three of whom were known to be CRIM negative. Based on these observations CRIM negative IOPD patients may have excess predisposition for this potential risk. Since CRIM negative IOPD patients also have the poorest prognosis among Pompe disease patients if untreated, the benefit of ERT with alglucosidase alfa outweighs the uncommon potential risk of immune complex mediated reactions.
Public health impact	Given the extremely small number of Pompe patients, immune complex disorders in relation to alglucosidase alfa treatment has a negligible public health impact.

CI: Confidence Interval; CRIM: Cross-Reactive Immunologic Material; DLP: Data Lock Point; ERT: Enzyme Replacement Therapy; IgG: Immunoglobulin G; IO: Infantile Onset; IOPD: Infantile-Onset Pompe Disease; MedDRA: Medical Dictionary for Regulatory Activities; rhGAA: Recombinant Human Acid Alfa-Glucosidase; RMP: Risk Management Plan.

Table 16 - Identified risk: Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)

Identified Risk	Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)
Potential mechanism	Possible factors associated with the induction of rhGAA IgG Antibody: Foreignness of rhGAA (recognized as non-self protein), chemical complexity, route, frequency and dose of administration. Induction of the antibody response involved the following steps: • Immune recognition-antigen associated with major histocompatibility complex molecule is recognized as non-self by the immunocompetent cells. • Stimulation of B-lymphocyte response by complex interactions between T, B and accessory cells. • Continuing proliferation and differentiation of B cells into plasma cells by several cytokines. • Plasma cells produce antibody specific to rhGAA.
Evidence source(s) and strength of evidence	Clinical trial, postmarketing surveillance, literature.
Characterization of the risk	**Frequency with 95% CI** In total, 402 patients treated with alglucosidase alfa in clinical trials and/or the commercial setting have been evaluated for in vitro inhibition of enzyme activity. Of these, 362 patients were also evaluated for inhibition of uptake. Fifty-five out of 402 patients tested positive for inhibition of cellular uptake. Additionally, of these 55 patients, eight (2% out of 402 patients) tested positive for both inhibitor of enzyme activity and cellular uptake. A summary table of patients tested for in vitro inhibition can be found in table below. Some patients positive for inhibitory antibodies reported the events of lack of efficacy in the commercial setting.

Identified Risk	Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)

Setting of Exposure	Patients tested by enzyme activity assay	Positive for in vitro inhibition of enzyme activity	Patients tested by cellular uptake assay	Positive for inhibition of cellular uptake
AGLU01602/2403 and 1702	35	2 (5.7%)	35	3 (8.6%)
AGLU03105	5	0 (0%)	5	2 (40%)
AGLU02704/3206	79	0 (0%)	79	18 (22.8%)
AGLU02203	30	1 (3.3%)	5	3 (60%)
AGLU02603	7	0 (0%)	0	NA
AGLU02804	5	0 (0%)	0	NA
AGLU03306	7	0 (0.0%)	7	0 (0.0%)
AGLU03707	4	1 (25%)	4	2 (50%)
AGLU03807	2	0 (0.0%)	2	0 (0.0%)
AGLU09411	77	0 (0.0%)	77	1 (1.3%)
Commercial/EAP	151	4 (2.6%)	148	26 (17.6%)
Total	402	8 (2.0%)	362	55 (15.0%)

EAP: Expanded Access Program; NA: Not Applicable.

The probability of developing HSATs and poor outcome appears higher among CRIM-negative patients (patients in whom no endogenous *GAA* protein was detected by western blot analysis) than among CRIM-positive patients (patients in whom endogenous *GAA* protein was detected by western blot analysis). However, high and sustained antibody titres also occur in some CRIM-positive patients.

In the commercial setting, some patients reported high sustained IgG antibody titres and neutralizing antibodies to alglucosidase alfa leading to loss of response and worsening of Pompe disease.

The retrospective analysis by Kishnani et al (2010) of 32 patients with IOPD treated with alglucosidase alfa 20 mg/kg or 40 mg/kg/2 weeks for 52 weeks, which included 11 CRIM negative and 21 CRIM-positive patients showed 6 CRIM-negative status was associated with earlier seroconversion after ERT initiation (100% by 4 weeks) than CRIM-positive status (90% by 12.7 weeks on average) and higher titre levels at 24 weeks (median of 51 200 versus 600, respectively) and at 52 weeks (153 600 versus 200, respectively). In the CRIM-negative group, antibody titres were sustained at higher levels and appear to play a role in the clinical decline in these patients. Three of the 5 CRIM-positive patients who did poorly (ie, died or were invasively ventilated) had peak titres of 12 800, 25 600, or 51 200. (34)

A chart review by Berrier et al (2015) of 20 CRIM-negative patients, found that the development of high and sustained antibody titres in 13 of the 17 patients who seroconverted after ERT initiation was associated with lower ventilator-free and overall survival compared to 4 patients with sustained intermediate titres and 3 patients with low titres. (35)

The cause of a poor clinical outcome in some of these patients is thought to be multifactorial.

Identified Risk	Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)
	Severity and nature of risk A small number of the IgG positive patients evaluated tested positive for inhibitory effects on in vitro testing. **Seriousness/outcomes** In clinical studies, samples testing positive for anti-rhGAA IgG antibodies were also tested for in vitro inhibition by both enzyme activity and cellular uptake assay. Testing in the commercial setting may have also occurred in patients who demonstrated clinical decline and/or became invasively ventilated. It is recommended that treated patients be tested for neutralization of enzyme uptake or activity if they experience a decrease in clinical benefit despite continued treatment with alglucosidase alfa. To measure inhibition of rhGAA enzymatic activity by antibody present in patient serum, patient samples that had percentage inhibition greater than 20% at any sera dilutions were considered positive by inhibitory antibody assay (enzyme activity). A flow cytometry based assay was developed to evaluate whether patient antibodies interfere with uptake of rhGAA by human fibroblast cells in culture. Samples that had enzyme uptake inhibition greater than 20% at two or more sera dilutions were considered positive at that time point by the flow cytometry cell-based assay. In the LO study, patients with positive inhibition generally had higher IgG titres than those who tested negative; however, there was no consistent relationship between patients experiencing adverse events or IARs and inhibitory antibody status. **Background incidence/prevalence** Development of inhibitory antibodies to rhGAA are specific to the biologic product and do not occur in patients with Pompe disease who are not intravenously exposed to the product. **Impact on individual patient** Some patients who develop high and sustained IgG antibody titres, including CRIM-negative patients may experience reduced clinical alglucosidase alfa treatment efficacy. The cause of a poor clinical response in some of these patients is thought to be multi-factorial. The development of HSAT have been shown in alglucosidase alfa treated patients to have poor outcome. HSAT were defined as titres $\geq$51 200 at or beyond 6 months on ERT. Such prolonged high ADA levels could result in suboptimal dosing of drug to patients due to immune complex formation. Neutralizing antibodies, particularly those inhibit drug cellular uptake, have developed in some IOPD patients treated with alglucosidase alfa and generally were associated with high ADA titres. CRIM-negative IOPD patients are at risk for developing HSAT and neutralizing antibodies with documented loss of clinical response.
Risk factors and risk groups	Patients with positive uptake inhibition generally had higher IgG antibody titres than patients who remained negative for uptake inhibition in IO and LO studies. The presence or absence of endogenous enzyme, reported as CRIM status, is a known risk factor. For patients with IOPD, the major risk group is CRIM-negative patients who do not produce any endogenous enzyme. If not given prophylactic immune tolerance induction, these patients develop high and sustained ADA titres, as well as neutralizing antibodies when treated with alglucosidase alfa, which contribute to poor clinical outcomes. Patients with LOPD produce low levels of endogenous enzyme and are considered CRIM-positive. These patients are generally not at risk for developing HSAT and very few make high ADA titres which then decrease over time.

Identified Risk	Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)
Preventability	Prophylactic treatment /induction of immune tolerance.
Impact on the benefit-risk balance of the product	Given the small percentage of patients (2%) tested positive for both inhibitor of enzyme activity and cellular uptake, the benefit-risk balance remains positive for patients who experience this potential risk.
Public health impact	Given the extremely small number of Pompe patients, development of antibodies in relation to alglucosidase alfa treatment has a negligible public health impact.

ADA: Anti-Drug Antibody; CI: Confidence Interval; CRIM: Cross-Reactive Immunologic Material; EAP: Expanded Access Program; ERT: Enzyme Replacement Therapy; GAA: Acid Alfa-Glucosidase; HSAT: High Sustained Antibody Titre; IAR: Infusion Associated Reaction; IgG: Immunoglobulin G; IO: Infantile-Onset ; LO: Late-Onset; LOPD: Late-Onset Pompe Disease; NA: Not Applicable; rhGAA: Recombinant Human Acid Alfa Glucosidase.

Table 17 - Potential risk: Medication errors in the home infusion setting

Potential Risk	Medication errors in the home infusion setting
Potential mechanism	Insufficient understanding of the instructions for use of the product (eg, dose calculation, reconstitution, administration).
Evidence source(s) and strength of evidence	It is expected and understood that the HCPs administering alglucosidase alfa in the home setting are experienced in the management of Pompe disease, as well as in the management of other ERTs. In the "Home infusion report" provided by the EMC expert center, where MYOZYME is routinely administered in the home setting as standard practice, the data confirmed that few IARs were identified associated with the administration of MYOZYME, similarly to the hospital set-up. No severe IARs were reported in the home setting, the majority of IARs were mild in intensity and did not necessitate advanced clinical intervention. (36)(37)(38) The MAH Global safety database was searched to identify all adverse events reported in association with alglucosidase alfa use in the home setting. As of 01-Jun-2023, 2806 (6.2%) adverse events were reported with home infusions. The adverse events reported during home infusions were largely from the Netherlands, Canada and the US. The patients were mostly adults with a mean age of 36.6 years and similarly reported by males and females. The medication errors reported in the home infusion setting were nonserious and similar to the commonly reported medication errors for alglucosidase alfa (ie, inline filter not used, dose/frequency changes, etc.). Overall, the adverse events including IARs and hypersensitivity reactions occurring with the home infusion are consistent with the known safety profile of alglucosidase alfa, the ongoing COVID-19 pandemic and the known complications of Pompe disease and therefore, do not raise any new safety concerns. However, as for other ERTs for which the home infusion is possible, there is a possible risk of medication errors in the home infusion setting, linked to insufficient understanding of the instructions for use of the product (eg, dose calculation, reconstitution, administration). Considering these facts, the MAH proposes to include "Medication errors in the home infusion setting" as an important potential risk in the RMP.
Characterization of the risk	**Frequency with 95% CI**: In the "Home infusion report" provided by the EMC expert center, where MYOZYME is routinely administered in the home setting as standard practice, the data confirmed that few IARs were identified associated with the administration of MYOZYME, similarly to the hospital set-up. No severe IARs were reported in the home setting, the majority of IARs were mild in intensity and did not necessitate advanced clinical intervention.

Potential Risk	Medication errors in the home infusion setting
	The MAH Global safety database analysis showed 2806 (6.2%) adverse events were reported in association with alglucosidase alfa use in the home setting and of these, 177 (6.3%) were reports of medication errors. **Severity and nature of risk:** Medication errors may be more likely to occur in the home setting because of potential insufficient understanding of the instructions for use of the product. In the MAH Global safety database, medication error reports with home infusion were related mostly to inline filter not used, dose/frequency changes, infusion administration issues, etc. **Seriousness/outcomes:** Insufficient understanding of the instructions for use may result in medication errors in the home infusion setting. In the MAH Global safety database, all of the medication errors reported with alglucosidase alfa use in the home setting were non-serious. The majority of adverse events and IARs were nonserious. **Background incidence/prevalence:** Not applicable **Impact on individual patient:** In the "Home infusion report" provided by the EMC expert center, the data confirmed that few IARs were identified associated with the administration of MYOZYME, similarly to the hospital set-up. No severe IARs were reported in the home setting, the majority of the IARs were mild in intensity and did not necessitate advanced clinical intervention. The MAH Global safety database analyses and literature review did not identify any new safety concerns regarding the administration of alglucosidase alfa in the home setting. The medication errors were related to inline filter not used, dose/frequency changes, infusion administration issues, etc. which could potentially occur regardless of the infusion setting.
Risk factors and risk groups	Unknown
Preventability	Recommendations regarding home infusion administration, are described in SmPC sections 4.2 and 6.6 with detailed instruction on risk mitigation including eligibility of patients for home infusion, and on reconstitution, dose calculation, infusion preparation and administration. Educational material in the form of an HCP guide is also proposed. This guide will provide clear instruction for the preparation, reconstitution, and administration of alglucosidase alfa at home to prevent the medication errors, as well as the recognition and management of the important identified risk "Infusion associated reactions".
Impact on the benefit-risk balance of the product	Enzyme replacement therapy with alglucosidase alfa provides clinical benefit to patients. The benefit-risk balance remains positive. There is no deleterious impact on the benefit-risk balance anticipated for this product.
Public health impact	Given the small number of patients treated either at home or in the hospital/clinic, the public health impact appears to be low.

CI: Confidence Interval; COVID-19: Coronavirus Disease-2019; EMC: Erasmus Medical Center; ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; MAH: Marketing Authorization Holder; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; US: United States.

[redacted]

SVII.3.2 Presentation of the missing information

Table 18 - Missing information: Use of MYOZYME in pregnant or lactating women

Missing Information	Use of MYOZYME in pregnant or lactating women
Evidence source(s) and strength of evidence	Registry and postmarketing data from the Global Safety Database.
Anticipated risk/consequence of the missing information	Caution in exposing this population as defined in the labeling. (See section 4.6 Fertility, pregnancy and lactation of SmPC)

SmPC: Summary of Product Characteristics.

Table 19 - Missing information: Use of MYOZYME in elderly patients

Missing Information	Use of MYOZYME in elderly patients
Evidence source(s) and strength of evidence	Postmarketing data from the Global Safety Database.
Anticipated risk/consequence of the missing information	Caution should be used in this patient population. (See section 4.2 Posology and method of administration of SmPC)

SmPC: Summary of Product Characteristics.

Table 20 - Missing information: Use of MYOZYME in patients with renal or hepatic insufficiency

Missing Information	Use of MYOZYME in patients with renal or hepatic insufficiency
Evidence source(s) and strength of evidence	Postmarketing data from the Global Safety Database and registry.
Anticipated risk/consequence of the missing information	Caution should be used in this patient population. (See section 4.2 Posology and method of administration of SmPC)

SmPC: Summary of Product Characteristics.

Table 21 - Missing information: Long-term safety information

Missing Information	Long-term safety information
Evidence source(s) and strength of evidence	Registry and postmarketing data from the Global Safety Database.
Anticipated risk/consequence of the missing information	Unknown

[redacted]

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Based on clinical experience with alglucosidase alfa as well as other ERT approved for treating lysosomal storage diseases, MAH has identified safety risks associated with alglucosidase alfa treatment. Most of the risks are well characterized, and MAH has established standardized procedures for identifying and/or managing these.

The following table summarizes the ongoing safety concerns with alglucosidase alfa.

Summary of the safety concerns

Important identified risks	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	Immune mediated reactions
	Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies)
Important potential risk	Medication errors in the home infusion setting
Missing information	Use of MYOZYME in pregnant or lactating women
	Use of MYOZYME in elderly patients
	Use of MYOZYME in patients with renal or hepatic insufficiency
	Long-term safety information

IgE: Immunoglobulin E; IgG: Immunoglobulin G.

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

Based on clinical experience with alglucosidase alfa, the MAH has identified safety risks associated with alglucosidase alfa treatment. Most of the risks are well characterized, and MAH has established standardized procedures for identifying and/or managing these.

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of alglucosidase alfa.

The safety profile of alglucosidase alfa will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of ADRs in periodic safety reports, product technical complaints (PTCs) relating to adverse events, and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activities in the postmarketing setting includes conducting noninterventional studies (Post-authorization safety study [PASS]) to characterize safety profile of alglucosidase alfa in pregnant-lactating female patients, renal/hepatic impairment patients and the long-term safety profile in patients of all ages with Pompe disease in a real-world setting. Details are presented in the following table.

Studies ALGMYC07390 and AGLU06909/LTS13930 have been completed and are thus proposed to be removed from the pharmacovigilance plan.

Table 22 - Additional pharmacovigilance activities (category 1 to 3) summary

Pompe Registry to collect long term data in patients of all ages treated with alglucosidase alfa (including elderly patients) (Cat. 3)
Study short name and title Pompe Registry to collect long term data in patients of all ages treated with alglucosidase alfa (including elderly patients).
Rationale and study objectives To obtain additional information about the use of alglucosidase alfa in patients of all ages.
Study design Observational study
Study populations Patients enrolled in the Pompe Registry (a multicenter, multinational, observational program that tracks the natural history and outcomes of patients with Pompe disease) who receive ERT with alglucosidase alfa.
Milestones Final report: Q4 2022

[redacted]

Pompe Registry to collect long-term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa (Cat. 3)

Study short name and title

Pompe Registry to collect long-term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa.

Rationale and study objectives

To obtain additional information about the use of alglucosidase alfa in patients with renal or hepatic insufficiency.

Study design

Observational registry

Study populations

Patients enrolled in the Pompe Registry (a multicenter, multinational, observational program that tracks the natural history and outcomes of patients with Pompe disease) who receive ERT with alglucosidase alfa.

Milestones

Final report: Q4 2022

Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients (NCT00567073) (commitment to US FDA) (Cat. 3)

Study short name and title

Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients (commitment to US FDA).

Rationale and study objectives

The objective is to track pregnancy outcomes in women with Pompe disease and to follow infants born to women with Pompe disease (commitment to US FDA).

Study design

Observational

Study populations

Pregnant females with Pompe disease and/or infants born to females with Pompe disease.

Milestones

Final report: Q4 2022

Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in breastfeeding patients (AGLU03406, NCT00566878) (commitment to US FDA) (Cat. 3)

Study short name and title

Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant and breastfeeding patients (commitment to US FDA).

Rationale and study objectives

The objective is to determine if alglucosidase alfa is present in breast milk from mothers with Pompe Disease being treated with alglucosidase alfa and to measure breast milk production and composition in women with Pompe Disease who receive alglucosidase alfa (commitment to US FDA).

Study design

Observational.

Study populations

Female Pompe Registry patients receiving alglucosidase alfa and lactating.

[redacted]

[redacted]

Milestones

Final report: Q4 2022

Note: In the previous RMP version, "General post approval safety surveillance, Immunosurveillance Program" was inadvertently classified as PASS and was included in the Pharmacovigilance Plan. However, this is not qualifying the definition of PASS study. This is an Immunosurveillance program, and its analysis is provided in each PBRER. Hence this is removed from the RMP 10.0.

ERT: Enzyme Replacement Therapy; FDA: Food and Drug Administration; PASS: Post-Authorization Safety Study; PBRER: Periodic Benefit-Risk Evaluation Report; PSUR: Periodic Safety Update Report; RMP: Risk Management Plan; US: United States.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 23 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Pompe Registry to collect long-term data in patients of all ages treated with alglucosidase alfa (including elderly patients) Started - ongoing	To obtain additional information about the use of alglucosidase alfa in patients of all ages	• Use of MYOZYME in the elderly patients • Long-term safety information	Final report	Q4 2022
Pompe Registry to collect long-term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa Started - ongoing	To obtain additional information about the use of alglucosidase alfa in patients with renal or hepatic insufficiency	Use of MYOZYME in patients with renal or hepatic insufficiency	Final report	Q4 2022
Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients (NCT00567073) Started - ongoing	To track pregnancy outcomes in women with Pompe disease and to follow infants born to women with Pompe disease (commitment to US FDA)	Use of MYOZYME in pregnant or lactating women	Final report	Q4 2022
Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in breastfeeding patients (AGLU03406, NCT00566878)	To determine if alglucosidase alfa is present in breast milk from mothers with Pompe Disease being treated with alglucosidase alfa and to measure breast	Use of MYOZYME in pregnant or lactating women	Final report	Q4 2022

[redacted]

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Started - ongoing	milk production and composition in women with Pompe Disease who receive alglucosidase alfa (commitment to US FDA)			

FDA: Food and Drug Administration; IgE: Immunoglobulin E; IgG: Immunoglobulin G; PBRER: Periodic Benefit Risk Evaluation Report; PSUR: Periodic Safety Update Report; rhGAA: Recombinant Human Acid Alfa-Glucosidase; US: United States.

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for alglucosidase alfa.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

[redacted]In particular, considering the current level of knowledge about immunological testing in clinical practice in IOPD and LOPD patients receiving or planning to receive alglucosidase alfa, as well as the SIP recommendations on the immunosurveillance program for alglucosidase alfa and full instructions for access to immunosurveillance program, [redacted] recommended a revision of the SIP to be submitted through a RMP update. The SIP revision is done as part of the RMP update (version 10.0) and submitted as a part of the RMP variation.

New aRMMs "Home infusion guide for HCP" and "Home infusion guide for Patient/Caregiver including an infusion diary" are introduced to minimize the following risks associated with home infusion of alglucosidase alfa:

- Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies (Home infusion guides for HCP and patient/caregiver)
- Medication errors in the home infusion setting (Home infusion guide for HCP)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 24 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	**Routine risk communication:** SmPC: Labelled in section 4.8. PL: Labelled in section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labelled in sections 4.2, 4.3, 4.4 and 4.7. PL: Labelled in section 2 **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Immune mediated reactions	**Routine risk communication:** SmPC: Labelled in section 4.8. PL: Labelled in section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labelled in section 4.4. PL: Labelled in section 2 **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine

[redacted]

Safety concern	Routine risk minimization activities
Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)	**Routine risk communication:** SmPC: Labelled in section 4.4. PL: Not mentioned **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labelled in section 4.4. PL: Not mentioned **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Medication errors in the home infusion setting	**Routine risk communication:** SmPC: Labelled in sections 4.2 and 6.6. PL: Labelled in section 3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: • Decision criteria to have a patient move to the home infusion setting are included in SmPC section 4.2, as well as the description of home infusion infrastructure, resources, and procedures. • The precautions for disposal, instructions for reconstitution and dilution as well as the description of infusion preparation and administration are included in SmPC section 6.6. PL: The precautions for disposal, instructions for reconstitution and dilution as well as the description of infusion preparation and administration are included in PL section 6. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Use of MYOZYME in pregnant or lactating women	**Routine risk communication:** SmPC: Labelled in section 4.6. PL: Labelled in section 2.0 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC: Labelled in section 4.6. PL: Labelled in section 2.0 **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Use of MYOZYME in elderly patients	**Routine risk communication:** SmPC: Labelled in section 4.2 PL: Not mentioned **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine

Safety concern	Routine risk minimization activities
Use of MYOZYME in patients with renal or hepatic insufficiency	**Routine risk communication:** SmPC: Labelled in section 4.2. PL: Not mentioned **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine
Long-term safety information	**Routine risk communication:** None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine

IgE: Immunoglobulin E; IgG: Immunoglobulin G; PL: Package Leaflet; rhGAA: Recombinant Human Acid Alfa-Glucosidase; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 25 - Additional risk minimization measures

Safety Information Packet containing a dosing and administration guide, comprehensive infusion associated reaction management guidelines, adverse event reporting guidelines, and immunological testing procedures	
Objectives	• To mitigate following important identified risks - Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies - Immune mediated reactions - Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies) The SIP provides information about the immunosurveillance service, put in place by MAH's EU Medical Services. This current testing service [redacted] described in the SIP for immunosurveillance service [redacted] of testing: anti-drug IgG antibody, adverse event related immunogenicity testing for patients with Pompe disease. The SIP is updated to reflect the current knowledge on the identified risks and management of these risks.
Rationale for the additional risk minimization activity	The educational resource is in the format of a SIP for HCPs. The SIP available to treating physicians provides detailed IAR management guidelines, as well as pretreatment recommendations. This SIP also includes information on the immunosurveillance service, particularly on the testing recommendations, contact details, and shipment instructions. It includes the description of the service as well as well as testing procedures.

[redacted]

Target audience and planned distribution path	Target audience: Healthcare professionals Distribution path: The distribution routes allowed are e-mail, mail, face to face or other. The web-posting of the SIP on Sanofi local site is authorized, but not mandatory. Periodicity of distribution of risk minimizations tools is defined as follows: One-time distribution. The Sanofi affiliates will check annually whether new treatment sites are opened and ensure the SIP is distributed to the updated treatment site list.
Plans to evaluate the effectiveness of the interventions and criteria for success	Plans to evaluate the effectiveness of the interventions • Routine safety surveillance Criteria for success • Number and severity of spontaneous reports over time
Home infusion guide for HCP	
Objectives	This guide will serve as a training document for HCPs to mitigate the following safety concerns in the home setting: • Medication errors in the home infusion setting and • Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
Rationale for the additional risk minimization activity	This guide will provide clear instructions for the preparation, reconstitution, and administration of alglucosidase alfa at home to prevent the medication errors, as well as the recognition and management of the important identified risk "Infusion associated reactions".
Target audience and planned distribution path	Target Audience: All HCPs including treating physicians and home care/infusion HCPs who will perform the infusion at home. Distribution path: This above-mentioned material will be adapted country by country and distribution will depend on each local situation: face to face, website, mailing. Local adaptations through digital solutions are possible according to local requirements/national health system. Periodicity of distribution: One single distribution after release of the material, redistribution if updated version of the materials, and for new prescribers.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine effectiveness measurements and monitoring of the distribution.
Home infusion guide for Patient/Caregiver including an infusion diary	
Objectives	To mitigate the risk of "Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies" in the home infusion setting.
Rationale for the additional risk minimization activity	This guide contains information on the signs and symptoms related to IARs and recommended actions for the management of the ADRs when symptoms occur, as well as an infusion diary for the patient/caregivers that can be used to record the infusions and document any product-related IARs, including allergic-type hypersensitivity reactions before, during or after the infusion.

Target audience and planned distribution path	**Target audience:** Patients and caregivers **Distribution path:** The patient guide will be distributed to the patients/caregivers by their treating/prescribing physician who has received the material. **Periodicity of distribution:** One single distribution after release of the material and redistribution if there is any update in the materials and for new patients.
Plans to evaluate the effectiveness of the interventions and criteria for success	Routine effectiveness measurements and monitoring of the distribution.

ADR: Adverse Drug Reaction; EU: European Union; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; MAH: Marketing Authorization Holder; SIP: Safety Information Packet.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 26 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.2, 4.3, 4.4, 4.7 and 4.8 • PL: Labelled in sections 2 and 4 **Additional risk minimization measures:** • Safety Information Packet • Home infusion guide for HCP • Home infusion guide for Patient/Caregiver including an infusion diary **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Immune mediated reactions	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.4 and 4.8. • PL: Labelled in sections 2 and 4 **Additional risk minimization measures:** Safety Information Packet **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)	**Routine risk minimization measures:** • SmPC: Labelled in section 4.4. • PL: Not mentioned. **Additional risk minimization measures:** Safety Information Packet	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

[redacted]

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other routine risk minimization measures beyond the Product Information: Prescription only medicine	**Additional pharmacovigilance activities:** None
Medication errors in the home infusion setting	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.2 and 6.6 • PL: Labelled in sections 3 and 6 **Additional risk minimization measures:** Home infusion guide for HCP **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use of MYOZYME in pregnant or lactating women	**Routine risk minimization measures:** • SmPC: Labelled in section 4.6. • PL: Labelled in section 2 **Additional risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** • Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients. (NCT00567073) • Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in breastfeeding patients. (AGLU03406, NCT00566878)
Use of MYOZYME in elderly patients	**Routine risk minimization measures:** • SmPC: Labelled in section 4.2. • PL: Not mentioned **Additional risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pompe Registry to collect long term data in patients of all ages treated with alglucosidase alfa (including elderly patients).

[redacted]

[redacted]

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use of MYOZYME in patients with renal or hepatic insufficiency	**Routine risk minimization measures:** • SmPC: Labelled in section 4.2. • PL: Not mentioned. **Additional risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pompe Registry to collect long term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa.
Long-term safety information	**Routine risk minimization measures:** None **Additional risk minimization measures:** None **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Pompe Registry to collect long term data in patients treated with alglucosidase alfa

HCP: Healthcare Professional; IgE: Immunoglobulin E; IgG: Immunoglobulin G; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

[redacted]

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for MYOZYME (Alglucosidase alfa)

This is a summary of the risk management plan (RMP) for MYOZYME. The RMP details important risks of MYOZYME how these risks can be minimized, and how more information will be obtained about MYOZYME's risks and uncertainties (missing information).

MYOZYME's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how MYOZYME should be used.

This summary of the RMP for MYOZYME should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of MYOZYME's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

MYOZYME is authorized for long term ERT in patients with a confirmed diagnosis of Pompe disease (acid α glucosidase deficiency). MYOZYME is indicated in adults and pediatric patients of all ages (see SmPC for the full indication). It contains alglucosidase alfa as the active substance and it is given by IV infusion.

Further information about the evaluation of MYOZYME's benefits can be found in MYOZYME's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/myozyme

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of MYOZYME, together with measures to minimize such risks and the proposed studies for learning more about MYOZYME's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;

- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of MYOZYME, these measures are supplemented with aRMMs mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of MYOZYME is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of MYOZYME are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Some of the risks are related to the biological nature of the product. Identified risks are concerns for which there is sufficient proof of a link with the use of MYOZYME. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 27 - List of important risks and missing information

Important identified risks	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	Immune mediated reactions
	Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)
Important potential risk	Medication errors in the home infusion setting
Missing information	Use of MYOZYME in pregnant or lactating women
	Use of MYOZYME in elderly patients
	Use of MYOZYME in patients with renal or hepatic insufficiency
	Long-term safety information

IgE: Immunoglobulin E; IgG: Immunoglobulin G.

II.B Summary of important risks

Table 28 - Important identified risk with corresponding risk minimization activities: Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies

Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	
Evidence for linking the risk to the medicine	Clinical trial, postmarketing surveillance, literature
Risk factors and risk groups	Infantile-onset patients who develop high antibody titres appear to be at higher risk for developing more frequent IARs and hypersensitivity. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody titres. Patients with an acute illness (eg, acute febrile illness, such as pneumonia or sepsis, or wheezing/bronchospasm) at the time of alglucosidase alfa infusion appear to be at greater risk for IARs. Patients with advanced Pompe disease or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. Patients treated with higher doses of alglucosidase alfa (>20 mg/kg) tended to develop a more robust IgG antibody response and experience more IARs. Patients who have experienced infusion reactions may be at increased risk of IARs when alglucosidase alfa is readministered. Additionally, IgE positive patients are at increased risk of developing IARs upon readministering the drug. In the LO study, there was no apparent association between higher IgG antibody titres and occurrence of IARs. It is recommended that patients be monitored for IgG antibody formation periodically. Baseline serum sample collection prior to the first infusion is encouraged. For IOPD patients, regular monitoring during first year of treatment (example: every 3 months) is suggested and subsequent monitoring dependent on clinical outcomes and antibody titre levels. For LOPD patients, antibody development should be assessed within 6 months and subsequent monitoring as clinically warranted based on safety and efficacy considerations. The probability of developing HSATs and poor outcome appears higher among CRIM-negative patients (patients in whom no endogenous *GAA* protein was detected by Western blot analysis) than among CRIM-positive patients (patients in whom endogenous *GAA* protein was detected by western blot analysis). However, high and sustained antibody titres also occur in some CRIM-positive patients. The cause of a poor clinical outcome in some of these patients is thought to be multifactorial. It is unknown who will develop immediate hypersensitivity reactions (IgE positive) to alglucosidase alfa.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.2, 4.3, 4.4, 4.7 and 4.8 • PL: Labelled in section 2 and 4 • Prescription only medicine **Additional risk minimization measures:** • Safety Information Packet • Home infusion guide for HCP • Home infusion guide for Patient/Caregiver including an infusion diary

CRIM: Cross-Reactive Immunologic Material; GAA: Acid Alfa-Glucosidase; HCP: Healthcare Professional; HSAT: High Sustained Antibody Titre; IAR: Infusion Associated Reaction; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LO: Late-Onset; LOPD: Late-Onset Pompe Disease; PL: Package Leaflet SmPC: Summary of Product Characteristics.

[redacted]

Table 29 - Important identified risk with corresponding risk minimization activities: Immune mediated reactions

Immune mediated reactions	
Evidence for linking the risk to the medicine	Nonclinical trials, clinical trial, postmarketing surveillance, literature.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.4 and 4.8 • PL: Labelled in sections 2 and 4 • Prescription only medicine **Additional risk minimization measures:** Safety Information Packet

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 30 - Important identified risk with corresponding risk minimization activities: Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)

Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)	
Evidence for linking the risk to the medicine	Clinical trial, postmarketing surveillance, literature.
Risk factors and risk groups	Patients with positive uptake inhibition generally had higher IgG antibody titres than patients who remained negative for uptake inhibition in IO and LO studies. The presence or absence of endogenous enzyme, reported as CRIM status, is a known risk factor. For patients with IOPD, the major risk group is CRIM-negative patients who do not produce any endogenous enzyme. If not given prophylactic immune tolerance induction, these patients develop high and sustained ADA titres, as well as neutralizing antibodies when treated with alglucosidase alfa, which contribute to poor clinical outcomes. Patients with LOPD produce low levels of endogenous enzyme and are considered CRIM-positive. These patients are generally not at risk for developing HSAT and very few make high ADA titres which then decrease over time.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.4 • PL: Not mentioned • Prescription only medicine **Additional risk minimization measures:** Safety Information Packet

IgG: Immunoglobulin G; IO: Infantile Onset; LO: Late-Onset; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 31 - Important potential risk with corresponding risk minimization activities: Medication errors in the home infusion setting

Medication errors in the home infusion setting	
Evidence for linking the risk to the medicine	It is expected and understood that the HCPs administering alglucosidase alfa in the home setting are experienced in the management of Pompe disease, as well as in the management of ERTs.

[redacted]

Medication errors in the home infusion setting	
	In the "Home infusion report" provided by the EMC expert center, where MYOZYME is routinely administered in the home setting as standard practice, the data confirmed that few IARs were identified associated with the administration of MYOZYME, similarly to the hospital set-up. No severe IARs were reported in the home setting, the majority of IARs were mild in intensity and did not necessitate advanced clinical intervention. (36)(37)(38) The MAH Global safety database was searched to identify all adverse events reported in association with alglucosidase alfa use in the home setting. As of 01-Jun-2023, 2806 (6.2%) adverse events were reported with home infusions. The adverse events reported during home infusions were largely from the Netherlands, Canada and the US. The patients were mostly adults with a mean age of 36.6 years and similarly reported by males and females. The medication errors reported in the home infusion setting were nonserious and similar to the commonly reported medication errors for alglucosidase alfa (ie, inline filter not used, dose/frequency changes, etc.). Overall, the adverse events including IARs and hypersensitivity reactions occurring with the home infusion are consistent with the known safety profile of alglucosidase alfa, the ongoing COVID-19 pandemic and the known complications of Pompe disease and therefore, do not raise any new safety concerns. However, as for other ERTs for which the home infusion is possible, there is a possible risk of medication errors in the home infusion setting, linked to insufficient understanding of the instructions for use of the product (eg, dose calculation, reconstitution, administration). Considering these facts, the MAH proposes to include "medication errors in the home infusion setting" as an important potential risk in the RMP.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.2 and 6.6 • PL: Labelled in sections 3 and 6 • Prescription only medicine **Additional risk minimization measures:** Home infusion guide for HCP

COVID-19: Coronavirus Disease-2019; EMC: Erasmus Medical Center; ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; MAH: Marketing Authorization Holder; PL: Package Leaflet; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; US: United States.

Table 32 - Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Use of MYOZYME in pregnant or lactating women

Use of MYOZYME in pregnant or lactating women	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.6. • PL: Labelled in section 2 • Prescription only medicine **Additional risk minimization measures:** None

Use of MYOZYME in pregnant or lactating women	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients. • Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in breastfeeding patients.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 33 - Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Use of MYZOZYME in elderly patients

Use of MYOZYME in elderly patients	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.2. • PL: Not mentioned • Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pompe Registry to collect long term data in patients of all ages treated with alglucosidase alfa (including elderly patients).

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 34 - Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Use of MYOZYME in patients with renal or hepatic insufficiency

Use of MYOZYME in patients with renal or hepatic insufficiency	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.2 • PL: Not mentioned • Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pompe Registry to collect long-term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa.

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 35 - Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety information

Long-term safety information	
Risk minimization measures	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None

Long-term safety information	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pompe Registry to collect long-term data in patients treated with alglucosidase alfa.

SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 *Studies which are conditions of the marketing authorization*

There are no studies which are conditions of the marketing authorization or specific obligation of MYOZYME.

II.C.2 *Other studies in post-authorization development plan*

Table 36 - Other studies in post-authorization development plan

Pompe Registry to collect long term data in patients of all ages treated with alglucosidase alfa (including elderly patients) (Cat. 3)
Purpose of the study: To obtain additional information about the use of alglucosidase alfa in patients of all ages.
Pompe Registry to collect long term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa (Cat. 3)
Purpose of the study: To obtain additional information about the use of alglucosidase alfa in patients with renal or hepatic insufficiency.
Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients (NCT00567073) (commitment to US FDA) (Cat. 3)
Purpose of the study: To track pregnancy outcomes in women with Pompe disease and to follow infants born to women with Pompe disease (commitment to US FDA).
Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in breastfeeding patients (AGLU03406, NCT00566878) (commitment to US FDA) (Cat. 3)
Purpose of the study: To determine if alglucosidase alfa is present in breast milk from mothers with Pompe Disease being treated with alglucosidase alfa and to measure breast milk production and composition in women with Pompe Disease who receive alglucosidase alfa (commitment to US FDA).

FDA: Food and Drug Administration; US: United States.

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[redacted]

RISK MANAGEMENT PLAN - PART VII: ANNEXES

[redacted]

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

[redacted]

Draft key messages of the additional risk minimization measures

The Marketing Authorization Holder (MAH) shall ensure that in each member state where alglucosidase alfa is marketed and/or home infusion is authorized, all healthcare professionals (HCPs) who are expected to prescribe, dispense and administer alglucosidase alfa have access to/are provided with the following educational guide as per local requirements/national health system:

- Safety information packet for HCP
- Home infusion guide for HCP

Additionally, the following educational guide will be distributed to the patients/caregivers by their treating/prescribing physician who has received the material from the MAH:

- Home infusion guide for Patient/Caregiver including an infusion diary

1.1 Safety information Packet (SIP) for health care professionals include the following key elements:

- Educational material providing support to HCPs in the management of the following safety concerns: Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies; Immune mediated reactions and Immunogenicity leading to loss of response (High sustained IgG antibody titres and or neutralizing antibodies);
- Testing recommendations:
  - Baseline serum sample collection prior to the first infusion is strongly encouraged.
  - Immunoglobulin G (IgG) antibody titers should be regularly monitored, and IgG anti-drug antibody (ADA) testing should be considered if patients do not respond to therapy.
  - Treated patients may be tested for inhibitory antibodies if they experience a decrease in clinical benefit despite continued treatment with Myozyme.
  - Adverse-event-driven immunologic testing, including IgG and Immunoglobulin E (IgE) ADA, should be considered for patients at risk for allergic reaction.
  - Adverse-event-driven immunologic testing should also be considered in patients who experience moderate/severe or recurrent infusion associated reactions (IARs) suggestive of hypersensitivity reactions, anaphylactic reactions.
- Testing practicalities of the testing service and contact details
  - Description of the testing services: available tests, indication for testing, sample type, frequency of testing, collection time.
  - Procedure for testing: diagram summarizing main steps for HCP requesting specialty testing services.

[redacted]

[redacted]

1.2 Healthcare Professional educational materials: Home infusion guide for HCPs

The HCP guide contains the following key safety information to support HCPs in the management of patients receiving alglucosidase alfa in the home setting:

Information for HCPs prescribing alglucosidase alfa:

- Criteria to determine eligibility for home infusion.
- Requirements and organization of the home infusion including equipment, pre-treatment, and emergency treatments.

Information for HCPs administering alglucosidase alfa:

- Medical evaluation of the patient prior to administration of the infusion at home
- Requirements and organization of the home infusion including equipment, pre-treatment, and emergency treatments.
- Details on the preparation and administration of alglucosidase alfa, including all the steps of preparation, reconstitution, dilution, and administration.
- Information on signs and symptoms related to infusion associated reactions and recommended actions for the management of the adverse drug reactions (ADRs) when symptoms occur.

1.3 Patient educational materials: Home infusion guide for Patient/Caregiver including an infusion diary

The patient/caregiver guide contains the following key safety information:

- Information on the signs and symptoms related to IARs and recommended actions for the management of the ADRs when symptoms occur.
- An Infusion Diary that can be used to record the infusions and document any product-related IARs, including allergic-type hypersensitivity reactions before, during or after the infusion.

[redacted]