EU-RISK MANAGEMENT PLAN FOR NEXVIADYME®
(AVAGLUCOSIDASE ALFA)

Risk Management Plan (RMP) Version number	Version 2.0
Data Lock Point (DLP)	19-MAR-2020
Date of final sign-off	09-DEC-2025

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

Rationale for submitting an updated RMP	The RMP has been revised in order to update the milestones of OBS17445-SAVANT post authorization safety study (PASS) (category 3) and to submit the protocol version 1 for review.
Summary of significant changes in this RMP	Pharmacovigilance Plan: Milestones of OBS17445-SAVANT PASS are updated. Annexes: The Annexes 2, 3 and 8 are updated in line with the changes, including the incorporation of the OBS17445-SAVANT PASS amended protocol version 1 for review.

PASS: Post Authorization Safety Study; 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	1.3
Approved with procedure	EMEA/H/C/005501 (Initial application)
Date of approval (opinion date)	11-Nov-2021

EMEA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted][a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV of Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

2-PAM:	Pralidoxime
6MWT:	6-Minute Walk Test
ADA:	Anti-Drug Antibody
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AIMS:	Alberta Infant Motor Scale
ALT:	Alanine Aminotransferase
AR:	Adverse Reaction
AST:	Aspartate Aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under the Curve
BBB:	Blood Brain Barrier
CHO:	Chinese Hamster Ovary
CI:	Confidence Interval
CNS:	Central Nervous System
CRF:	Case Report Form
CRIM:	Cross-Reactive Immunologic Material
DALA:	Drug Abuse Liability Assessment
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
DSMB:	Data and Safety Monitoring Board
ECG:	Electrocardiogram
eCTD:	Electronic Common Technical Document
EEA:	European Economic Area
eGFR:	Estimated Glomerular Filtration Rate
[redacted]	[redacted]
EMEA:	European Medicines Agency
EPAR:	European Public Assessment Report
ERT:	Enzyme Replacement Therapy
ETP:	Extension Treatment Period
EU:	European Union
F:	Female
FVC:	Forced Vital Capacity
GAA:	Acid Alpha-Glucosidase
GD:	Gestation Day
GLP:	Good Laboratory Practice
GTI:	Genotoxic Impurity
Hex4:	Hexose Tetrasaccharide
HHD:	Hand-Held Dynamometry
HSAT:	High and Sustained Antibody Titer
IAR:	Infusion Associated Reaction
IOPD:	Infantile-Onset Pompe Disease
IV:	Intravenous

LOPD:	Late-Onset Pompe Disease
LSC:	List of Safety Concern
LV:	Left Ventricular
LVM-Z:	Left Ventricular Mass-Z
M:	Male
M6P:	Mannose-6-Phosphate
MAH:	Marketing Authorization Holder
MedDRA:	Medical Dictionary for Regulatory Activities
MEP:	Maximal Expiratory Pressure
MIP:	Maximal Inspiratory Pressure
n:	Number
NAb:	Neutralizing Antibody
NCA:	National Competent Authority
NOAEL:	No-Observed-Adverse-Effect-Level
OP:	Organophosphate
PAP:	Primary Analysis Period
PASS:	Post Authorization Safety Study
PBRER:	Periodic Benefit-Risk Evaluation Report
PD:	Pharmacodynamic
PI:	Product Information
PIP:	Paediatric Investigation Plan
PK:	Pharmacokinetic
PL:	Package Leaflet
PPD:	Postpartum Day
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
Q:	Quarter
QMFT:	Quick Motor Function Test
qow:	Every Other Week
QPPV:	Qualified Person Responsible for Pharmacovigilance
RMM:	Risk Minimization Measure
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SD:	Standard Deviation
SF-12:	12-Item Short Form Health Survey
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
SOC:	System Organ Class
TTC:	Threshold of Toxicologic Concern
US:	United States

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance (International Nonproprietary Name [INN] or common name)	Avalglucosidase alfa
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	A16AB22
Marketing Authorization Holder (MAH)	Sanofi B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Nexviadyme
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Hydrolase enzyme.
	Summary of mode of action: Avalglucosidase alfa provides an exogenous source of acid alpha glucosidase (GAA). Binding to mannose 6 phosphate (M6P) receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity.
	Important information about its composition: Avalglucosidase alfa is a human acid α glucosidase produced in Chinese hamster ovary (CHO) cells by recombinant deoxyribonucleic acid (DNA) technology, which is subsequently conjugated with an approximately 7 hexamannose structures each containing two terminal M6P moieties to oxidized sialic acid residues on the molecule, thereby increasing bis M6P levels.
Hyperlink to the product information (PI)	Refer to electronic common technical document (eCTD) sequence0041, Module 1.3.1 English proposed PI
Indication in the EEA	Current: Avalglucosidase alfa is indicated for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of avalglucosidase alfa is 20 mg/kg of body weight administered once every 2 weeks. Dose modification for infantile-onset Pompe disease (IOPD) patients: For IOPD patients who experience lack of improvement or insufficient response in cardiac, respiratory, and/or motor function while receiving 20 mg/kg, a dose increase to 40 mg/kg every

	other week (qow) should be considered in the absence of safety concerns (eg, severe hypersensitivity, anaphylactic reactions, or risk of fluid overload). In patients who do not tolerate avalglucosidase alfa at 40 mg/kg every other week (eg, severe hypersensitivity, anaphylactic reactions, or risk of fluid overload), consider decreasing the dose to 20 mg/kg every other week.
	Proposed: Not applicable.
Pharmaceutical form and strength	Current: 100 mg, powder for concentrate for solution for infusion. White to pale yellow lyophilized powder.
	Proposed: Not applicable.
Is/will the product (be) subject to additional monitoring in the European Union (EU)?	Yes

ATC: Anatomical Therapeutic Chemical; CHO: Chinese Hamster Ovary; DNA: Deoxyribonucleic Acid; eCTD: Electronic Common Technical Document; EEA: European Economic Area; ERT: Enzyme Replacement Therapy; EU: European Union; GAA: Acid Alpha-Glucosidase; MAH:Marketing Authorization Holder; INN: International Nonproprietary Name; IOPD: Infantile-Onset Pompe Disease; M6P: Mannose-6-Phosphate; PI: Product Information; qow: Every Other Week; RMP: Risk Management Plan.

PART II: SAFETY SPECIFICATION

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

Avalglucosidase alfa is indicated for long-term enzyme replacement therapy (ERT) for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

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, acid maltase deficiency 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 (expressed in years of age) 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, non-typical infantile-onset, 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 infantile-onset form (IOPD) to a more slowly progressive late-onset form (late-onset Pompe disease [LOPD]), 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.

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)

Pompe Registry

The Sanofi Genzyme Pompe Registry was established in 2004. It is a multicenter, international, longitudinal, observational, and voluntary program for patients with Pompe disease that was designed to track the natural history and treatment outcomes of patients, both treated and not. This is a non-interventional observational program. Patients undergo clinical assessments and receive standard of care as determined by the patient's physician. While the protocol provides a recommended schedule of assessments, which has been developed based on the input of physicians

from the international medical community with expertise in the care of patients with Pompe disease and from regulatory agencies, each physician is solely responsible for determining the appropriate clinical care for each patient.

The primary objectives of the Pompe Registry are to:

- To enhance understanding of the variability, progression, identification, and natural history of Pompe disease, with the ultimate goal of better guiding and assessing therapeutic intervention.
- To assist the Pompe medical community with the development of recommendations for monitoring patients, and to provide reports on patient outcomes, to optimize patient care.
- To characterize the Pompe disease population.
- To evaluate the long-term effectiveness of alglucosidase alfa.

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

Table 6 - Epidemiology of Pompe disease

<table>
<tr><th>Indication</th><th>Pompe disease</th></tr>
<tr><td>Incidence</td><td>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. 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). 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)</td></tr>
<tr><td>Prevalence</td><td>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 infantile-onset 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 United States (US), Europe, Mexico and Taiwan, and at least half of which are expected to manifest as late-onset disease. (16)(17)(18)(19)</td></tr>
<tr><td>Demographics of the population in the authorized/proposed indication</td><td>Demographics of patients with Pompe disease can be derived from the Pompe Registry. As of 01-May-2020, (information post-DLP), 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 1.1 - Pompe Registry Demographics, May-2020
<table>
<tr><th>Parameter</th><th>Statistics</th><th>All Enrolled Patients</th><th>IOPD</th><th>LOPD</th></tr>
<tr><td>Total Number of Patients</td><td>n</td><td>2254</td><td>390</td><td>1640</td></tr>
<tr><td>Age at Enrollment (Year)</td><td>n</td><td>2254</td><td>390</td><td>1640</td></tr>
<tr><td></td><td>Mean (SD)</td><td>32.7 (24.06)</td><td>3.2 (3.93)</td><td>41.5 (20.50)</td></tr>
</table></td></tr>
</table>

Indication	Pompe disease

	Median (25th, 75th)	36.1 (6.3, 53.2)	1.8 (0.7, 4.1)	44.3 (27.9, 57.6)
	Min, Max	0.0, 83.9	0.0, 29.2	0.1, 83.9
Age at Last Follow-up (Year)	n	2249	390	1640
	Mean (SD)	36.3 (24.91)	5.2 (4.65)	45.9 (20.67)
	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 patients with symptom onset ≤12 months of age without cardiac enlargement/myopathy, or with symptom 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; Max: Maximum; Min: Minimum; n: Number; 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.

Main existing treatment options	Among the available approaches to treat Pompe disease, ERT based on alglucosidase alfa is the only approved treatment that specifically targets the underlying cause of the disease by replacing the enzyme that is deficient. Alglucosidase alfa at 20 mg/kg body weight/qow is the only approved medicinal product 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, orthopaedist, 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, infantile-onset 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 milestones are achieved, they are subsequently lost. Death from cardiac and/or respiratory failure occurs before most patients reach 1 year of age. Patients presenting with this typical disease course have been described in the literature as having “classic” IOPD. A subset of patients with IOPD characterized by a

Indication	Pompe disease
	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. (20) 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. Patients with LOPD manifest signs and symptoms anywhere from infancy 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. (21)(22) 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. (23)(24)(25)
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. (26)(27) **Concomitant medications 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. Cardiovascular: In the presence of Left Ventricular (LV) outflow tract obstruction, the use of digoxin, other inotropes, diuretics and afterload reducing agents such as angiotensin-converting enzyme inhibitor may exacerbate the LV outflow tract obstruction. Patients may develop cardiac arrythmias and need antiarrhythmic concomitant medications. Respiratory: Liberal use of bronchodilators is recommended in conjunction with airway clearance techniques and assisted coughing maneuvers to maximize the patient’s pulmonary toilet care. Supplementary oxygen 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. Patients may have gastroesophageal reflux disease and need specific treatment. 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.

Indication	Pompe disease

DLP: Data Lock Point; ERT: Enzyme Replacement Therapy; GAA: Acid Alpha Glucosidase; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; LV: Left Ventricular; n: Number; qow: Every Other Week; SD: Standard Deviation; US: United States.

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

Safety pharmacology endpoints were incorporated into the 26-week toxicity study of avalglucosidase alfa in cynomolgus monkeys. There were no test article-related changes in neurobehavioral, electrocardiogram (ECG) parameters, heart rate, body temperature, activity or respiratory rate following administration at the highest dose administered 200 mg/kg intravenously (IV).

Avalglucosidase alfa was generally well tolerated in repeat-dose toxicity studies in mice and monkeys. While equivocal findings were noted in the testes and liver in a 14-day exploratory mouse study, similar findings were not observed at equal or higher doses in subsequent studies in any species. As such, the relationship of these effects to avalglucosidase alfa in the 14-day exploratory study is unlikely. Signs of hypersensitivity, including mortality, were observed in mice; therefore, the chronic toxicity of avalglucosidase alfa was evaluated in monkeys only. The no-observed-adverse-effect-level (NOAEL) in monkeys following IV administration for 26-weeks was the highest dose tested of 200 mg/kg qow avalglucosidase alfa. The exposure ratio (NOAEL in monkeys/adult human dose of 20 mg/kg) is 23-fold based on area under the curve (AUC).

Genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. However, an exploratory in vivo micronucleus test was conducted in mice and the results were negative up to the maximal dose tested, 150 mg/kg IV (50 mg/kg three times daily).

Standard carcinogenicity bioassays are generally not considered necessary for biotechnology derived pharmaceuticals. As part of the nonclinical safety evaluation, a carcinogenicity risk assessment was conducted based on:

- An evaluation of avalglucosidase alfa nonclinical toxicity from (1) repeat-dose toxicity studies in mice and monkeys, and (2) an exploratory *in-vivo* genotoxicity study in mice. Considerations were given to the potential for hypersensitivity reactions, including anaphylactoid, in mice administered a humanized product such as avalglucosidase alfa, in regard to the feasibility of conducting long-term carcinogenicity studies;
- A review of Genz-669342 (also referred to as E13 or glycan) toxicity from (1) an *in silico* genotoxicity search, (2) the published literature, (3) a repeat-dose toxicity study of Genz-669342 spiked avalglucosidase alfa in monkeys, and (4) *in vitro* genotoxicity studies on Genz-669342;
- A review of the marketed drugs for Pompe disease Myozyme® and Lumizyme® (alglucosidase alfa) and any relationship to tumor development or cancer as per (1) clinical trials, (2) epidemiology data, (3) global pharmacovigilance database, (4) external databases, and (5) published literature.

Furthermore, *in vitro* stability and metabolism data demonstrate that avalglucosidase alfa and Genz-669342 (aka E13 or glycan) are not metabolized to the free linker to an appreciable extent.

The weight-of-evidence does not support an increased risk of cancer with avalglucosidase alfa. As such, no studies have been conducted to evaluate the carcinogenic potential of avalglucosidase alfa.

Avalglucosidase alfa produced no adverse effects in a combined male and female fertility study in mice up to 50 mg/kg IV every other day.

In an embryo-fetal toxicity study of avalglucosidase alfa in pregnant mice, increased post-implantation loss and mean number of late resorptions were observed at the highest dose evaluated of 50 mg/kg/day. This dose also resulted in an immunologic response, including an anaphylactoid response, in some dams. Placental transfer examinations determined that avalglucosidase alfa is not transported from the maternal to the fetal circulation in mice, suggesting that the embryo-fetal effects were a result of the maternal toxicity related to the immunologic response. The developmental NOAEL in mice was 20 mg/kg/day (Maternal AUC_{0-24} 582 µg•h/mL).

In the embryo-fetal toxicity study in pregnant rabbits, there were no effects on intrauterine growth and survival of the kits, and no malformations or developmental variations were observed up to 100 mg/kg/day. In a pre- and post-natal developmental toxicity study in mice, administration of avalglucosidase alfa once qow on gestation day 6 (GD6) through Postpartum Day (PPD)-20 resulted in no untoward effects. The NOAEL for reproduction in the dams and for viability and growth in the offspring was 50 mg/kg/dose.

In juvenile mice, avalglucosidase alfa was generally well-tolerated following administration for 9 weeks at doses up to 100 mg/kg qow, the highest dose administered. The exposure ratio (exposure at the NOAEL in juvenile mice / human exposure at 40 mg/kg in IOPD patients in ACT14132) is 2- to 5-fold based on AUC.

Additional studies were conducted to support drug product specification limits of impurities. Increasing concentrations of Genz-669342 in the avalglucosidase alfa dose administered to monkeys for 13-weeks had no effect on toxicity up to the high dose of 50 mg/kg avalglucosidase alfa / 12.55 mg/kg Genz-669342 qow. Genz-669342 was non-genotoxic *in vitro* in a reverse bacterial mutation assay (up to 5000 µg/plate) and an *in-vitro* chromosome aberration test (up to 500 µg/mL).

Examination of the IV infusion sites in monkeys showed no adverse effects related to avalglucosidase alfa administration.

As a general policy, Sanofi Genzyme studies the presence of potential genotoxic impurities (GTIs) using a threshold of toxicologic concern (TTC) approach, taking into account the intended therapeutic doses and duration of dosing in clinical studies. To clarify the mutagenic potential, a bacterial reverse mutation test was performed on N-hydroxysuccinimide, a reagent in the synthesis of avalglucosidase alfa. There were no increases in the number of revertant colonies in any bacterial strains in the presence or absence of metabolic activation up to 5000 µg/plate.

The key non-clinical findings are presented in Table 7.

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

Key Safety Findings	Relevance to human usage
Toxicity: • **Repeat-dose toxicity studies**	
Hypersensitivity/anaphylactic reactions observed in repeat-dose toxicity studies in mice. In the 28-day toxicity study, evidence of hypersensitivity was observed after the third dose in all avalglucosidase alfa treated groups. The lowest dose administered was 4mg/kg/week (AUC_{0-24} = 50 µg•h/mL after dose 4). Hypersensitivity / anaphylactic reactions are not unexpected following administration of a humanized protein to rodents. These findings have not been observed in monkey.	In Human, these reactions have been observed (ie, Infusion associated reactions (IARs) including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies). These are described in [Part II SVII].
• **Reproductive/developmental toxicity studies** - In an embryo-fetal toxicity study in pregnant mice, maternal mortality related to hypersensitivity was observed at 50 mg/kg/day. Increased post-implantation loss and mean number of late resorptions were also observed at 50 mg/kg/day. Avalglucosidase alfa is not transported from the maternal to the fetal circulation in mice, suggesting that the findings were related to maternal toxicity from the immunologic response. The developmental NOAEL was 20 mg/kg/day IV (AUC_{0-24} = 582 µg•h/mL on GD6). - Similar findings were not observed in pregnant rabbits up to 100mg/kg/day IV, the highest dose administered (AUC_{0-24} = 7910 µg•h/mL on GD19).	In Human, the use of avalglucosidase alfa during pregnancy or in lactating women is considered as missing information (see [Part II SIV]). The use of avalglucosidase alfa is not recommended during pregnancy unless clearly necessary.

AUC: Area Under Curve; GD: Gestation Day; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IV: Intravenous; NOAEL: No-Observed-Adverse-Effect-Level.

In juvenile mice, avalglucosidase alfa was generally well-tolerated following administration for 9 weeks at doses up to 100 mg/kg qow, the highest dose administered.

In conclusion, the nonclinical studies conducted adequately characterize the safety of avalglucosidase alfa and provide sufficient data to support administration of avalglucosidase alfa to patients with Pompe disease.

No additional non-clinical data have been collected on the use of avalglucosidase alfa in any special populations.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

OVERVIEW OF DEVELOPMENT

The clinical development program for avalglucosidase alfa was conducted to demonstrate a reduction in the remaining burden of the disease in children and adults with Pompe disease as compared with the standard of care treatment, alglucosidase alfa. In total, 146 patients with Pompe disease were enrolled in 4 clinical studies. In order to match the heterogeneity of the Pompe disease patient population, the 4 clinical studies with avalglucosidase alfa were conducted in a broad spectrum of patients.

Three studies were conducted in patients with LOPD, either naive or previously treated with alglucosidase alfa:

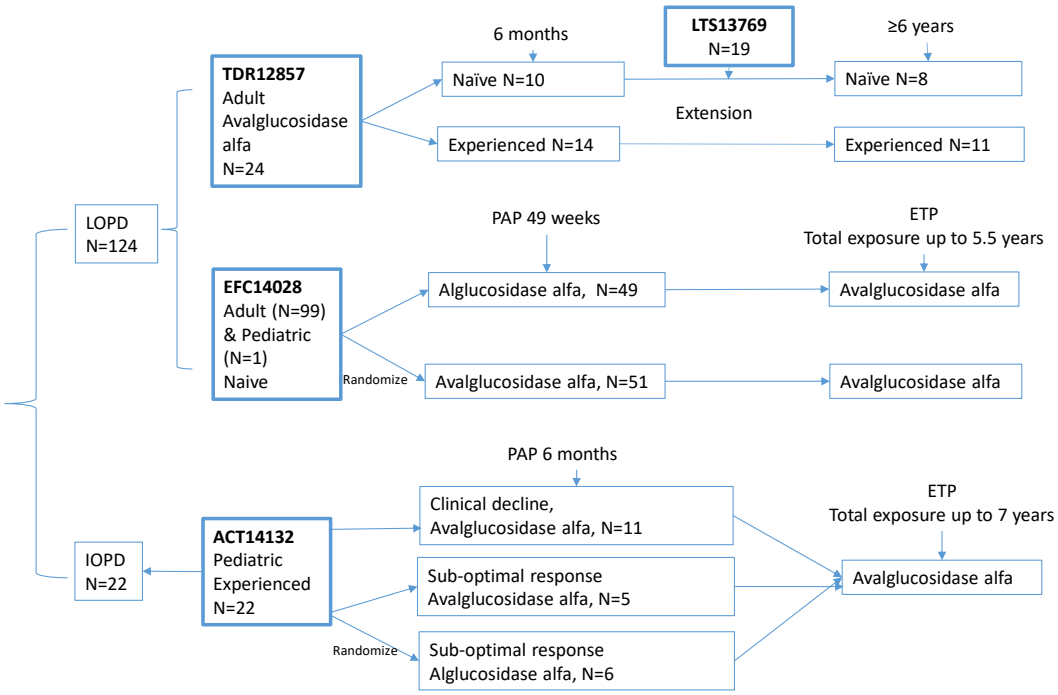
- Study TDR12857 (NEO-1) was a 6-month Phase 1/2, open-label, ascending-dose study (5, 10 or 20 mg/kg qow) of avalglucosidase alfa in both treatment-naïve and previously alglucosidase alfa-treated adult patients with LOPD. Twenty-four patients (10 naïve and 14 experienced) were enrolled and treated.
- Study LTS13769 (NEO-EXT) is an at least 6-year open-label treatment extension study enrolling patients who completed Study TDR12857. Nineteen patients were enrolled and treated, initially the patients continued on TDR12857 doses (5, 10 and 20 mg/kg) and after a period going between weeks 104 and 156, all the patients receiving 5 or 10 mg/kg qow were switched to a dose of 20 mg/kg qow.
- Study EFC14028 (COMET) is a 49-week Phase 3, randomized, double-blind, comparator-controlled study in treatment-naïve patients 3 years of age or older with LOPD. One hundred patients (99 adults and 1 pediatric) were enrolled and treated (51 with avalglucosidase alfa 20 mg/kg qow, 49 with alglucosidase alfa 20 mg/kg qow). After completion of the 1-year primary analysis period (PAP), the patients continue on a long-term extension treatment period (ETP) for up to 5.5 years with all patients receiving avalglucosidase alfa 20 mg/kg qow.

One (1) study was conducted in pediatric patients with IOPD who previously had shown incomplete responses to alglucosidase alfa:

- Study ACT14132 (Mini-COMET) is a 6-month Phase 2, open-label, ascending-dose study (20 and 40 mg/kg qow) of avalglucosidase alfa in patients under 18 years of age with IOPD. Twenty-two patients insufficiently controlled or declining with previous treatment with alglucosidase alfa were enrolled and treated (16 with avalglucosidase alfa 20 or 40 mg/kg qow, 6 with alglucosidase alfa at previous dose). After completion of the 6-month PAP, the patients continue on a long-term ETP for a total exposure of up to 7 years with all patients receiving avalglucosidase alfa in the study.

Study TDR12857 is completed, as well as the PAP of studies, EFC14028 and ACT14132, while ETP of these 3 studies are ongoing (Figure 1).

Figure 1 - Ongoing and completed studies



To fully analyze safety data, the avalglucosidase alfa safety set is used. This includes pooled avalglucosidase alfa safety data from the 4 clinical studies listed up to the individual study's data cut-off date as follows:

- Completed Phase 1/2 LOPD study (TDR12857) and its ongoing open-label extension study (LTS13769), and
- Two (2) studies for which the PAPs has been completed (LOPD Study EFC14028 and IOPD study ACT14132); the open-label extension periods for these 2 studies are ongoing.

As part of the pediatric investigation plan, EFC14462 is scheduled to start in 2021. This is a Phase 3 study to assess the efficacy, safety, pharmacokinetics (PKs) and pharmacodynamics (PDs) of avalglucosidase alfa in IOPD patients less or equal to 6 months of age who have not yet been treated with ERT. This study is to assess avalglucosidase alfa in the most severe phenotype of Pompe disease in neonates and infants who have not been evaluated so far in previous studies. This open-label, single arm study will enroll 16 patients. The highest dose previously evaluated in patients with IOPD (40 mg/kg qow) will be used to treat the most vulnerable patients aged ≤6 months of age with the most profound enzyme deficiency by providing a high amount of recombinant ERT and halt the disease progression as soon as possible for better outcomes. The proposed dose regimen is aligned with the doses evaluated in study ACT14132 and is also based on experience with alglucosidase alfa treatment. In case of safety reason, a dose of 20 mg/kg weekly may be used. In case of insufficient efficacy response, the dose may be increased to 40 mg/kg weekly.

CLINICAL TRIAL EXPOSURE

The avalglucosidase alfa exposure is presented in the tables below (Tables 1 to 10), focusing on the parameters of interest for the RMP.

It should be emphasized that the current exposure data gained from the clinical trials at the cut-off will be substantially extended with the upcoming experience from the ongoing studies (LTS13769, EFC14028, ACT14132).

Among the 146 patients who were enrolled in the clinical studies, 3 patients in alglucosidase alfa arm of ACT14132 study had not entered yet into ETP at data cut-off of 30 September 2019 and 5 patients in alglucosidase alfa arm of EFC14028 study didn't enter ETP due to early discontinuation during PAP. Therefore, 8 patients were not exposed to avalglucosidase alfa reaching a total number of 138 patients exposed to treatment and are included in the avalglucosidase safety set.

- Duration of exposure (Table 8 and Table 9).
- Exposure by age, gender and race:
  - At the cut-off date, the number of elderly patients (≥65 years) is 17 patients (about 12%) among the exposed patients. The number of patients aged ≥75 years is 3 (about 2% of the exposed patients) (see Table 10 and Table 11). The proportion of exposed elderly patients is non-negligible as compared to what is expected in the target population of this rare disease.
  - Patients in the category of ≥18 years to <45 years had the highest total exposure followed by patients in the ≥45 years to <65 years (see Table 10 and Table 11).
  - The number of paediatric patients (aged less than 18 years) is 20 (about 14%) among the exposed patients, including 6 patients aged less than 6 years (see Table 10 and Table 11).
  - Total exposure was higher in males compared with females (Table 10 and Table 11) and was highest in White patients (Table 16 and Table 17).
- Exposure in special populations:
  - Renal impairment: Six (6) patients with mild renal impairment (based on estimated glomerular filtration rate [eGFR] data) have been exposed to avalglucosidase alfa in EFC14028 study.

Table 8 - Duration of exposure (Studies TDR12857/LTS13769, EFC14028, and ACT14132)

Duration of exposure	Patients n (%)	Person time (person-weeks)
<12 weeks	9 (6.5)	37.3
≥12 - <24 weeks	9 (6.5)	133.4
≥24 - <48 weeks	19 (13.8)	642.0
≥48 - <96 weeks	45 (32.6)	3220.9
≥96 - <144 weeks	27 (19.6)	3053.0

Duration of exposure	Patients n (%)	Person time (person-weeks)
≥144 - <192 weeks	12 (8.7)	1936.3
≥192 - <240 weeks	0	
≥240 weeks	17 (12.3)	5280.6
Total	138[a] (100.0)	14 303.4

a Three (3) patients in alglucosidase alfa arm of ACT14132 study had not entered to ETP by data cut-off of 30-Sep-2019 and 5 patients in alglucosidase alfa arm of EFC14028 study didn't enter ETP due to early discontinuation. Therefore, 8 patients were not exposed to avalglucosidase alfa.

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028

Note: Only exposure to avalglucosidase alfa data are included.

Person time is defined as the sum of the treatment exposure of all patients in each category.

PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_t.sas
OUT=REPORT/OUTPUT/dem_ex_durexp_t_i.rtf (24JUL2020 17:05)

ETP: Extension Treatment Period; n: Number.

Table 9 - Duration of exposure and by disease subtype (STUDIES TDR12857/LTS13769, EFC14028, and ACT14132)

	IOPD		LOPD	
Duration of exposure	**Patients n (%)**	**Person time (person-weeks)**	**Patients n (%)**	**Person time (person-weeks)**
<12 weeks	0		9 (7.6)	37.3
≥12 - <24 weeks	3 (15.8)	39.3	6 (5.0)	94.1
≥24 - <48 weeks	5 (26.3)	177.6	14 (11.8)	464.4
≥48 - <96 weeks	8 (42.1)	605.3	37 (31.1)	2615.6
≥96 - <144 weeks	3 (15.8)	298.4	24 (20.2)	2754.6
≥144 - <192 weeks	0		12 (10.1)	1936.3
≥192 - <240 weeks	0		0	
≥240 weeks	0		17 (14.3)	5280.6
Total	19 (100.0)	1120.6	119 (100.0)	13 182.9

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028

IOPD: study ACT14132; LOPD: studies TDR12857/LTS13769 and EFC14028

Note: Only exposure to avalglucosidase alfa data are included.

Person time is defined as the sum of the treatment exposure of all patients in each category.

PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_dis_t.sas
OUT=REPORT/OUTPUT/dem_ex_dur_dis_t_i.rtf (24JUL2020 17:05)

IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; n: Number.

Table 10 - Exposure by age group and gender (Studies TDR12857/LTS13769, EFC14028, and ACT14132)

	Patients n (%)		Person time (person-weeks)	
Age Group	**F**	**M**	**F**	**M**
<6 years	4 (6.3)	2 (2.7)	193.7	54.0

	Patients n (%)		Person time (person-weeks)	
Age Group	**F**	**M**	**F**	**M**
≥6 to <18 years	4 (6.3)	10 (13.5)	157.6	783.6
≥18 to <45 years	30 (46.9)	24 (32.4)	3985.7	2963.1
≥45 to <65 years	18 (28.1)	29 (39.2)	1725.7	2475.7
≥65 to <75 years	7 (10.9)	7 (9.5)	654.9	914.4
≥75 to <85 years	1 (1.6)	2 (2.7)	26.0	369.0
≥85 years	0	0		
Total	64 (100.0)	74 (100.0)	6743.6	7559.9

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028
Note: Only exposure to avalglucosidase alfa data are included.
Person time is defined as the sum of the treatment exposure of all patients in each category.
PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_agegrp_sex_t.sas
OUT=REPORT/OUTPUT/dem_ex_agegrp_sex_t_i.rtf (24JUL2020 17:04).
F: Female; M: Male; n: Number.

Table 11 - Exposure by age group and gender and by disease subtype (STUDIES TDR12857/LTS13769, EFC14028, and ACT14132)

	IOPD				LOPD			
	Patients n (%)		Person time (person-weeks)		Patients n (%)		Person time (person-weeks)	
Age Group	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**
<6 years	4 (50.0)	2 (18.2)	193.7	54.0	0	0		
≥6 to <18 years	4 (50.0)	9 (81.8)	157.6	715.3	0	1 (1.6)		68.3
≥18 to <45 years	0	0			30 (53.6)	24 (38.1)	3985.7	2963.1
≥45 to <65 years	0	0			18 (32.1)	29 (46.0)	1725.7	2475.7
≥65 to <75 years	0	0			7 (12.5)	7 (11.1)	654.9	914.4
≥75 to <85 years	0	0			1 (1.8)	2 (3.2)	26.0	369.0
≥85 years	0	0			0	0		
Total	8 (100.0)	11 (100.0)	351.3	769.3	56 (100.0)	63 (100.0)	6392.3	6790.6

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028
IOPD: study ACT14132; LOPD: studies TDR12857/LTS13769 and EFC14028
Note: Only exposure to avalglucosidase alfa data are included.
Person time is defined as the sum of the treatment exposure of all patients in each category.
PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_agegrp_sex_dis_t.sas
OUT=REPORT/OUTPUT/dem_ex_agegrp_sex_dis_t_i.rtf (24JUL2020 17:03).
F: Female; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; M: Male; n: Number.

Table 12 - Exposure by initial assigned dose (STUDIES TDR12857/LTS13769, EFC14028, and ACT14132)

Initial assigned Dose of exposure	Patients n (%)	Person time (person-weeks)
5 mg/kg qow	8 (5.8)	1988.4
10 mg/kg qow	7 (5.1)	1321.9
20 mg/kg qow	110 (79.7)	10 419.1
40 mg/kg qow	13 (9.4)	574.0
Total	138 (100.0)	14 303.4

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028
Note: Only exposure to avalglucosidase alfa data are included.
Note: Initial assigned dose is used in the table.
Person time is defined as the sum of the treatment exposure of all patients in each category.
PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_t.sas
OUT=REPORT/OUTPUT/dem_ex_ini_dos_t_i.rtf (24JUL2020 17:05)
n: Number; qow: Every Other Week.

Table 13 - Exposure by initial assigned dose and by disease subtype (Studies TDR12857/LTS13769, EFC14028, and ACT14132)

	IOPD		LOPD	
Initial assigned Dose of exposure	Patients n (%)	Person time (person-weeks)	Patients n (%)	Person time (person-weeks)
5 mg/kg qow	0		8 (6.7)	1988.4
10 mg/kg qow	0		7 (5.9)	1321.9
20 mg/kg qow	6 (31.6)	546.6	104 (87.4)	9872.6
40 mg/kg qow	13 (68.4)	574.0	0	
Total	19 (100.0)	1120.6	119 (100.0)	13 182.9

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cutoff dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028
IOPD: study ACT14132; LOPD: studies TDR12857/LTS13769 and EFC14028.
Note: Only exposure to avalglucosidase alfa data are included.
Note: Initial assigned dose is used in the table.
Person time is defined as the sum of the treatment exposure of all patients in each category.
PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_dis_t.sas
OUT=REPORT/OUTPUT/dem_ex_ini_dos_dis_t_i.rtf (24JUL2020 17:05)
IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; n: Number; qow: Every Other Week.

Table 14 - Exposure by last dose (Studies TDR12857/LTS13769, EFC14028, and ACT14132

Last Dose of exposure	Patients n (%)	Person time (person-weeks)
5 mg/kg qow	2 (1.4)	43.6
10 mg/kg qow	3 (2.2)	79.6
20 mg/kg qow	118 (85.5)	13 429.9
40 mg/kg qow	15 (10.9)	750.4

Last Dose of exposure	Patients n (%)	Person time (person-weeks)
Total	138 (100.0)	14 303.4

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028
Note: Only exposure to avalglucosidase alfa data are included.
Person time is defined as the sum of the treatment exposure of all patients in each category.
PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_t.sas
OUT=REPORT/OUTPUT/dem_ex_last_dos_t_i.rtf (24JUL2020 17:05)
n: Number; qow: Every Other Week.

Table 15 - Exposure by last dose and by disease subtype (Studies TDR12857/LTS13769, EFC14028, and ACT14132

	IOPD		LOPD	
Last Dose of exposure	Patients n (%)	Person time (person-weeks)	Patients n (%)	Person time (person-weeks)
5 mg/kg qow	0		2 (1.7)	43.6
10 mg/kg qow	0		3 (2.5)	79.6
20 mg/kg qow	4 (21.1)	370.1	114 (95.8)	13 059.7
40 mg/kg qow	15 (78.9)	750.4	0	
Total	19 (100.0)	1120.6	119 (100.0)	13 182.9

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cutoff dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028
IOPD: study ACT14132; LOPD: studies TDR12857/LTS13769 and EFC14028.
Note: Only exposure to avalglucosidase alfa data are included.
Person time is defined as the sum of the treatment exposure of all patients in each category.
PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_dis_t.sas
OUT=REPORT/OUTPUT/dem_ex_last_dos_dis_t_i.rtf (24JUL2020 17:05)
IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; n: Number; qow: Every Other Week.

Table 16 - Exposure by race (Studies TDR12857/LTS13769, EFC14028, and ACT14132)

Race	Patients n (%)	Person time (person-weeks)
American Indian or Alaska Native	0	
Asian	11 (8.0)	776.3
Black or African American	3 (2.2)	530.0
Native Hawaiian or other Pacific Island	0	
White	122 (88.4)	12 943.1
Multiple-White/Black or African American	1 (0.7)	28.0
Not reported	1 (0.7)	26.0
Total	138 (100.0)	14 303.4

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cutoff dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028
Note: Only exposure to avalglucosidase alfa data are included.
Person time is defined as the sum of the treatment exposure of all patients in each category.
PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_t.sas
OUT=REPORT/OUTPUT/dem_ex_race_t_i.rtf (24JUL2020 17:05)

n: Number.

Table 17 - Exposure by Race and by Disease Subtype (Studies TDR12857/LTS13769, EFC14028, and ACT14132)

	IOPD		LOPD	
Race	**Patients n (%)**	**Person time (person-weeks)**	**Patients n (%)**	**Person time (person-weeks)**
American Indian or Alaska Native	0		0	
Asian	8 (42.1)	550.0	3 (2.5)	226.3
Black or African American	0		3 (2.5)	530.0
Native Hawaiian or other Pacific Island	0		0	
White	11 (57.9)	570.6	111 (93.3)	12 372.6
Multiple-White/Black or African American	0		1 (0.8)	28.0
Not reported	0		1 (0.8)	26.0
Total	19 (100.0)	1120.6	119 (100.0)	13 182.9

Note: TDR12857 is completed. For the other 3 on-going studies, only data up to cut-off dates will be included: 30-Sep-2019 for ACT14132; 27-Feb-2020 for LTS13769 and 19-Mar-2020 for EFC14028

IOPD: study ACT14132; LOPD: studies TDR12857/LTS13769 and EFC14028.

Note: Only exposure to avalglucosidase alfa data are included.

Person time is defined as the sum of the treatment exposure of all patients in each category.

PGM=PRODOPS/GZ402666/PERIODIC_SAFETY/RMP_2020/REPORT/PGM/dem_ex_dur_dos_race_dis_t.sas OUT=REPORT/OUTPUT/dem_ex_race_dis_t_i.rtf (24JUL2020 17:04)

IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; n: Number.

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

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

The main exclusion criteria from the pivotal clinical studies, which have been conducted in the target population, are summarized in the Table 18 below:

Table 18 - 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
Clinically significant organic disease (with the exception of symptoms relating to Pompe disease), including clinically significant cardiovascular, hepatobiliary, pulmonary, neurologic, or renal disease, or other medical condition, serious intercurrent illness, or extenuating circumstance that, in the opinion of the Investigator, precludes participation in the study or potentially decreases survival.	These exclusion criteria were considered due to methodological considerations, to prevent any potential direct or indirect impact on study conduction or in efficacy or safety analyses.	No	This criterion is not a contraindication. It does not imply an increased risk or a different safety profile.
Persistent high antibody titer of alglucosidase alfa.	The safety profile of avalglucosidase alfa was unknown at initiation of study TDR12857 (adults with LOPD) and ACT14132 (children with IOPD), and there was a potential risk in patients with persistent high antibody titer of alglucosidase alfa for important allergic reaction to avalglucosidase alfa. Inclusion of patients with persistent high anti-drug antibody (ADA) titers would have confounded this analysis and assessment of the safety profile of avalglucosidase alfa. It was therefore an exclusion criterion in these studies.	No	No impact of anti-alglucosidase alfa antibodies was observed in studies TDR12857/LTS13769 and in study ACT14132. High titer of anti-alglucosidase alfa antibodies was not a limitation to switching to avalglucosidase alfa in studies EFC14028 and ACT14132. No unforeseen safety signal was reported after switching.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patient with LOPD <3 years of age or with known Pompe specific cardiac hypertrophy.	These criteria may be confounding factors making the difference with IOPD uncertain.	No	This criterion is not a contraindication. Patients with IOPD <3 years of age are included in study ACT14132.
Patient with LOPD wheelchair dependent or not able to ambulate 40 meters without stopping and without an assistive device.	These criteria are confounding factors in the evaluation of the main secondary endpoint 6-Minute Walk Test (6MWT).	No	This criterion is not a contraindication. It does not imply an increased risk or a different safety profile.
Patient with LOPD requiring invasive-ventilation not able to successfully perform repeated Forced Vital Capacity (FVC) measurements in upright position of ≥30% predicted and ≤85% predicted.	These criteria are confounding factors in the evaluation of the primary endpoint FVC.	No	This criterion is not a contraindication. It does not imply an increased risk or a different safety profile.
Patient with LOPD with prior or current use of immune tolerance induction therapy.	This criterion is confounding factor in the evaluation of the safety (immunogenicity and hypersensitivity reactions).	No	This criterion is not a contraindication. It does not imply an increased risk or a different safety profile.
Women of childbearing potential with no effective contraceptive method. Pregnancy, lactation.	These exclusion criteria were considered due to methodological considerations, to prevent any potential direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development in the absence of information on the use of avalglucosidase alfa during pregnancy or lactation in humans.	Yes	Not applicable

6MWT: 6-Minute Walk Test; ADA: Anti-Drug Antibody; FVC: Forced Vital Capacity; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe disease.

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

The clinical development programme is unlikely to detect certain types of adverse reactions (ARs) such as rare or very rare ARs, ARs with a long latency, ARs caused by prolonged or cumulative exposure.

Ability to detect adverse reactions	Limitation of trial programme	Discussions of implications for target population
Which are common	One hundred thirty-eight (138) patients being treated with avalglucosidase alfa via clinical trials. At the DLP, 138 patients have been exposed to avalglucosidase alfa.	Pompe disease is a rare disease with an estimated incidence of 1:40 000. The adverse drug reactions (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	Some studies are designed with long-term exposure: 6 years of exposure are available in TDR12857/ LTS13769, up to 3 years 4 months in the EFC14028 trial and up to 2 years in the ACT14132 trial.	To date, no different profile is observed in these populations with prolonged exposure.
Due to cumulative effects	Pharmacokinetic data show no accumulation at any dose.	Not applicable
Which have a long latency	Malignancies have often long latency.	Routine postmarketing surveillance may provide insight into these theoretical effects.

ADR: Adverse Drug Reaction; DLP: Data Lock Point.

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

Table 19 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. In LTS13769, there were 2 patient pregnancies and one partner who had 2 pregnancies (one spontaneous abortion and one full term pregnancy) for a total of 3 patients and 4 pregnancies. In EFC14028, there were 1 ectopic pregnancy in PAP and 2 partner pregnancies in ETP. Both pregnancies resulted in healthy babies.
Breastfeeding women	The mothers did not receive the treatment during breast-feeding period. Use in pregnant and lactating women is considered as missing information for avalglucosidase alfa.
Patients with relevant comorbidities: • Patients with hepatic impairment	Not included in the clinical development program.
• Patients with renal impairment	Six (6) patients with mild renal impairment (based on eGFR data) have been exposed to avalglucosidase alfa in EFC14028 study. No impact on the safety profile has been identified for these patients. No dose adjustment is required in patients with mild renal impairment.

Type of special population	Exposure
Populations with relevant different ethnic origin	Not relevant
Subpopulations carrying known and relevant genetic polymorphisms	Not relevant
Other:	
• Elderly patients	A substantial proportion of elderly patients (17 patients over 65 of age) have been exposed to avalglucosidase alfa (about 12% of the exposed patients at the cut-off date) The safety profile observed in these patients is consistent with the knowledge of avalglucosidase alfa safety profile, and consistent with the age group. There is no recommended dose adjustment for patients over the age of 65 years.
• Children below 6 months of age	No patient below 6 months of age have been exposed to avalglucosidase alfa. The study EFC14462 planned to start in 2021 will include treatment-naive patients less or equal to 6 months of age with IOPD.

eGFR: Estimated Glomerular Filtration Rate; ETP: Extension Treatment Period; IOPD: Infantile-Onset Pompe disease; PAP: Primary Analysis Period.

Very limited data are available concerning the use of avalglucosidase alfa in pregnant or breast-feeding women. The use of avalglucosidase alfa in pregnant and lactating women is considered as missing information.

Based on experience with alglucosidase alfa, it is not anticipated that exposure will affect hepatic, renal impaired patients differently.

To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by avalglucosidase alfa.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

Because this is the initial submission of the RMP for avalglucosidase alfa and the drug is not yet registered in any market worldwide, this module is “Not applicable”.

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

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The properties of avalglucosidase alfa do not indicate a potential for misuse for illegal purposes.

Based on the data from non-clinical and clinical studies conducted to date, as well as an evaluation of the mechanism of action of avalglucosidase alfa, there is no evidence of central nervous system (CNS) activity or signs associated with drugs of abuse for avalglucosidase alfa.

A drug abuse liability assessment (DALA) study was not performed with avalglucosidase alfa as the compound has no or only a limited ability to cross the blood-brain barrier (BBB) with negligible exposure in the brain, and has shown no propensity for eliciting any neurological effects in toxicology studies. Potential for misuse of avalglucosidase 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.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

The safety risk profile is evidenced based on the in-depth review of the clinical program. The MAH has benefited from the large clinical experience with alglucosidase alfa for which class effects have been evaluated. The specificity of chemical structure of avalglucosidase was evaluated as well (see below). The conclusion of this evaluation is that the MAH does not consider that "Hepatic and/or renal toxicity" is relevant for inclusion in the RMP. (see Section SVII.1.1).

Following the evaluation of the RMP v1.0 and RMP v1.1 made by the CHMP and PRAC (procedure EMEA/H/C/005501), the safety topics listed below have been considered important for inclusion in the list of safety concerns (LSCs) in the updated RMP version 1.2. They are discussed in Section SVII.1.2.

- Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE.
- Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies).
- Medication error in home infusion setting.
- Immune complex related reactions.
- Use in pregnant and lactating women.
- Use in patients with renal or hepatic insufficiency.

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

Reason(s) for not including an identified or potential risk in the LSCs in the RMP

- Risk linked to the specificity of chemical structure of avalglucosidase: hepatic and/or renal toxicity:
  - The review of literature, non-clinical and clinical data did not support the possibility of a risk of hepatic and/or renal toxicity from the breakdown of the synthetic linker as described below:

  A theoretical target-liability assessment was performed very early in the development of avalglucosidase alfa. A key functional group in the linker between alglucosidase alfa and the hexamannose glycan of avalglucosidase alfa is an oxime (O-N=C). The published literature provides inconclusive evidence that some oximes may cause kidney and/or liver toxicity. More recently, a detailed risk assessment was performed to clarify the potential of avalglucosidase alfa to induce renal and hepatic toxicity related to the oxime moiety.

  Articles on oxime-induced nephrotoxicity are few. Oximes are best known for their role as antidotes for organophosphate (OP) insecticide and nerve agent poisoning. In 1 review article, pralidoxime (2-PAM) was reported to produce nephrotoxicity, although no details were provided. (28) Conflicting reports have been described for oxime-induced

hepatotoxicity in humans and animals. (29)(30) Many reports involve patients and animals that have been exposed to OPs and treated with various antidotes, including atropine and oximes. Organophosphate poisoning alone has been shown to affect the liver and kidney, (31) thereby complicating conclusions on oxime-induced renal and hepatic toxicity.

Nonclinical and clinical studies conducted with avalglucosidase alfa did not support the hypothesis that oximes may cause kidney and/or liver toxicity. There was no evidence of renal toxicity in any nonclinical species. While one exploratory (non-good laboratory practices [GLPs]) 14-day repeat-dose toxicity study of avalglucosidase alfa in mice showed effects in the liver (minimal multifocal necrosis and minimal to mild inflammatory infiltrates), similar findings were not observed in subsequent studies of longer duration and higher doses in either mice or monkeys. As such, the relationship of the hepatic findings to avalglucosidase alfa in the 14-day exploratory study is unlikely.

In clinical studies TDR12857/LTS13769, ACT14132 and EFC14028 no events related to avalglucosidase alfa in the Hepatobiliary disorders, Renal and urinary disorders and the Investigations system organ class (SOC) were identified that suggested a relationship.

In conclusion, the weight-of-evidence does not support a risk of renal or hepatic toxicity from avalglucosidase alfa. As such, it has not been considered as an important risk for inclusion in the RMP.

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

Table 20 - Important identified risk considered for inclusion in the list of safety concerns: 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	
Scientific evidence that has led to the inclusion	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open-label, dose-escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double-blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies is completed. The ETP for these two studies are ongoing. Infusion associated reactions were observed in all 4 clinical studies. Anaphylaxis, a severe potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergen was observed in 2 (1.4%) patients in the avalglucosidase alfa program. As described, the level of data and evidence is sufficient to demonstrate that avalglucosidase alfa can be associated with “IARs including hypersensitivity and anaphylactic reactions”. This is a known risk associated with ERTs. The safety profile of avalglucosidase alfa is consistent with that of alglucosidase and possibly more favorable in the treatment of adult and pediatric patients with Pompe disease (LOPD and IOPD). Infusion associated reactions including hypersensitivity have been reported in avalglucosidase clinical trials. It was deemed that the data was sufficient to include as an identified risk. Considering the possible impact of this event on the benefit-risk balance, and the fact that this risk is planned to be mitigated notably through the labeling, the MAH has proposed to include it as an important identified risk in LSCs.
Risk-benefit impact	Infusion associated reactions are a known risk with ERTs. This risk is managed routinely by the prescribing physicians that are experienced in the risk and management of IARs. The

Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	
	impact of IARs on the benefit-risk balance is considered manageable based on the anticipated experience of this specialized HCP community.

ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; LSC: List of Safety Concern; MAH: Marketing Aurhorization Holder; PAP: Primary Analysis Period; PK: Pharmacokinetic.

Table 21 - Important potential risk considered for inclusion in the list of safety concerns: Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)

Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)	
Scientific evidence that has led to the inclusion	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open label, dose escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies is completed. The ETP for these two studies is ongoing. A small number of patients developed ADA peak titers ≥51 200 in the avalglucosidase alfa studies. Of the 61 treatment-naïve patients, there were 4 patients (3 in EFC14028 and 1 in TDR12857/ LTS13769) with ADA titers ≥51 200.
Risk-benefit impact	Immunogenicity is a known risk with therapeutic proteins. The formation of antibodies has been reported with all enzyme replacement therapies. The majority (95.1%) of treatment-naive patients with LOPD became ADA-positive which was anticipated given the clinical experience with alglucosidase alfa and common aspects including identical protein sequence, posology and patient disease factors. Previous exposure to alglucosidase alfa in patients with LOPD and IOPD appeared to provide a degree of attenuation of immunologic response possibly due to development of some immunologic tolerance given the shared protein sequence. Anti-drug antibodies did not impact measures of efficacy while limited impact on PK and PD was observed primarily with high titer patients. Thus far there has been no correlation between antibodies and clinical decline in the clinical trials of avalglucosidase alfa, therefore the impact on the benefit-risk balance is limited. As described, avalglucosidase alfa antibodies were identified in all clinical studies, as expected with ERTs. The antibody formation has been reported with ERTs. For avalglucosidase alfa, no association has been established between antibody formation and loss of clinical response. Considering this lack of current association between antibody formation and loss of response, the MAH has proposed to include “Immunogenicity leading to loss of response (high sustained IgG Antibody Titers and/or neutralizing antibodies” as an important potential risk in the RMP LSCs. The MAH has planned to further characterize this important potential risk through the pharmacovigilance plan.

ADA: Anti-Drug Antibody; ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; LSC: List of Safety Concern; MAH: Marketing Authorization Holder; PAP: Primary Analysis Period; PD: Pharmacodynamic; PK: Pharmacokinetic; RMP: Risk Management Plan.

Table 22 - Important potential risk considered for inclusion in the list of safety concerns: Medication error in home infusion setting

Medication error in home infusion setting	
Scientific evidence that has led to the inclusion	It is expected and understood that the HCP administering avalglucosidase alfa in the home setting are experienced in the management of the Pompe disease, as well as in the management of other ERTs. As of 31-May-2021, 15 patients have ever received home infusion in trials (LTS13769 [N = 2], EFC14028 [N = 11] and ACT14132 [N = 2]). Safety events occurred in 4 patients. One EFC14028 patient receiving avalglucosidase alfa in the home setting experienced an IAR. A [redacted] patient who began treatment with avalglucosidase alfa in Mar-2019, started to receive home infusions in Apr-2020 (first home infusion given at Week 59 in the open-label period). During the first home infusion and two hours after infusion start, the patient had eyelid edema and flushing. Both events were assessed as a non-serious adverse event of special interest (AESI) and IAR of mild intensity. Therapy with avalglucosidase alfa was interrupted and the patient received methylprednisolone and dexchlorpheniramine as corrective treatments. The patient recovered from both events the same day. After this dose interruption the patient returned to the study site to receive infusions and was monitored for any recurring IARs before resuming home infusions again with no recurrence of IARs. Six unrelated non-serious adverse events (AEs) in 2 other patients in EFC14028 and 1 unrelated non-serious AE in 1 patient in LTS13769 were reported. No medication error occurred in the setting of home infusion. In the "Home infusion report" provided by the [redacted] where Myozyme is routinely administered in 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. 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-benefit impact	The benefit of avalglucosidase alfa outweighs this potential risk.

AE: Adverse Event; AESI: Adverse Event of Special Interest; [redacted] ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; MAH: Marketing Authorization Holder; RMP: Risk Management Plan.

Table 23 - Important potential risk considered for inclusion in the list of safety concerns: Immune complex related reactions

Immune complex related reactions	
Scientific evidence that has led to the inclusion	Evidence of immune complexes was not observed in any tissue or organ in mice or monkeys. As for other ERTs, due to the biological mechanism of immune complex mediated reactions, this risk cannot be totally ruled out. Neither cases of potential immune-mediated reactions were identified in patients during the clinical studies, nor cases contained events consistent with immune mediated reactions. Considering this lack of cases and the biological plausibility, the MAH has proposed to include "Immune complex related reactions" as an important potential risk in the RMP.
Risk-benefit impact	The benefit of avalglucosidase alfa outweighs the potential risk of "Immune complex related reactions".

Immune complex related reactions

ERT: Enzyme Replacement Therapy; MAH: Marketing Authorization Holder; RMP: Risk Management Plan.

Table 24 - Missing information considered for inclusion in the list of safety concerns: Use in pregnant and lactating women

Use in pregnant and lactating women	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Pregnant or breast-feeding women were excluded from the clinical trials. In an embryo fetal toxicity study in pregnant mice, maternal mortality related to hypersensitivity was observed at 50 mg/kg/day. Increased post-implantation loss and mean number of late resorptions were also observed at 50 mg/kg/day. avalglucosidase alfa is not transported from the maternal to the fetal circulation in mice, suggesting that the findings were related to maternal toxicity from the immunologic response. The developmental NOAEL was 20 mg/kg/day IV (AUC_{0-24} = 582 µg•h/mL on GD6). Similar findings were not observed in pregnant rabbits up to 100 mg/kg/day IV, the highest dose administered (AUC_{0-24} = 7910 µg•h/mL on GD19). From [Part II SII], there was no animal data regarding transfer in maternal milk. In EFC14028, there was one patient and 2 partner pregnancies. In TDR12857/ LTS13769, there were 2 patient pregnancies and one partner who had 2 pregnancies (one spontaneous abortion and one full-term pregnancy) for a total of 3 patients and 4 pregnancies.
Risk-benefit impact	Caution in exposing this sub-population as defined in the labeling. (see section 4.6 Fertility, pregnancy and lactation of SmPC)

AUC: Area Under the Curve; GD: Gestation Day; IV: Intravenous; NOAEL: No Observed Adverse Effect Level; SmPC: Summary of Product Characteristics.

Table 25 - Missing information considered for inclusion in the list of safety concerns: Use in patients with renal or hepatic insufficiency

Use in patients with renal or hepatic insufficiency	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	As part of the avalglucosidase alfa clinical program, on the basis of a population PK analysis conducted in 75 LOPD patients including 6 patients with mild renal impairment (glomerular filtration rate: 60 to 89 mL/min at baseline), renal function was not identified as a covariate potentially influencing avalglucosidase alfa PK. No relevant effect of impaired renal function on avalglucosidase alfa exposure was observed in these patients with mild renal impairment and no impact on the safety profile was identified. The safety and efficacy of avalglucosidase alfa in patients with hepatic impairment have not been evaluated in the clinical program. However, population PK analysis did not identify bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) as significant covariates influencing avalglucosidase alfa PK. No meaningful difference in exposure was observed for any of the 3 parameters after 20 mg/kg qow administration.
Risk-benefit impact	No dose adjustment is required in patients with mild renal impairment. No specific dose regimen is recommended for patients with hepatic insufficiency.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LOPD: Late-Onset Pompe Disease; PK: Pharmacokinetic; qow: Every Other Week.

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

Following the evaluation of the RMP v1.1 made by the CHMP and PRAC (procedure EMEA/H/C/005501), the additional safety topic listed below have been considered important for inclusion in the LSCs in this updated RMP version 1.2:

- Use in patients with renal or hepatic insufficiency.

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

The following risks have been identified for avalglucosidase alfa:

- Important identified risk:
  - Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies.
- Important potential risks:
  - Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies).
  - Medication error in home infusion setting.
  - Immune complex related reactions.
- Missing information:
  - Use in pregnant and lactating women.
  - Use in patients with renal or hepatic insufficiency.

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

Table 26 - Important identified risk: Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies

Important identified risk	**Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies**
Potential mechanism	Avalglucosidase alfa is a biological medicinal product produced in a CHO production system. Potential mechanisms for IARs including hypersensitivity/anaphylactic reactions include: IgE mediated, IgG mediated with complement activation.
Evidence source(s) and strength of evidence	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open-label, dose-escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double-blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies are completed. The ETP for these two studies is ongoing.

Important identified risk	**Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies**
	Infusion associated reactions were observed in all 4 clinical studies. Anaphylaxis, a severe potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergen was observed in 2 (1.4%) patients in the avalglucosidase alfa program. As described, the level of data and evidence is sufficient to demonstrate that avalglucosidase alfa can be associated with "IARs including hypersensitivity and anaphylactic reactions". This is a known risk associated with ERTs. The safety profile of avalglucosidase alfa is consistent with that of alglucosidase and possibly more favorable in the treatment of adult and pediatric patients with Pompe disease (LOPD and IOPD). Infusion associated reactions including hypersensitivity have been reported in avalglucosidase clinical trials. It was deemed that the data was sufficient to include as an identified risk. Considering the possible impact of this event on the benefit-risk balance, and the fact that this risk is planned to be mitigated notably through the labeling, the MAH has proposed to include it as an important identified risk in LSCs.
Characterization of the risk	In the protocols, IARs are defined as AESIs that occur during either the infusion or the observation period following the infusion which are deemed to be related or possibly related to the investigational medicinal product. At the discretion of the Investigator, AEs occurring after completion of the post-infusion observation period that are assessed as related may also be considered IARs. **Frequency with 95% confidence interval (CI):** Infusion associated reactions include hypersensitivity and anaphylactic reactions. <u>TDR12857/LTS13769</u> A total of 6/24 patients (25.0%) reported protocol defined IARs (40 events). Events occurring in 2 patients were: dizziness, nausea, erythema and rash Two patients developed anaphylaxis, one patient in TDR12857 and one patient in LTS13769. <u>ACT14132</u> Four patients reported protocol defined IARs during the PAP. Three patients had rash (1 patient in Cohort 2, 1 patient on avalglucosidase alfa in Cohort 3, and 1 patient on alglucosidase alfa in Cohort 3), 1 patient in Cohort 2 had urticaria and 1 patient on alglucosidase alfa in Cohort 3 had pruritus. All were mild; none of the protocol defined IARs were serious adverse events (SAEs) or led to treatment discontinuation. The distribution of patients with protocol defined IARs was nearly equal, with 1 patient ± 1 patient having IARs in each cohort or treatment arm. The percentage of patients with IARs during the 25-week PAP was highest in the 2 avalglucosidase alfa 40 mg/kg treatment groups (40.0% in Cohort 2 and 20% in the Cohort 3 avalglucosidase alfa arm) and lowest in the avalglucosidase alfa 20 mg/kg treatment group (none in Cohort 1); however, the apparent differences were not considered to be dose related (due to the difference in results between Cohort 2 and the Cohort 3 avalglucosidase alfa arm, which had the same exposure) or treatment related (due to the similarity in results between the treatment arms in Cohort 3). <u>EFC14028, COMET study</u> In the PAP, fewer patients in the avalglucosidase alfa group reported at least 1 protocol-defined IAR (13 [25.5%]) in comparison to the alglucosidase alfa group (16 [32.7%]). The most frequently reported protocol defined IARs by preferred term (PT) (>2 patients) in the avalglucosidase alfa group were pruritus (7.8%) and urticaria (5.9%) and in the alglucosidase alfa group were nausea (8.2%), pruritus (8.2%) and flushing (6.1%). The majority of protocol defined IARs reported in patients were of mild severity (7 [13.7%] patients in the avalglucosidase alfa group and 10 [20.4%] patients in the alglucosidase alfa group). There were no severe IARs in the avalglucosidase alfa group.

Important identified risk	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	Severe protocol defined IARs were reported in 2 patients in the alglucosidase alfa group (dizziness, visual impairment, hypotension, dyspnea, cold sweat and chills). The majority of IARs resolved. Only 2 IARs were reported as not resolved (abdominal distension in 1 patient and hyperhidrosis in 1 patient), both in the alglucosidase alfa group. Pooled data A total of 42/138 (30.4%) patients reported one or more IARs. The proportion of patients reporting IARs was similar across the 4 patient populations (range: 25.0% [5 pediatric patients] to 31.4% [37 adult patients]). The most frequently reported IAR for all patients was pruritis (13 patients [9.4%]) followed by rash (10 patients [7.2%]) and urticaria and headache (8 patients [5.8%] each). The severe IARs considered related to avalglucosidase alfa, include, chest discomfort, nausea and increase in blood pressure. Anaphylaxis occurred in 2 patients at the time of DLP. **Severity and nature of risk:** Serious and severe hypersensitivity reactions, including anaphylactic reactions have been observed in patients during or after infusion of avalglucosidase alfa. There were no life-threatening reports of anaphylaxis in avalglucosidase alfa. Anaphylaxis is a severe and potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergy causing substance. It may manifests with numerous signs and symptoms and often involves more than one organ system. Across the 4 clinical trials for alglucosidase alfa, 8 patients met the broad and narrow combined standardized medical dictionary for regulatory activities (MedDRA) query (SMQ) for anaphylactic reaction. A review of these cases and their associated reported terms was undertaken to determine whether they fulfilled the criteria for anaphylaxis. The criteria used in this assessment included the Sampson classification of anaphylaxis (Annals of Emergency Medicine vol. 47, No 4, Apr-2006), the severity/seriousness of the reported events and the action taken. Utilizing the above criteria only 2 case were determined to meet the clinical requirements for anaphylaxis in the TDR12857/LTS13769 study. Recurrent reactions (IARs) consisting of flu-like illness or a combination of signs and symptoms such as fever, chills, myalgia, arthralgia, pain, or fatigue occurring post-infusion from a few hours to 2 days following the infusion and persisting for a few days, have also been observed in some patients treated with avalglucosidase alfa. The majority of patients were successfully re-challenged using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and have continued to receive treatment under close clinical supervision. **Seriousness/outcomes:** Five patients experienced serious IARs. The terms included chills, fever, respiratory distress and chest discomfort, nausea, dyspnea, headache, skin discoloration, blood pressure increased, body temperature increased, heart rate increased and oxygen Saturation decreased. **Background incidence/prevalence:** Aranda et al note that IARs in patients receiving ERTs for lysosomal storage disorders are well recognized, with mild reactions reported in 15%-50% of patients, and severe or anaphylactic reactions in 0.2%-7.7% of patients. (32) Chen et al, in a systematic review of ERT for IOPD, reported over 50% (533/1000) with infusion related events. (33)

Important identified risk	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	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: 4 patients in EFC14028: 2 in alglucosidase alfa arm (dizziness, visual impairment, hypotension, dyspnea, cold sweat and chills) and 2 in avalglucosidase alfa arm (2 events of Nausea and 1 event of Blood pressure increased). In the TDR12857/LTS13769 study 1 patient had severe protocol defined IAR (Chest discomfort). In some cases of anaphylactic reaction, epinephrine was administered. The majority of patients continued to receive treatment with avalglucosidase alfa, under close clinical supervision.
Risk factors and risk groups	Pompe disease is classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. These phenotypes range from a rapidly progressive infantile-onset form to a more slowly progressive late-onset form, with considerable variability and overlap between these 2 extremes. Infantile-onset Pompe disease presents in the first months of life and is characterized by severe cardiomyopathy, hypotonia, respiratory failure, and without treatment, leads to death within the first year. Patients with advanced Pompe disease or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their undergoing co-morbidity during infusions. In the EFC14028 study, the frequency of IARs and hypersensitivity in patients increased with higher ADA titers (≥12 800). Additionally, IgE ADA positive patients are at increased risk of developing anaphylactic reactions upon re-administering the drug.
Preventability	Recommendations regarding administration, pre-treatment, corrective actions and treatments to be conducted in case of IARs are described in SmPC sections 4.2 and 4.4.
Impact on the benefit-risk balance of the product	Infusion associated reactions are a known risk with enzyme replacement therapies. This risk is well managed by the prescribing physician who are experienced in the risk and management of IARs. Thus, the impact of IARs on the benefit-risk balance is somewhat mitigated by the knowledge base of the HCP community and by appropriate information in the SmPC.
Public health impact	Infusion associated reactions are known risks whose management is well understood by prescribing physicians.

ADA: Anti-Drug Antibody; AE: Adverse Event; AESI: Adverse Event of Special Interest; CHO; Chinese Hamster Ovary; CI: Confidence Interval; DLP: Data Lock Point; ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; LSC: List of Safety Concern; MAH: Marketing Authorization Holder; MedDRA: Medical Dictionary for Regulatory Activities; PAP: Primary Analysis Period; PK: Pharmacokinetic; PT: Preferred Term; SAE: Serious Adverse Event; SmPC: Summary of Product Characteristics; SMQ: Standardized MedDRA Query.

Table 27 - Important potential risk: Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)

Important potential risk	Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)
Potential mechanism	In Pompe disease, the acid alpha glucosidase mutation effects the enzyme protein expressed in patients which is usually measured by the amount of residual enzyme activity. Differences in the enzyme structure between the abnormal endogenous enzyme the patient produces and the fully human sequence of avalglucosidase alfa could be immunologically recognized as

Important potential risk	Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)
	novel, resulting in development of ADA to these areas. The magnitude of the ADA response with respect to ADA titers, development of neutralizing antibodies and duration of the ADA response is influenced by the enzyme produced by each patient. At the extreme, patients who have pathogenic mutations resulting in no to very little enzyme produced develop high ADA titers that are sustained. This occurs less frequently in LOPD patients as they produce some endogenous enzyme. In addition, ADA that developed in patients receiving ERT with alglucosidase alfa could also bind to avalglucosidase alfa since both drugs share the same protein sequence. The development of high and sustained antibody titers (HSAT) have been shown in alglucosidase alfa treated patients to have poor outcome. HSAT were defined as titers ≥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 titers. Cross-reactive immunologic material (CRIM)-negative IOPD patients are at risk for developing HSAT and neutralizing antibodies with documented loss of clinical response.
Evidence source(s) and strength of evidence	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open label, dose escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies is completed. The ETP for these two studies is ongoing. A small number of patients developed ADA peak titers ≥51 200 in the avalglucosidase alfa studies. Of the 61 treatment-naive patients, there were 4 patients (3 in EFC14028 and 1 in TDR12857/ LTS13769) with ADA titers ≥51 200.
Characterization of the risk	**Frequency with 95% CI:** Only a small number of avalglucosidase alfa treatment-naïve patients (4 of 61 patients) developed ADA titers ≥51 200. <u>TDR12857 Phase 1/2 avalglucosidase alfa study</u> Treatment-naive: Nine (9) of 10 patients developed treatment induced avalglucosidase alfa antibodies with a median peak titer of 1600 (range: 200-25 600) in the Phase 1/2 study with only 1 patient developing ADA ≥12 800. Treatment-experienced: Six (6) of 14 patients developed treatment emergent ADA, with 4 patients that were ADA-negative at study entry developed treatment induced ADA and 2 patients made a boosted response. ADA titers ranged from 100-12 800 with only 1 patient developing ADA titer of 12 800. Across both groups, no patient tested positive for inhibition of enzyme activity while one (treatment-naive) patient tested positive for inhibition of enzyme uptake. <u>TDR12857/LTS13769</u> No additional patient developed ADA to alglucosidase alfa after entry in the extension study. Only 1 patient developed ADA titers ≥51 200 and neutralizing antibody (NAb) that inhibited cellular uptake. This patient's titers decreased over time. <u>ACT14132</u> Of 18 treatment experienced patients who received avalglucosidase alfa, 5 patients developed treatment emergent avalglucosidase alfa ADA (titer range 100-6400) and 1 patient developed treatment induced ADA in the study extension with a titer of 100. Overall, no patients developed neutralizing antibodies to avalglucosidase alfa.

Important potential risk	Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)
	EFC14028 Among the treatment naïve patients, 49 of 51 patients (96.1%) developed antibodies to avalglucosidase alfa. The median peak titer was 3 200 and 12 patients had a peak titer of ≥12 800, of which 3 patients were ≥51 200. There were 14 patients (27.5%) that inhibited enzyme activity, majority being transient, and 18 patients (35.3%) who inhibited cellular uptake. Among the 44 treatment-experienced patients, 5 patients developed treatment induced ADA with titers ranging from 100-800. Neutralizing antibody that inhibited activity was sporadic and transient in nature therefore not suggestive of being clinically meaningful. Presence of NAb that inhibits cellular uptake was intermittent over time and no pattern was observed based on ADA titers. **Severity and nature of risk:** The incidence of developing avalglucosidase alfa ADA titers ≥51 200 is low. **Seriousness/outcomes:** There were no reports of loss of response in any of the clinical trials. **Background incidence/prevalence:** In 2017 systematic review of ERT for IOPD, 89% (16/18) reportedly developed IgG antibodies to alglucosidase alfa and 6% (1/18) developed inhibitory antibodies at the initial phase of treatment. (33) The estimates are comparable with the incidence of over 90% of clinical immunogenicity reported in an assessment of therapeutic proteins. (34) Most patients with LOPD (63% to 100%) receiving alglucosidase alfa develop ADA titers at varying levels, with titers typically peaking within 12 to 26 weeks before stabilizing or declining. Clinical experience in IOPD patients with alglucosidase alfa ERT showed most patients (85% to 100%) receiving alglucosidase alfa develop ADAs. **Impact on individual patient:** To date there were no reports of loss of response in any of the avalglucosidase alfa clinical trials.
Risk factors and risk groups	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 titers, as well as NAb when treated with alglucosidase alfa, which contribute to poor clinical outcomes. A retrospective analysis by a lead Investigator of 32 IOPD patients receiving alglucosidase alfa showed median titers in CRIM-negative patients of 51 200 at 24 weeks and 153 600 at 52 weeks whereas median titers in CRIM-positive patients were 600 at 24 weeks and 200 at 52 weeks. 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 titers which then decrease over time. The effects of antibody development on the long-term safety and efficacy of avalglucosidase alfa continue under investigation in longer term studies.
Preventability	Anti-avalglucosidase alfa antibody testing following local practices. Recommendations regarding immunogenicity testing are described in SmPC section 4.4.
Impact on the benefit-risk balance of the product	Antibody formation has been reported with ERT. Thus far there has been no association between antibodies and efficacy outcome measures in the avalglucosidase alfa clinical trials.
Public health impact	Not applicable

Important potential risk	Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)

ADA: Anti-Drug Antibody; CI: Confidence Interval; CRIM: Cross-Reactive Immunologic Material; ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; HSAT: High and Sustained Antibody Titers; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; NAb: Neutralizing Antibody; PAP: Primary Analysis Period; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics.

Table 28 - Important potential risk: Medication error in home infusion setting

Important potential risk	Medication error in 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 HCP administering avalglucosidase alfa in the home setting are experienced in the management of the Pompe disease, as well as in the management of other ERTs. As of 31-May-2021, 15 patients received avalglucosidase alfa in the home setting (LTS13769 [N = 2], EFC14028 [N = 11] and ACT14132 [N = 2]). Safety events occurred in 4 patients. One EFC14028 patient receiving avalglucosidase alfa in the home setting experienced an infusion-associated reaction. A [redacted] patient who began treatment with avalglucosidase alfa in Mar-2019, started to receive home infusions in Apr-2020 (first home infusion given at Week 59 in the open-label period). During the first home infusion and two hours after infusion start, the patient had eyelid edema and flushing. Both events were assessed as a non-serious AESI and IAR of mild intensity. Therapy with avalglucosidase alfa was interrupted and the patient received methylprednisolone and dexchlorpheniramine as corrective treatments. The patient recovered from both events the same day. After this dose interruption the patient returned to the study site to receive infusions and was monitored for any recurring IARs before resuming home infusions again with no recurrence of IARs. Six unrelated non-serious AEs in 2 other patients in EFC14028 and 1 unrelated non-serious AE in 1 patient in LTS13769 were reported. No medication error occurred in the setting of home infusion. In the “Home infusion report” provided by the [redacted] where Myozyme is routinely administered in 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. 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**: No case of medication error in the home infusion setting has been identified among the patients who received infusion at home (As of 31-May-2021, 15 patients received avalglucosidase alfa in the home setting in the clinical program. Safety events occurred in 4 patients. In the “Home infusion report” provided by the [redacted], where Myozyme is routinely administered in 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

Important potential risk	Medication error in home infusion setting
	severe IARs were reported in the home setting, the majority of IARs were mild in intensity and did not necessitate advanced clinical intervention. **Severity and nature of risk:** Medication errors may occur more likely in the home setting because of potential insufficient understanding of the instructions for use of the product. **Seriousness/outcomes:** Insufficient understanding of the instructions for use may result in medication errors in the home setting. **Background incidence/prevalence:** Not applicable **Impact on individual patient:** No case of medication error in the home infusion setting has been identified among the patients who received infusion at home (15 patients received avalglucosidase alfa in the home setting in the clinical program).
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.
Impact on the benefit-risk balance of the product	Enzyme replacement therapy with avalglucosidase alfa patients provides clinical benefit. 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 patients treated either at home or in hospital/clinic, the public health impact appears to be low.

AE: Adverse Event; AESI: Adverse Event of Special Interest; CI: Confidence Interval; [redacted] ERT: Enzyme Replacement Therapy; HCP: HCP: Healthcare Professional; IAR: Infusion Associated Reaction; MAH: Marketing Authorization Holder; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 29 - Important potential risk: Immune complex related reactions

Important potential risk	Immune complex related reactions
Potential mechanism	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. In most cases this will be an inconsequential process of events in 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

Important potential risk	Immune complex related reactions
	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	Evidence of immune complexes was not observed in any tissue or organ in mice or monkeys. As for other ERTs, due to the biological mechanism of immune complex mediated reactions, this risk cannot be totally ruled out. Neither cases of potential immune-mediated reactions were identified in patients during the clinical studies, nor cases contained events consistent with immune mediated reactions. Considering this lack of cases and the biological plausibility, the MAH has proposed to include "immune complex related reactions" as an important potential risk in the RMP.
Characterization of the risk	**Frequency with 95% CI:** Neither cases of potential immune-mediated reactions were identified in patients from the clinical studies, nor cases contained events consistent with immune mediated reactions. **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). No cases were identified in avalglucosidase alfa clinical trials. **Background incidence/prevalence:** Development of immune complex disease 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:** No cases were identified in avalglucosidase alfa clinical trials 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.
Risk factors and risk groups	Unknown.
Preventability	Unknown. This would be re-evaluated if cases occur for avalglucosidase alfa.
Impact on the benefit-risk balance of the product	The benefit of avalglucosidase alfa outweighs the potential risk of "immune complex related reactions".
Public health impact	Negligible public health impact is anticipated.

CI: Confidence Interval; ERT: Enzyme Replacement Therapy; MAH: Marketing Authorization Holder; RMP: Risk Management Plan.

SVII.3.2. Presentation of the missing information

Table 30 - Missing information: Use in pregnant and lactating women

Missing Information	Use in pregnant and lactating women
Evidence source(s) and strength of evidence	Currently there are no clinical trials that include pregnant or lactating women.
Anticipated risk/consequence of the missing information	A pregnancy form is proposed to be put in place in the postmarketing safety data collection

Table 31 - Missing information: Use in patients with renal or hepatic insufficiency

Missing Information	Use in patients with renal or hepatic insufficiency
Evidence source(s) and strength of evidence	Six patients with mild renal impairment (based on eGFR data) have been exposed to avalglucosidase alfa in EFC14028 study.
Anticipated risk/consequence of the missing information	No dose adjustment is required in patients with mild renal impairment. No specific dose regimen is recommended for patients with hepatic insufficiency.

eGFR: Estimated Glomerular Filtration Rate.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 32 - Summary of the safety concerns

Important identified risk	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
Important potential risks	Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)
	Medication error in home infusion setting
	Immune complex related reactions
Missing information	Use in pregnant and lactating women
	Use in patients with renal or hepatic insufficiency

IgE: Immunoglobulin E; IgG: Immunoglobulin G.

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

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

In the clinical program, AESI are monitored. This includes IARs, Pregnancy, Symptomatic overdose and clinical laboratory changes from baseline for ALT, AST increase and serum creatinine increase.

The safety profile of avalglucosidase alfa will continue to be further characterized in real life setting through annual reviews, expeditious reporting of applicable spontaneous events, discussion within the periodic safety update report (PSUR)/periodic benefit-risk evaluation report (PBRER) and ongoing signal detection as appropriate.

In addition, continued safety data review by an independent Data and Safety Monitoring Board (DSMB) for ongoing clinical trials of avalglucosidase alfa is in place.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Three (3) studies with long-term follow-up ongoing at the cut-off date are proposed as part of this pharmacovigilance plan to further characterize the important risks of this risk management plan (studies LTS13769, EFC14028 and ACT14132).

The study EFC14462 which was agreed as part of the paediatric investigation plan (PIP) will provide relevant safety data in the population of naive patients less than or equal to 6 months of age with IOPD.

These studies are described in Table 33 and Table 34. They will bring further characterization of the important identified risk “Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies” and of the important potential risks “Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)”, “Medication error in home infusion setting” and “Immune complex related reactions”.

In addition to these pharmacovigilance activities, the applicant is proposing additional measures to further characterize the important risks and missing information. These studies are described in Table 33 and Table 34:

- The Pompe Disease Registry is an international, longitudinal, observational, and voluntary program for patients with Pompe disease, designed to track the disease’s natural history and treatment outcomes in patients, including those using avalglucosidase alfa. The Pompe Registry will collect real world data on patients who also report renal and/or hepatic insufficiency. Renal insufficiency and hepatic insufficiency status in the Pompe Registry database relies solely on physician’s assessment who will report the renal insufficiency or hepatic insufficiency based on check box in the case report forms (CRFs).
- The Pompe Pregnancy Sub-registry is an international, longitudinal, observational, and voluntary program designed to track pregnancy outcomes for any pregnant woman, including

women using avalglucosidase alfa, enrolled in the Pompe Registry and who then consents to the Pregnancy Sub-registry. If a patient consents to this sub-registry, information about her medical and obstetric history, pregnancy, and birth will be collected. If a patient consents to additional data collection for her infant, data on lactation, infant growth and health status through month 36 postpartum will be collected.

- The OBS17445 (SAVANT) PASS will provide further characterization of the important identified risk "Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies" and the important potential risk "Medication errors in Home infusion setting".

Table 33 - Additional pharmacovigilance activities (category 1 to 3) summary

LTS13769 (Category 3)
Study short name and title:
An open label, multicenter, multinational extension study of the long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa in patients with Pompe Disease.
Rationale and study objectives:
Evaluate long-term safety (including IARs and immunogenicity) and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa.
Study design:
Open-label clinical study.
Study populations:
Treatment naive and previously treated LOPD patients.
Milestones:
Report submission: Quarter (Q)4 2022
EFC14028 (COMET) (Category 3)
Study short name and title:
A phase 3 randomized, multicenter, multinational, double-blinded study comparing the efficacy and safety of repeated biweekly infusions of avalglucosidase alfa (neoGAA, GZ402666) and alglucosidase alfa in treatment naive patients with late onset Pompe disease.
Rationale and study objectives:
Primary objective is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC% predicted in the upright position, as compared to alglucosidase alfa. Secondary objectives are to determine the safety (including IARs and immunogenicity) and effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (maximal inspiratory pressure [MIP]), expiratory muscle strength (maximal expiratory pressure [MEP]), lower extremity muscle strength (hand-held dynamometry [HHD]), motor function (quick motor function test [QMFT]), and health-related quality of life (12-item short form health survey [SF-12]). The main purpose of this ongoing long-term ETP is to provide long-term safety up to 96 weeks, followed by an extended open-label long-term follow-up period up to 144 additional weeks. Adverse events, including AESI and potential immune complex mediated reactions, are collected every 2 weeks. Anti-avalglucosidase alfa antibodies (ADAs) (with neutralizing antibodies in ADA-positive patients) are evaluated 1 week following the 1st infusion in ETP, then monthly through Week 73, then every 12 weeks up to the end of the follow-up.
Study design:
Randomized, double-blind study.

Study populations:

Treatment naïve patients with late onset Pompe disease.

Milestones:

Report submission: Q1 2025

ACT14132 (mini-COMET) (Category 3)

Study short name and title:

An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of avalglucosidase alfa (neoGAA, GZ402666) in patients with IOPD treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response.

Rationale and study objectives:

The primary objective of the study is to evaluate the safety profile, including IARs and immunogenicity of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa.

Study design:

Open label ascending dose cohort.

Study populations:

Patients with IOPD treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response.

Milestones:

Report submission: Q4 2025.

EFC14462 (Category 3)

Study short name and title:

Open-label, multinational, multicenter, intravenous infusion study of the safety, efficacy, PK, and PD of avalglucosidase alfa in treatment-naive pediatric patients less than or equal to 6 months of age with IOPD.

Rationale and study objectives:

The primary objective is to determine the safety, tolerability, and effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival of IOPD patients less than or equal to 6 months of age after 52 weeks of treatment.

Secondary objectives are to determine the effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival at 12 and 18 months of age, as well the change in left ventricular mass-Z (LVM-Z) score; alberta infant motor scale (AIMS) score; body length, body weight, and head circumference Z scores; and urinary hexose tetrasaccharide (Hex4) at Week 52; to determine the PK profile at week 12 and week 52; to determine safety, tolerability, and immunogenicity of avalglucosidase alfa.

Study design:

Open-label study.

Study populations:

Infantile-onset Pompe disease patients less than or equal to 6 months of age.

Milestones:

Report submission: Q2 2027

DIREGC07005 (Pompe Disease Registry) (Category 3)

Study short name and title:

The Pompe Registry is a multicenter, international, longitudinal, observational, and voluntary program designed to track the natural history and treatment outcomes of patients with Pompe disease.

Rationale and study objectives:

The Pompe Registry collects and analyzes clinical data regularly collected by clinicians related to the onset, progression, and management of Pompe disease including patients treated with avalglucosidase alfa who also report renal and/or hepatic insufficiency.

Study design:

Observational registry.

Study populations:

All patients with a confirmed diagnosis of Pompe disease are eligible to participate.

Milestones:

Start of data collection: Q3 2021

End of data collection: Q4 2031

Final cumulative report submission: Q3 2032

AGLU03506 (Pompe Disease Pregnancy Sub-registry) (Category 3)

Study short name and title:

A sub-registry to observe the effect of alglucosidase alfa and avalglucosidase Alfa treatment on pregnancy and infant growth in women with Pompe disease.

Rationale and study objectives:

The primary objective of this Sub-registry is to track pregnancy outcomes, including complications and infant growth, in all women with Pompe disease during pregnancy, regardless of whether they receive disease-specific therapy, such as ERT with alglucosidase alfa or avalglucosidase alfa.

This sub-registry is a multicenter, international, longitudinal, observational, and voluntary program designed to track pregnancy outcomes for any pregnant woman enrolled in the Pompe Registry, regardless of whether she is receiving disease-specific therapy (such as ERT with alglucosidase alfa or avalglucosidase alfa) and irrespective of the commercial product with which she may be treated.

Study design:

Observational

Study populations:

All pregnant women in the Pompe Registry are eligible to participate in this Pregnancy Sub-registry, regardless of treatment status.

Milestones:

Start of data collection: Q3 2021

End of data collection: Q4 2031

Final cumulative report submission: Q3 2032

OBS17445 (SAVANT) PASS (Category 3)

Study short name and title:

A post-authorization safety study to assess long-term safety in patients with Pompe disease treated with avalglucosidase alfa in the commercial setting.

Rationale and study objectives:

This study aims at gathering more comprehensive safety information on avalglucosidase alfa in a structured way to further characterize the important identified risk of IARs, including hypersensitivity and anaphylactic reactions, and the important potential risk of medication error in the setting of clinical/ hospital and home infusion.

Study design:

Non-interventional study of focused safety data collection in patients with Pompe disease who are receiving or plan to receive ERT with avalglucosidase alfa and participate in the existing Pompe Registry.

Study populations: Patients will be enrolled at worldwide sites participating in the Pompe Registry.
Milestones: Start of data collection (first subject enrolled): Q3 2024 Interim report submission: Q4 2026 Final report submission: Q3 2028

6MWT: 6-Minute Walk Test; ADA: Anti-Drug Antibody; AESI: Adverse Event of Special Interest; AIMS: Alberta Infant Motor Scale; ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; IgE: Immunoglobulin E; IgG: Immunoglobulin G; FVC: Forced Vital Capacity; Hex4: Hexose Tetrasaccharide; HHD: Hand-Held Dynamometry; IAR: Infusion Associated Reaction; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; LVM-Z: Left Ventricular Mass-Z; MEP: Maximal Expiratory Pressure; MIP: Maximal Inspiratory Pressure; PASS: Post Authorization Safety Study; PD: Pharmacodynamic; PK: Pharmacokinetic; Q: Quarter; QMFT: Quick Motor Function Test; SF-12: 12-Item Short Form Health Survey.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 34 - 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				
LTS13769 Ongoing	Evaluate long-term safety and pharmacokinetics of repeated biweekly infusions of avalglucosidase alfa.	• Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies. • Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies). • Medication error in home infusion setting. • Immune complex related reactions.	Report submission	Q4 2022
EFC14028 (COMET) Ongoing	Primary objective is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC% predicted in the upright position, as compared to alglucosidase alfa.	• Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies.	Report submission	Q1 2025

	Secondary objectives are to determine the safety and effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health-related quality of life (SF-12). The main purpose of this ongoing long-term ETP is to provide long-term safety up to 96 weeks, followed by an extended open-label long-term follow-up period up to 144 additional weeks. Adverse events, including AESI and potential immune complex mediated reactions, are collected every 2 weeks. Anti-avalglucosidase alfa antibodies (ADAs) (with neutralizing antibodies in ADA-positive patients) are evaluated 1 week following the 1st infusion in ETP, then monthly through Week 73, then every 12 weeks up to the end of the follow-up.	• Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies). • Medication error in home infusion setting. • Immune complex related reactions.		
ACT14132 (Mini-COMET) Ongoing	Primary objective is to evaluate the safety profile of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa.	• Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies. • Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies). • Medication error in home infusion setting. • Immune complex related reactions.	Report submission	Q4 2025
EFC14462 Planned	Primary objective is to determine the safety, tolerability, and effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival of IOPD patients less than or equal to 6 months of age after 52 weeks of treatment. Secondary objectives are to determine the effect of	• Infusion associated reactions including hypersensitivity and anaphylactic reactions with or without development of IgG and IgE antibodies. • Immunogenicity leading to loss of response (High Sustained IgG Antibody	Report submission	Q2 2027

	avalglucosidase alfa treatment on survival and invasive ventilator-free survival at 12 and 18 months of age, as well the change in LVM-Z score; AIMS score; body length, body weight, and head circumference Z scores; and urinary Hex4 at Week 52; to determine the PK profile at week 12 and week 52; to determine safety, tolerability, and immunogenicity of avalglucosidase alfa.	Titers and/or neutralizing antibodies). • Medication error in home infusion setting. • Immune complex related reactions.		
DIREGC07005 (Pompe Disease Registry) Planned	The Pompe Registry collects and analyzes clinical data regularly collected by clinicians related to the onset, progression, and management of Pompe disease including patients treated with avalglucosidase alfa who also report renal and/or hepatic insufficiency.	• Use in patients with renal or hepatic insufficiency.	Start of data collection End of data collection Final cumulative report submission	Q3 2021 Q4 2031 Q3 2032
AGLU03506 (Pompe Disease Pregnancy Sub-registry) Planned	The primary objective of this Sub-registry is to track pregnancy outcomes, including complications and infant growth, in all women with Pompe disease during pregnancy, regardless of whether they receive disease-specific therapy, such as ERT with alglucosidase alfa or avalglucosidase alfa. This Sub-registry is a multicenter, international, longitudinal, observational, and voluntary program designed to track pregnancy outcomes for any pregnant woman enrolled in the Pompe Registry, regardless of whether she is receiving disease-specific therapy (such as ERT with alglucosidase alfa or avalglucosidase alfa) and irrespective of the commercial product with which she may be treated.	• Use in pregnant and lactating women.	Start of data collection End of data collection Final cumulative report submission	Q3 2021 Q4 2031 Q3 2032
OBS17445 (SAVANT) Ongoing	This PASS study aims at gathering more comprehensive safety information on avalglucosidase alfa in a structured way to further characterize the important identified risk of IARs, including hypersensitivity and anaphylactic reactions, and the important	• Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies. • Medication errors in home infusion setting.	Start of data collection (first subject enrolled): Interim report submission:	Q3 2024 Q4 2026

	potential risk of medication error in the setting of clinical/ hospital and home infusion.	Final report submission:	Q3 2028

6MWT: 6-Minute Walk Test; ADA: Anti-Drug Antibody; AESI: Adverse Event of Special Interest; AIMS: Alberta Infant Motor Scale; ETP: Extended Treatment Period; ERT: Enzyme Replacement Therapy; FVC: Forced Vital Capacity; Hex4: Hexose Tetrasaccharide; HHD: Hand-Held Dynamometry; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LVM-Z: Left Ventricular Mass-Z; MEP: Maximal Expiratory Pressure; MIP: Maximal Inspiratory Pressure; PASS: Post Authorization Safety Study; PK: Pharmacokinetic; Q: Quarter; QMFT: Quick Motor Function Test; SF-12: 12-Item Short Form Health Survey.

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 avalglucosidase alfa.

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

V.1 ROUTINE RISK MINIMIZATION MEASURES

Avalglucosidase alfa is part of the class of ERT routinely used by the HCPs specialized in the treatment of Pompe disease. Previous studies with alglucosidase alfa, the only commercially available ERT for Pompe disease have shown that the knowledge on the treatments of HCPs in Pompe disease was very high. It has been also shown that the awareness and the knowledge of the HCPs are already appropriate. (35)

The applicant has revised the proposed risk minimization measures (RMMs) following the CHMP/ PRAC assessment received at D180 for the initial MAA evaluation for avalglucosidase alfa (EMEA/H/C/005501). The proposed risk minimization measures have been updated to answer the RMP outstanding concerns raised by the CHMP and PRAC after D181, as part of the above-mentioned procedure.

In addition to the routine minimization which includes clear, reinforced and detailed instructions for use in the SmPC and patient leaflet to convey the messages regarding the risks associated with avalglucosidase alfa, as well as their management and specific recommendations in the context of an infusion administration the applicant is proposing to develop aRMMs consisting of educational materials which include an HCP guide for immunosurveillance service and a home infusion guide. This home infusion guide will serve as training document.

With respect to immunogenicity, as part of labeling recommendation, detailed information are provided, as well as:

- Anti-drug antibodies testing based on local practice is suggested and may be considered in patients who are not responding to therapy.
- Adverse event driven immunologic testing, including IgG and IgE, ADA may be considered for patients who have risk for allergic reaction or previous anaphylactic reaction to alglucosidase alfa.

Table 35 - 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:** Labeled in sections 4.4 and 4.8 of SmPC. Labeled in section 2 of package leaflet (PL). **Routine risk minimization activities recommending specific clinical measures to address the risk:** Instructions for treatment administration, pretreatment, decision criteria to have a patient move to home infusion and instructions in case of ARs are included in SmPC section 4.2. Instructions to mitigate the IARs are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL section 4.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Legal status: Prescription only medicine.
Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)	**Routine risk communication:** Labeled in sections 4.4 and 4.8 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations and description of the testing to be considered for immunogenicity monitoring are labeled in section 4.4 of SmPC. **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only medicine.
Medication error in home infusion setting	**Routine risk communication:** Labeled in sections 4.2 and 6.6 of SmPC. Labeled in sections 3 and 5 of PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** Decision criteria to have a patient move to home 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. **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Immune complex related reactions	**Routine risk communication:** Not applicable **Routine risk minimization activities recommending specific clinical measures to address the risk:** Not applicable **Other routine risk minimization measures beyond the Product Information:** Prescription only medicine.
Use in pregnant and lactating women	**Routine risk communication:** Labeled in section 4.6 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:** Legal status: Prescription only medicine.
Use in patients with renal or hepatic insufficiency	**Routine risk communication:** Labeled in sections 4.2 and 5.2 of SmPC. **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measures beyond the Product Information:**

Safety concern	Routine risk minimization activities
	Legal status: Prescription only medicine.

AR: Adverse Reaction; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Table 36 - Additional risk minimization measures

HCP guide for immunosurveillance service	
Objectives	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 and Immunogenicity leading to loss of response (High Sustained IgG antibody titers and/or neutralizing antibodies). This guide will provide information about the immunosurveillance service, put in place by Sanofi Genzyme EU Medical Services. This current testing service with LabCorp, described in the HCP guide for immunosurveillance service provides a complimentary offer of testing: anti-drug IgG antibody, adverse event related immunogenicity testing and biomarker testing services for patients with Pompe disease and other rare disease. This is a service offered to the HCPs which can be also managed through a local laboratory for some of the testing.
Rationale for the additional risk minimization activity	This guide will reinforce the HCP education by informing about the immunosurveillance service, particularly on the testing recommendations, contact details, and shipment instructions. It includes as well the description of the service as well as testing procedures.
Target audience and planned distribution path	Target Audience: Treating and prescribing physicians, HCPs involved in the patient management and other recipients to be agreed with national competent authority (NCAs). Distribution path: To be adapted country by country depending on each local situation: mailing, face to face, other (website). 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	
Objectives	This guide will serve as training document for HCPs who will perform infusion at home to increase prevention of the following safety concerns “Medication error 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 guidances on preparation, reconstitution, and administration of the product at home, as well as recognition and management of the important identified risks “Infusion associated reactions”. This guide will provide information on the risk of medication error in the home setting and actions to prevent them.

Target audience and planned distribution path	Target Audience: All HCPs (ie, home care/infusion nurses) who will perform the infusion at home. Distribution path: This above-mentioned materials will be adapted country by country and dispensation 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.

EU: European Union; HCP: Healthcare Professional; IgE: Immunoglobulin E; IgG: Immunoglobulin G; NCA: National Competent Authority.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 37 - 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**: Labeled in sections 4.4 and 4.8 of SmPC. Labeled in section 2 of PL. Instructions for treatment administration, pretreatment, decision criteria to have a patient move to home infusion and instructions in case of ARs are included in SmPC section 4.2. Instructions to mitigate IARs are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL section 4. Prescription only medicine. **Additional risk minimization measures**: Educational materials (HCP guide for immunosurveillance service and Home infusion guide).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET), EFC14462 and OBS17445 (SAVANT).
Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)	**Routine risk minimization measures**: Labeled in sections 4.4 and 4.8 of SmPC. Recommendations and description of the testing to be considered for immunogenicity monitoring are labeled in section 4.4 of SmPC. Prescription only medicine. **Additional risk minimization measures**:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) and EFC14462.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Educational materials (HCP guide for immunosurveillance service).	
Medication error in home infusion setting	**Routine risk minimization measures**: Labeled in sections 4.2 and 6.6 of SmPC. Labeled in sections 3 and 5 of PL. Decision criteria to have a patient move to home 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. Prescription only medicine. **Additional risk minimization measures**: Educational materials (Home infusion guide).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Reporting in PSURs. **Additional pharmacovigilance activities**: Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET), EFC14462 and OBS17445 (SAVANT).
Immune complex related reactions	**Routine risk minimization measures**: Not applicable Prescription only medicine. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: Studies LTS13769, EFC14028 (COMET), ACT14132, (mini-COMET) and EFC14462.
Use in pregnant and lactating women	**Routine risk minimization measures**: Labeled in section 4.6 of SmPC. Prescription only medicine. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: AGLU03506 (Pompe Disease Pregnancy Sub-registry).
Use in patients with renal or hepatic insufficiency	**Routine risk minimization measures** Labeled in sections 4.2 and 5.2 of SmPC. Prescription only medicine. **Additional risk minimization measures**: None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: DIREGC07005 (Pompe Disease Registry).

AR: Adverse Reaction; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G; PL: Package Leaflet; PSUR: Periodic Safety Update Report; SmPC: Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Nexviadyme (Avalglucosidase alfa)

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

Nexviadyme's SmPC and its PL give essential information to HCPs and patients on how Nexviadyme should be used.

This summary of the RMP for Nexviadyme 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 Nexviadyme's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Nexviadyme is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

It contains avalglucosidase alfa as the active substance and it is given by intravenous infusion.

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

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

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

Important risks of Nexviadyme, together with measures to minimize such risks and the proposed studies for learning more about Nexviadyme'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 addition to these measures, information about ARs 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 Nexviadyme 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 Nexviadyme 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. Identified risks are concerns for which there is sufficient proof of a link with the use of Nexviadyme. 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 38 - List of important risks and missing information

Important identified risk	Infusion associated reactions (IARs) including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
Important potential risks	Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)
	Medication error in home infusion setting
	Immune complex related reactions
Missing information	Use in pregnant and lactating women
	Use in patients with renal or hepatic insufficiency

IAR: Infusion Associated Reaction; IgE: Immunoglobulin E; IgG: Immunoglobulin G.

II.B Summary of important risks

Table 39 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance 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	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open-label, dose-escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double-blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies is completed. The extended treatment period (ETP) for these two studies are ongoing.

Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	
	Infusion associated reactions were observed in all 4 clinical studies. Anaphylaxis, a severe potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergen was observed in 2 (1.4%) patients in the avalglucosidase alfa program. As described, the level of data and evidence is sufficient to demonstrate that avalglucosidase alfa can be associated with "IARs including hypersensitivity and anaphylactic reactions". This is a known risk associated with ERTs. The safety profile of avalglucosidase alfa is consistent with that of alglucosidase and possibly more favorable in the treatment of adult and pediatric patients with Pompe disease (LOPD and IOPD). IARs including hypersensitivity have been reported in avalglucosidase clinical trials. It was deemed that the data was sufficient to include as an identified risk. Considering the possible impact of this event on the benefit-risk balance, and the fact that this risk is planned to be mitigated notably through the labeling, the MAH has proposed to include it as an important identified risk in LSCs.
Risk factors and risk groups	Pompe disease is classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. These phenotypes range from a rapidly progressive infantile-onset form to a more slowly progressive late-onset form, with considerable variability and overlap between these 2 extremes. Infantile-onset Pompe disease presents in the first months of life and is characterized by severe cardiomyopathy, hypotonia, respiratory failure, and without treatment, leads to death within the first year. Patients with advanced Pompe disease or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their undergoing co-morbidity during infusions. In the EFC14028 study, the frequency of IARs and hypersensitivity in patients increased with higher ADA titers ($\geq$12 800). Additionally, IgE ADA positive patients are at increased risk of developing anaphylactic reactions upon re-administering the drug.
Risk minimization measures	**Routine risk minimization measures** Labeled in sections 4.4 and 4.8 of SmPC. Labelled in section 2 of PL. Instructions for treatment administration, pretreatment, decision criteria to have a patient move to home infusion and instructions in case of ARs are included in SmPC section 4.2. Instructions to mitigate the IARs are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL section 4. Prescription only medicine. **Additional risk minimization measures** Educational materials (HCP guide for Immunosurveillance service and Home infusion guide).
Additional pharmacovigilance activities	Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET), EFC14462 and OBS17445 (SAVANT).

ADA: Anti-Drug Antibody; AR: Adverse Reaction; ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; LSC: List of Safety Concern; MAH: Marketing Authorization Holder; PAP: Primary Analysis Period; PK: Pharmacokinetic; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 40 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)

Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)	
Evidence for linking the risk to the medicine	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open label, dose escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies is completed. The ETP for these two studies is ongoing. A small number of patients developed ADA peak titers ≥51 200 in the avalglucosidase alfa studies. Of the 61 treatment-naïve patients, there were 4 patients (3 in EFC14028 and 1 in TDR12857/ LTS13769) with ADA titers ≥51 200.
Risk factors and risk groups	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 titers, as well as NAb when treated with alglucosidase alfa, which contribute to poor clinical outcomes. A retrospective analysis by a lead investigator of 32 IOPD patients receiving alglucosidase alfa showed median titers in CRIM-negative patients of 51 200 at 24 weeks and 153 600 at 52 weeks whereas median titers in CRIM-positive patients were 600 at 24 weeks and 200 at 52 weeks. 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 titers which then decrease over time. The effects of antibody development on the long-term safety and efficacy of avalglucosidase alfa continue under investigation in longer term studies.
Risk minimization measures	**Routine risk minimization measures** Labeled in sections 4.4 and 4.8 of SmPC. Recommendations and description of the testing to be considered for immunogenicity monitoring are labeled in Section 4.4 of SmPC. Prescription only medicine. **Additional risk minimization measures** Educational materials (HCP guide for Immunosurveillance service).
Additional pharmacovigilance activities	Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) and EFC14462.

ADA: Anti-Drug Antibody; CRIM: Cross-Reactive Immunologic Material; ETP: Extended Treatment Period; HCP: Healthcare Professional; HSAT: High and Sustained Antibody Titer; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; NAb: Neutralizing Antibody; PAP: Primary Analysis Period; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics.

Table 41 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Medication error in home infusion setting

Medication error in home infusion setting	
Evidence for linking the risk to the medicine	It is expected and understood that the HCP administering avalglucosidase alfa in the home setting are experienced in the management of the Pompe disease, as well as in the management of other ERTs. As of 31-May-2021, 15 patients have ever received home infusion in trials (LTS13769 [N = 2], EFC14028 [N = 11] and ACT14132 [N = 2]). Safety events occurred in 4 patients. One EFC14028 patient receiving avalglucosidase alfa in the home setting experienced an IAR. A [redacted] patient who began treatment with avalglucosidase alfa in Mar-2019, started to receive home infusions in Apr-2020 (first home infusion given at week 59 in the open-label period). During the first home infusion and two hours after infusion start, the patient had eyelid edema and flushing. Both events were assessed as a non-serious AESI and IAR of mild intensity. Therapy with avalglucosidase alfa was interrupted and the patient received methylprednisolone and dexchlorpheniramine as corrective treatments. The patient recovered from both events the same day. After this dose interruption the patient returned to the study site to receive infusions and was monitored for any recurring IARs before resuming home infusions again with no recurrence of IARs. Six unrelated non-serious AEs in 2 other patients in EFC14028 and 1 unrelated non-serious AE in 1 patient in LTS13769 were reported). No medication error occurred in the setting of home infusion. In the "Home infusion report" provided by the [redacted] where Myozyme is routinely administered in 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. 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** Labeled in sections 4.2 and 6.6 of SmPC. Labeled in sections 3 and 5 of PL. Decision criteria to have a patient move to home 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. Prescription only medicine. **Additional risk minimization measures** Educational materials (Home infusion guide).
Additional pharmacovigilance activities	Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) EFC14462 and OBS17445 (SAVANT).

Medication error in home infusion setting

AE: Adverse Event; AESI: Adverse Event of Special Interest; [redacted] 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.

Table 42 - Important potential risk with corresponding risk minimisation activities and additional pharmacovigilance activities: Immune complex related reactions

Immune complex related reactions	
Evidence for linking the risk to the medicine	Evidence of immune complexes was not observed in any tissue or organ in mice or monkeys. As for other ERTs, due to the biological mechanism of immune complex mediated reactions, this risk cannot be totally ruled out. Neither cases of potential immune-mediated reactions were identified in patients during the clinical studies, nor cases contained events consistent with immune mediated reactions. Considering this lack of cases and the biological plausibility, the MAH has proposed to include “Immune complex related reactions” as an important potential risk in the RMP.
Risk factors and risk groups	Unknown.
Risk minimization measures	**Routine risk minimization measures** Not applicable Prescription only medicine. **Additional risk minimization measures** None
Additional pharmacovigilance activities	Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) and EFC14462.

ERT: Enzyme Replacement Therapy; MAH: Marketing Authorization Holder; RMP: Risk Management Plan.

Table 43 - Missing information with corresponding risk minimisation activities: Use in pregnant and lactating women

Missing information: Use in pregnant or lactating women	
Risk minimization measures	**Routine risk minimization measures** Labeled in section 4.6 of SmPC. Prescription only medicine. **Additional risk minimization measure** None
Additional pharmacovigilance activities	AGLU03506 (Pompe Disease Pregnancy Sub-registry).

SmPC: Summary of Product Characteristics.

Table 44 - Missing information with corresponding risk minimisation activities: Use in patients with renal or hepatic insufficiency

Missing information: Use in patients with renal or hepatic insufficiency	
Risk minimization measures	**Routine risk minimization measures** Labeled in sections 4.2 and 5.2 of SmPC. Prescription only medicine.

Missing information: Use in patients with renal or hepatic insufficiency	
	Additional risk minimization measure None
Additional pharmacovigilance activities	DIREGC07005 (Pompe Disease Registry).

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 Nexviadyme.

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

Table 45 - Other studies in post-authorization development plan

LTS13769 (Category 3)
Purpose of the study: Evaluate long-term safety (including IARs and immunogenicity) and PK of repeated biweekly infusions of avalglucosidase alfa.
EFC14028 (COMET) (Category 3)
Purpose of the study: Primary objective is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC % predicted in the upright position, as compared to alglucosidase alfa. Secondary objectives are to determine the safety (including IARs and immunogenicity) and effect of avalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health-related quality of life (SF-12). The main purpose of this ongoing long-term ETP is to provide long-term safety up to 96 weeks, followed by an extended open-label long-term follow-up period up to 144 additional weeks. Adverse events, including AESI and potential immune complex mediated reactions, are collected every 2 weeks. Anti-avalglucosidase alfa antibodies (ADAs) (with NAb in ADA-positive patients) are evaluated 1 week following the 1st infusion in ETP, then monthly through Week 73, then every 12 weeks up to the end of the follow-up.
ACT14132 (mini-COMET) (Category 3)
Purpose of the study: The primary objective of the study is to evaluate the safety profile, including IARs and immunogenicity of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa.
EFC14462 (Category 3)
Purpose of the study: The primary objective is to determine the safety, tolerability, and effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival of IOPD patients less than or equal to 6 months of age after 52 weeks of treatment. Secondary objectives are to determine the effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival at 12 and 18 months of age, as well the change in LVM-Z score, AIMS score; body length, body weight, and head circumference Z scores; and urinary Hex4 at Week 52; to determine the PK profile at week 12 and week 52; to determine safety, tolerability, and immunogenicity of avalglucosidase alfa.

DIREGC07005 (Pompe Disease Registry) (Category 3)

Purpose of the study:

The Pompe Registry collects and analyzes clinical data regularly collected by clinicians related to the onset, progression, and management of Pompe disease including patients treated with avalglucosidase alfa who also report renal and/or hepatic insufficiency.

AGLU03506 (Pompe Disease Pregnancy Sub-registry) (Category 3)

Purpose of the study:

The primary objective of this sub-registry is to track pregnancy outcomes, including complications and infant growth, in all women with Pompe disease during pregnancy, regardless of whether they receive disease-specific therapy, such as ERT with alglucosidase alfa or avalglucosidase alfa.

This Sub-registry is a multicenter, international, longitudinal, observational, and voluntary program designed to track pregnancy outcomes for any pregnant woman enrolled in the Pompe Registry, regardless of whether she is receiving disease-specific therapy (such as ERT with alglucosidase alfa or avalglucosidase alfa) and irrespective of the commercial product with which she may be treated.

OBS17445 (SAVANT) (Category 3)

Purpose of the study:

This study aims at gathering more comprehensive safety information on avalglucosidase alfa in a structured way to further characterize the important identified risk of IARs, including hypersensitivity and anaphylactic reactions, and the important potential risk of medication error in the setting of clinical/ hospital and home infusion.

6MWT: 6-Minute Walk Test; ADA: Anti-Drug Antibody; AESI: Adverse Event of Special Interest; AIMS: Alberta Infant Motor Scale; ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; FVC: Forced Vital Capacity; Hex4: Hexose Tetrasaccharide; HHD: Hand-Held Dynamometry; IAR: Infusion Associated Reaction; IOPD: Infantile-Onset Pompe disease; LVM-Z: Left Ventricular Mass-Z; MEP: Maximal Expiratory Pressure; MIP: Maximal Inspiratory Pressure; NAb: Neutralizing Antibody; PK: Pharmacokinetic; QMFT: Quick Motor Function Test; SF-12: 12-Item Short Form Health Survey.

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PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Draft key messages of the additional risk minimization measures

Prior to the launch of Nexviadyme in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority. The educational program is aimed at increasing the awareness about the immunosurveillance service and to support the correct and safe administration of the product in the home setting.

The MAH shall ensure that in each member state where Nexviadyme is marketed, all healthcare professionals (HCPs) who are expected to prescribe, dispense and administer Nexviadyme are provided with the following educational package to be disseminated through professional bodies:

- Healthcare professionals (HCPs) guide for immunosurveillance service and
- Home infusion guide for HCPs

1.1 Guide for healthcare professionals for Immunosurveillance Service shall include the following key elements:

- 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 Nexviadyme
  - Adverse-event-driven immunologic testing, including IgG and Immunoglobulin E (IgE) ADA, should be considered for patients at risk for allergic reaction or previous anaphylactic reaction to Myozyme (alglucosidase alfa).
  - 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.

1.2 The home infusion guide for HCPs which will serve as training document to HCPs who will perform the infusion at home shall contain the following key elements:

- Requirements and organization of the home infusion including equipment, pre-treatment and emergency treatments.

- Details on the preparation and administration of Nexviadyme, including all the steps of preparation, reconstitution, dilution and administration.
- Medical evaluation of the patient prior to administration of the infusion at home.
- 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.