Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMS documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Avalglucosidase alfa 100 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains 100 mg of avalglucosidase alfa.

After reconstitution, the solution contains 10 mg of avalglucosidase alfa* per ml. Following reconstitution, each vial contains 10.3 mL reconstituted solution and a total extractable volume of 10.0 mL at 10 mg/mL avalglucosidase alfa. Each vial contains an overfill to compensate for liquid loss during preparation. This overfill ensures that after dilution with the entire content there is solution containing 10 mg/ml avalglucosidase alfa.

*Avalglucosidase alfa is a human acid α-glucosidase produced in Chinese hamster ovary cells (CHO) by recombinant DNA technology, which is subsequently conjugated with approximately 7 hexamannose structures (each containing two terminal mannose-6-phosphate (M6P) moieties) to oxidized sialic acid residues on the molecule, thereby increasing bis-M6P levels.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White to pale yellow lyophilized powder

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Treatment of late-onset Pompe disease (LOPD) in symptomatic patients who have received Pompe disease ERT with alglucosidase alfa for ≥ 2 years.

Treatment of infantile-onset Pompe disease (IOPD) in symptomatic patients ≥ 1 year old who have received Pompe disease ERT with alglucosidase alfa for ≥ 6 months.

4.2 Posology and method of administration

Avalglucosidase alfa treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases.

Posology

Patients with late-onset Pompe disease (LOPD)
The recommended dose of avalglucosidase alfa is 20 mg/kg of body weight administered every other week.

Patients with infantile-onset Pompe disease (IOPD)
The recommended dose of avalglucosidase alfa is 40 mg/kg of body weight administered every other week.

Special populations

Paediatric population
The safety and efficacy of avalglucosidase alfa have not been established in paediatric patients younger than 1 year.

Elderly patients
No dose adjustment is required for patients over the age of 65 years.

Hepatic impairment
The safety and efficacy of avalglucosidase alfa have not been studied in patients with hepatic impairment. No dose adjustment is required.

Renal impairment
No dose adjustment is required in patients with mild renal impairment (see section 5.2). Avalglucosidase alfa has not been studied in patients with moderate or severe renal impairment.

Method of administration

Avalglucosidase alfa should be administered as an intravenous infusion.

Infusion should be administered incrementally as determined by patient response and comfort.
It is recommended that the infusion begins at an initial rate of 1 mg/kg/hour and is gradually increased every 30 minutes if there are no signs of infusion-associated reactions (IARs), in accordance with Table 1. Vital signs should be obtained at each step, before increasing the infusion rate.

Table 1 – Infusion rate schedule

Patient		**Infusion rate (mg/kg/hour)**					**Approximate duration (h)**
		step 1	**step 2**	**step 3**	**step 4**	**step 5**	
LOPD		1	3	5	7	NA	4 to 5
IOPD	4-step process	1	3	5	7	NA	7
	5-step process	1	3	6	8	10	5

In the event of anaphylaxis or severe hypersensitivity reaction or severe infusion associated reactions (IARs), immediately discontinue administration of avalglucosidase alfa and initiate appropriate medical treatment. In the event of mild to moderate hypersensitivity reactions or IARs, the infusion rate may be slowed or temporarily stopped and/or appropriate medical treatment initiated (see section 4.4).

Symptoms may persist despite temporarily stopping the infusion; therefore, the treating physician should wait at least 30 minutes for symptoms of the reactions to resolve before deciding to stop the infusion for the remainder of the day. If symptoms subside, resume infusion rate for 30 minutes at half the rate, or less, of the rate at which the reactions occurred, followed by an increase in infusion rate by 50% for 15 to 30 minutes. If symptoms do not recur, increase the infusion rate to the rate at which the reactions occurred and consider continuing to increase the rate in a stepwise manner until the maximum rate is achieved.

Home infusion
Infusion of avalglucosidase alfa at home may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months. The decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the treating physician. A patient's underlying co-morbidities and ability to adhere to the home infusion requirements need to be taken into account when evaluating the patient for eligibility to receive home infusion. The following criteria should be considered:

- The patient must have no ongoing concurrent condition that, in the opinion of the physician, may affect patient's ability to tolerate the infusion.
- The patient is considered medically stable. A comprehensive evaluation must be completed before the initiation of home infusion.
- The patient must have received avalglucosidase alfa infusions under the supervision of a physician with expertise in management of Pompe patients for a few months, which could be in a hospital or in another appropriate setting of outpatient care. Documentation of a pattern of well-tolerated infusions with no IARs, or mild IARs that have been controlled with premedication, is a prerequisite for the initiation of home infusion.
- The patient must be willing and able to comply with home infusion procedures.
- Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional. The healthcare professional should be available at all

times during the home infusion and a specified time after infusion, depending on patient's tolerance prior to starting home infusion.

If the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately and appropriate medical treatment should be initiated (see section 4.4). Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction occurs. Dose and infusion rate must not be changed without consulting the responsible physician.

For instructions on reconstitution and dilution of medicinal product before administration, see section 6.6.

4.3 Contraindications

Life-threatening hypersensitivity to the active substance or to any of the excipients when re-challenge was unsuccessful (see section 4.4).

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity Reactions including Anaphylaxis
Hypersensitivity reactions, including anaphylaxis, have been reported in avalglucosidase alfa -treated patients (see section 4.8).

Appropriate medical support measures, including cardiopulmonary resuscitation equipment especially for patients with cardiac hypertrophy and patients with significantly compromised respiratory function, should be readily available when avalglucosidase alfa is administered.

If severe hypersensitivity or anaphylaxis occur, avalglucosidase alfa should be discontinued immediately, and appropriate medical treatment should be initiated. The risks and benefits of re-administering avalglucosidase alfa following anaphylaxis or severe hypersensitivity reaction should be considered. Some patients have been re-challenged using slower infusion rates at a dose lower than the recommended dose. In patients with severe hypersensitivity, desensitization procedure to avalglucosidase alfa may be considered. If the decision is made to re-administer the product, extreme caution should be exercised, with appropriate resuscitation measures available. Once a patient tolerates the infusion, the dose may be increased to reach the approved dose.

If mild or moderate hypersensitivity reactions occur, the infusion rate may be slowed or temporarily stopped.

If a patient has previously had a severe hypersensitivity or anaphylactic reaction to alglucosidase, the risks and benefits of administering avalglucosidase alfa should be considered. In these circumstances advice from an allergy specialist could be sought.

Infusion Associated Reactions
In clinical studies, IARs were reported to occur at any time during and/or within a few hours after the infusion of avalglucosidase alfa and were more likely with higher infusion rates. The majority of IARs were reported within 24 hours of infusion (see section 4.8).

Patients with an acute underlying illness at the time of avalglucosidase alfa infusion appear to be at greater risk for IARs. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs. Antihistamines, antipyretics, and/or corticosteroids can be given to prevent or reduce IARs. However, IARs may still occur in patients after receiving pretreatment.

If severe IARs occur, administration of avalglucosidase alfa should be immediately discontinued and appropriate medical treatment should be initiated. The benefits and risks of re-administering avalglucosidase alfa following severe IARs should be considered. Some patients have been re-challenged using slower infusion rates at a dose lower than the recommended dose. Once a patient tolerates the

infusion, the dose may be increased to reach the approved dose. If a mild or moderate IAR occurs regardless of pre-treatment, decreasing the infusion rate or temporarily stopping the infusion may ameliorate the symptoms.

Immunogenicity
Treatment-emergent anti-drug antibodies (ADAs) were reported in both treatment-naïve (95%) and treatment-experienced patients (49%) (see section 4.8).

IARs and hypersensitivity reactions may occur independent of the development of ADAs. In clinical trials in treatment-naïve patients, a trend for increases in the incidence of IARs was observed with increasing ADA titres. In enzyme replacement therapy (ERT) experienced adult patients, the occurrences of IARs and hypersensitivity were higher in patients who developed treatment-emergent ADAs compared to patients who were ADA-negative. In clinical studies, the development of ADAs did not impact clinical efficacy (see section 4.8).

ADA testing may be considered if patients do not respond 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. Contact Sanofi via email at UK-medicalinformation@sanofi.com for information on the ADA testing programme.

Risk of acute cardiorespiratory failure
Caution should be exercised when administering avalglucosidase alfa to patients susceptible to fluid volume overload or patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusion. Appropriate medical support and monitoring measures should be readily available during avalglucosidase alfa infusion, and some patients may require prolonged observation times that should be based on the individual needs of the patient.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Because it is a recombinant human protein, avalglucosidase alfa is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no available data on the use of avalglucosidase alfa in pregnant women. Animal studies do not indicate direct harmful effects with respect to reproductive toxicity. Indirect fetal effects in mice were considered related to an anaphylactic response to avalglucosidase alfa (see section 5.3). The potential risk for humans is unknown.

Avalglucosidase alfa should be used during pregnancy only if the potential benefits to the mother outweigh the potential risks, including those to the fetus.

Breast-feeding
There are no available data on the presence of avalglucosidase alfa in human milk or the effects of avalglucosidase alfa on milk production or the breastfed infant.

Avalglucosidase alfa should be used during breastfeeding only if the potential benefits to the mother outweigh the potential risks, including those to the breastfed child (see section 5.3).

Fertility
There are no clinical data on the effects of avalglucosidase alfa on human fertility. Animal studies in mice showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because dizziness has been reported as an IAR, this may affect the ability to drive and use machines on the day of the infusion (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The pooled safety analysis from 4 clinical studies included a total of 138 patients (118 adult and 20 paediatric patients) treated with avalglucosidase alfa.

The most frequently reported adverse drug reactions (ADRs) were hypersensitivity reactions in 43.5% of the patients.

Serious adverse reactions reported in patients treated with avalglucosidase alfa were headache, dyspnea, respiratory distress, nausea, skin discoloration, chills, chest discomfort, pyrexia, blood pressure increased, body temperature increased, heart rate increase, and oxygen saturation decreased. A total of 2 (1.4%) patients receiving avalglucosidase alfa in clinical studies permanently discontinued treatment due to an adverse drug reaction.

Tabulated list of adverse reactions

Adverse reactions per System Organ Class, presented by frequency categories: very common (≥1/10), common (≥1/100 to<1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Due to the small patient population, an adverse reaction reported in 2 patients is classified as common.

Table 2 - Adverse Reactions occurring in patients treated with avalglucosidase alfa in pooled analysis of clinical studies (N=138)

System Organ Class	Frequency	Adverse reaction (Preferred Term Level)
Immune disorders	Very common Common	Hypersensitivity Anaphylaxis
Nervous system disorders	Very common Common Uncommon	Headache Dizziness Tremor Paresthesia
Eye disorders	Common Uncommon	Ocular hyperaemia Eye pruritus Lacrimation increased Conjunctivitis
Cardiac disorders	Uncommon	Tachycardia Ventricular extrasystoles
Vascular disorders	Common Uncommon	Hypertension Flushing Hypotension
Respiratory, thoracic and mediastinal disorders	Common Uncommon	Cough Dyspnoea Tachypnoea Laryngeal oedema Respiratory distress Throat irritation
Gastrointestinal disorders	Very common Common Uncommon	Nausea Diarrhoea Vomiting Lip swelling Swollen tongue Abdominal pain
Skin and subcutaneous tissue disorders	Very common Common Uncommon	Pruritus Rash Urticaria Erythema Palmer erythema

		Angioedema Hyperhidrosis
Musculoskeletal and connective tissue disorders	Common	Muscle spasms Myalgia
General disorders and administration site conditions	Very common Common Uncommon	Fatigue Chills Chest discomfort Pain Influenza like illness Pyrexia Infusion site reaction† Facial pain Localised oedema Peripheral swelling
Investigations	Common	Oxygen saturation decreased

† Infusion site reactions include pain, extravasation, joint pain, rash and urticaria

Description of selected adverse reactions

Hypersensitivity Reactions including Anaphylaxis
In clinical studies, 60 (43.5%) patients experienced hypersensitivity reactions including 6 (4.3%) patients who reported severe hypersensitivity reactions and 2 (1.4%) patients who experienced anaphylaxis. Some of the hypersensitivity reactions were IgE mediated. Anaphylaxis symptoms included respiratory distress, chest pressure, generalized flushing, cough, dizziness, nausea, redness on palms, swollen lower lip, decreased breath sounds, redness on feet, swollen tongue, itchy palms and feet, and oxygen desaturation. Symptoms of severe hypersensitivity reactions included respiratory failure, respiratory distress and rash (see section 4.4).

Infusion Associated Reactions
IARs were reported in approximately 26% of patients treated with avalglucosidase alfa in clinical studies. The majority of IARs were assessed as mild to moderate and included symptoms such as chills, cough, diarrhea, erythema, fatigue, headache, influenza-like illness, nausea, ocular hyperaemia, pain in extremity, pruritus, rash, erythematous rash, tachycardia, urticaria, and vomiting. In clinical studies, 3 (2.2%) patients reported severe IARs including symptoms of chest discomfort, nausea and increased blood pressure (see section 4.4).

Immune-mediated reactions
No events consistent with immune-mediated reactions were identified in patients treated with avalglucosidase in clinical trials. Immune-mediated reactions have been reported with alglucosidase alfa, including severe cutaneous reactions and nephrotic syndrome (in subjects who had high IgG antibody titres (≥102, 400), and a potential class effect cannot be excluded (see section 4.4).

Immunogenicity

The incidence of ADA response to avalglucosidase alfa in avalglucosidase alfa -treated patients with Pompe disease is shown in Table 3. The median time to seroconversion was 8.3 weeks.

In the clinical trials, almost all treatment-naïve adult patients developed ADAs. An increase in the incidence of IAR and hypersensitivity were observed with higher IgG ADA titres. In ERT-experienced adult patients, the occurrences of IARs and hypersensitivity were higher in patients who developed treatment-emergent ADAs compared to patients who were ADA-negative. One treatment-naïve patient and 1 treatment-experienced patient developed anaphylaxis. The occurrences of IARs were similar between paediatric patients with ADA positive and negative status. There were no paediatric patients who developed anaphylactic reactions.

In one clinical study, 2 LOPD patients reported high sustained antibody titres (HSAT) to avalglucosidase alfa but this was not associated with a loss of efficacy. ADA cross-reactivity studies showed that the majority of patients generate antibodies that are cross-reactive to alglucosidase alfa. At week 49, antibodies specific to avalglucosidase alfa were detected in 3 (5.9%) patients. ADAs did not impact measures of efficacy while limited impacts on PK and PD were observed primarily with high titre patients (see section 5.2).

Table 3 – Treatment-emergent ADA incidence in LOPD and IOPD patient population

	Avalglucosidase alfa (AVAL)				Alglucosidase alfa (ALGLU)	
	Treatment-naïve patients AVAL ADA	Treatment experienced patients AVAL ADA			Treatment-naïve patients (PAP) ALGLU ADA	
	Adults 20 mg/kg eow (N=61) N (%)	Adults 20 mg/kg eow (N=55) N (%)	Paediatric 20 mg/kg eow (N=6) N (%)	Paediatric 40 mg/kg eow (N=10) N (%)	Adults 20 mg/kg eow (N=48) N (%)	Paediatric 20 mg/kg eow to 40 mg/kg weekly (N=6) N (%)
ADA at baseline	2 (3)	40 (73)	1 (17)	1 (10)	2 (4)	3 (50)
Treatment emergent ADA[a]	**58 (95)**	**27 (49)**	**1 (17)**	**5 (50)**	**46 (96)**	**3 (50)**
Treatment-induced ADA	56 (95)	9 (60)[c]	1 (20)	4 (44)	44 (96)	1 (33)
Treatment-boosted ADA	2 (100) [b]	18 (45) [b]	0	1 (100)	2 (100)	2 (67)
Neutralising antibody	**27 (44)**	**18 (33)**	**0**	**0**	**23 (48)**	**2 (33)**
Both NAb types	13 (21)	2 (4)	0	0	ND[d]	ND[d]
Inhibition enzyme activity only	4 (7)	8 (15)	0	0	4 (8)	2 (33)
Inhibition of enzyme uptake only	10 (16)	8 (15)	0	0	19 (40)	0

[a] Treatment emergent = treatment induced + treatment boosted; [b] Treatment-boosted ADA incidence defined as 100x (treatment boosted ADA positive patients)/(number of evaluable patients with ADA positive at baseline); [c] Treatment induced ADA incidence is defined as 100 x (treatment induced ADA positive patients)/(number of evaluable patients with ADA negative at baseline); [d] Not determined; eow: every other week; PAP: primary analysis period

Paediatric population

Adverse drug reactions reported from clinical trials in the paediatric population (19 paediatric patients with IOPD and 1 paediatric patient with LOPD) were similar to those reported in adults.

In the clinical trial population, paediatric patients treated with 40mg/kg every other week had a higher incidence of IARs, ADA development and treatment emergent adverse events potentially related to study treatment compared with those treated with 20mg/kg every other week.

4.9 Overdose

There have been no reports of overdose with avalglucosidase alfa.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16

Mechanism of action

Pompe disease (also known as glycogen storage disease type II, acid maltase deficiency, and glycogenosis type II) is a rare metabolic muscle disease inherited in an autosomal recessive manner defined by a deficiency of acid α-glucosidase (GAA), which is necessary for the degradation of lysosomal glycogen. GAA cleaves alpha-1,4 and alpha-1,6 linkages in glycogen under the acidic conditions of the lysosome. Pompe disease results in intra-lysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles, leading to the development of cardiomyopathy, progressive muscle weakness, and impairment of respiratory function.

Avalglucosidase alfa is a recombinant human acid α-glucosidase (rhGAA) that provides an exogenous source of GAA. Avalglucosidase alfa is a modification of alglucosidase alfa, which has a 15-fold increase in mannose-6-phosphate (M6P) moieties compared with alglucosidase alfa. Increasing the level of bis-M6P on rhGAA provides a mechanism to drive uptake into the diaphragm and other skeletal muscle via

the cation-independent M6P receptor, where it can degrade glycogen and ameliorate tissue damage. Binding to 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.

Pharmacodynamic effects

In treatment-naïve LOPD patients aged 16 to 78, the mean percentage (SD) change from baseline in urinary hexose tetrasaccharides for patients treated with avalglucosidase alfa 20 mg/kg every other week and alglucosidase alfa 20 mg/kg every other week was -53.9% (24.0) and -10.8% (32.3), respectively, at week 49.

In paediatric IOPD patients (≤12 years of age) treated with avalglucosidase alfa at 40 mg/kg every other week who demonstrated either clinical decline or sub-optimal clinical response while on treatment with alglucosidase alfa, the mean percentage (SD) change from baseline in urinary hexose tetrasaccharides was -41.0% (16.7) and -37.5% (17.2), respectively, after 6 months. In patients previously declining treated with avalglucosidase alfa at 20 mg/kg every other week, mean (SD) percentage change was -0.3% (42.1).

Clinical efficacy and safety

The safety and efficacy of avalglucosidase alfa have been evaluated in clinical studies of patients who were either naïve- or treatment-experienced at the initiation of treatment.

Clinical trials in patients with LOPD

Study 1, EFC14028/COMET, was a multinational, multicentre, randomised, double-blinded study comparing the efficacy and safety of avalglucosidase alfa and alglucosidase alfa in 100 treatment-naïve LOPD patients aged 16 to 78 years at the initiation of treatment. Patients were randomised in a 1:1 ratio based on baseline forced vital capacity (FVC), gender, age, and country to receive 20 mg/kg of avalglucosidase alfa or alglucosidase alfa once every other week for 12 months (49 weeks). The study included an open-label, long-term, follow-up phase of up to 5 years for all patients, in which patients in the alglucosidase alfa arm were switched to treatment with avalglucosidase alfa.

The primary endpoint was the change in FVC (% predicted) in the upright position from baseline to week 49. At week 49, the LS mean difference of 2.43% (95% CI: -0.13, 4.99) between avalglucosidase alfa and alglucosidase alfa exceeded the pre-defined non-inferiority margin of -1.1 and achieved statistical non-inferiority (p=0.0074). The study did not demonstrate statistical significance for superiority (p=0.0626) and the testing of the secondary endpoints was performed without multiplicity adjustment.

The key secondary endpoint was the change in total distance walked in 6 minutes (6-Minute Walk Test, 6MWT) from baseline to week 49. Additional secondary endpoints of the study were maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), Hand-held dynamometry (HHD) summary score, quick motor function test (QMFT) total score, and SF-12 (health-related survey on quality of life, both physical and mental component scores). The results for these endpoints are detailed in Tables 4 and 5.

Table 4 - LS Mean change from baseline to week 49 for the main endpoints

		Avalglucosidase alfa (n=51)	Alglucosidase alfa (n=49)
FVC (% predicted) in upright position			
Pre-treatment baseline	Mean (SD)	62.5 (14.4)	61.6 (12.4)
Week 49	Mean (SD)	65.5 (17.4)	61.2 (13.5)
Change from baseline to week 49 (MMRM)	LS mean (SE)	2.89* (0.88)	0.46* (0.93)
Difference in change from baseline to week 49 (MMRM)	LS mean (95% CI) p-value** p-value ***	2.43* (-0.13, 4.99) 0.0074 0.0626	
MMRM: mixed model repeated measure. *On the basis of MMRM model, the model includes baseline FVC (% predicted, as continuous), sex, age (in years at baseline), treatment group, visit, interaction term between treatment group and visit as fixed effects. ** Non-inferiority margin of -1.1%; *** Superiority not achieved			
6MWT (6-minute walk test – total distance in metres)			
Pre-treatment baseline	Mean (SD)	399.3 (110.9)	378.1 (116.2)
Week 49	Mean (SD)	441.31 (109.77)	383.56 (141.09)
Change from baseline to week 49 (MMRM)	LS mean (SE)	32.21* (9.93)	2.19* (10.40)
Difference in change from baseline to week 49 (MMRM)	LS mean (95% CI) p-value**	30.01* (1.33, 58.69) 0.0405	
*The MMRM model for 6MWT distance adjusts for 6MWT distance at baseline, baseline % predicted FVC and baseline 6MWT (distance walked in meter), age (in years, at baseline), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects. ** p-value at nominal level, without multiplicity adjustment			

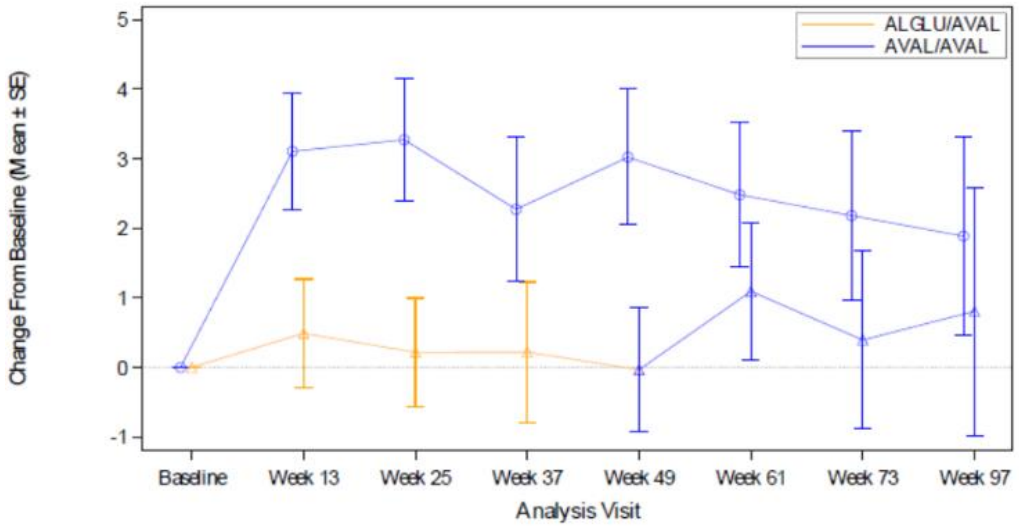
Table 5 – LS mean change from baseline to week 49 for additional secondary endpoints

Endpoint	Avalglucosidase alfa LS mean change (SE)	Alglucosidase alfa LS mean change (SE)	LS mean difference (95% CI)
Maximum Inspiratory Pressure (MIP) (% predicted) *	8.70 (2.09)	4.29 (2.19)	4.40 (-1.63,10.44)
Maximum Expiratory Pressure (% predicted) *	10.89 (2.84)	8.38 (2.96)	2.51 (-5.70, 10.73)
Hand-held dynamometry (HHD) composite score	260.69 (46.07)	153.72 (48.54)	106.97 (-26.56, 240.50)
Quick Motor function Test (QMFT) total score	3.98 (0.63)	1.89 (0.69)	2.08 (0.22, 3.95)
Health-related survey on quality of life (SF-12)	PCS score: 2.37 (0.99) MCS score: 2.88 (1.22)	1.60 (1.07) 0.76 (1.32)	0.77 (-2.13, 3.67) 2.12 (-1.46, 5.69)

*Post-hoc sensitivity analysis excluding 4 patients with supraphysiologic baseline MIP and MEP values.

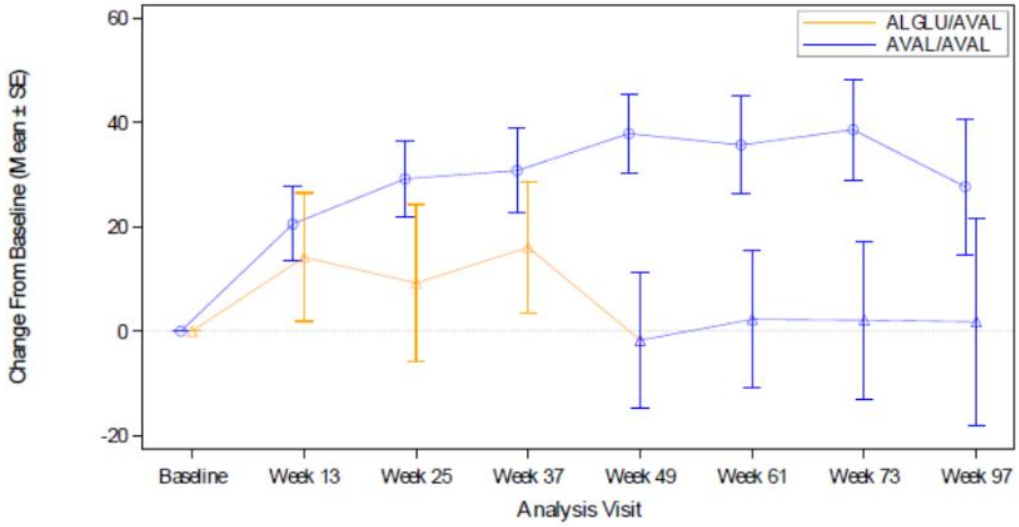
In this study, efficacy data were available in 24 patients at week 97 and showed that FVC% predicted values remained elevated over baseline throughout dosing with avalglucosidase alfafor as long as 97 weeks. Patients who switched from alglucosidase alfa to avalglucosidase alfa at week 49 showed numerical improvement for FVC % predicted, 6MWT and QMFT (Figures 1-3).

Figure 1 - Mean (SE) change from baseline of FVC (% predicted) - in upright position over time



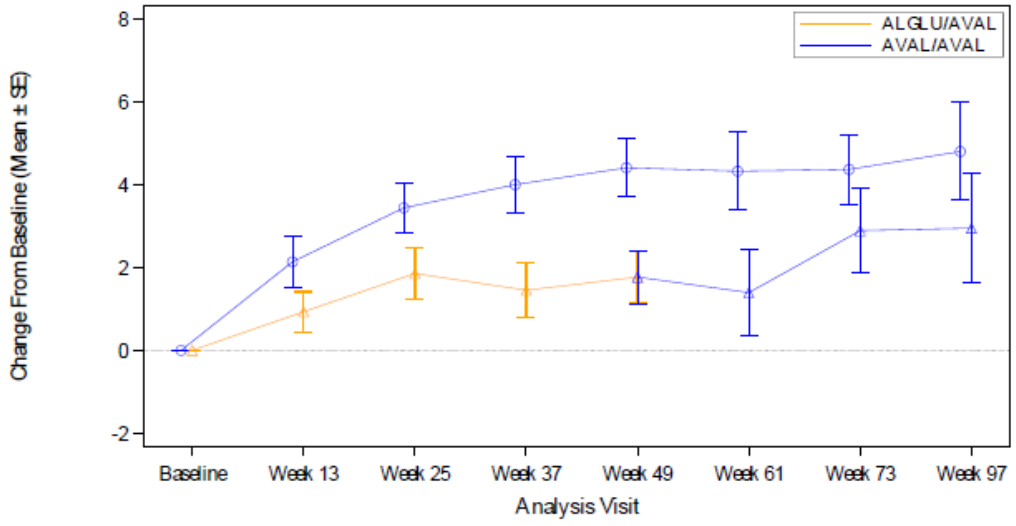
ALGLU/AVAL	49	47	45	44	43	37	33	24
AVAL/AVAL	51	51	51	51	49	46	39	27

Figure 2 - Mean (SE) change from baseline of 6MWT (m) over time



ALGLU/AVAL	49	47	45	45	43	43	34	27
AVAL/AVAL	51	51	49	50	48	47	41	29

Figure 3 - Mean (SE) change from baseline of QMFT score over time



ALGLU/AVAL	46	44	42	42	39	33	27	20
AVAL/AVAL	51	51	50	49	49	43	38	25

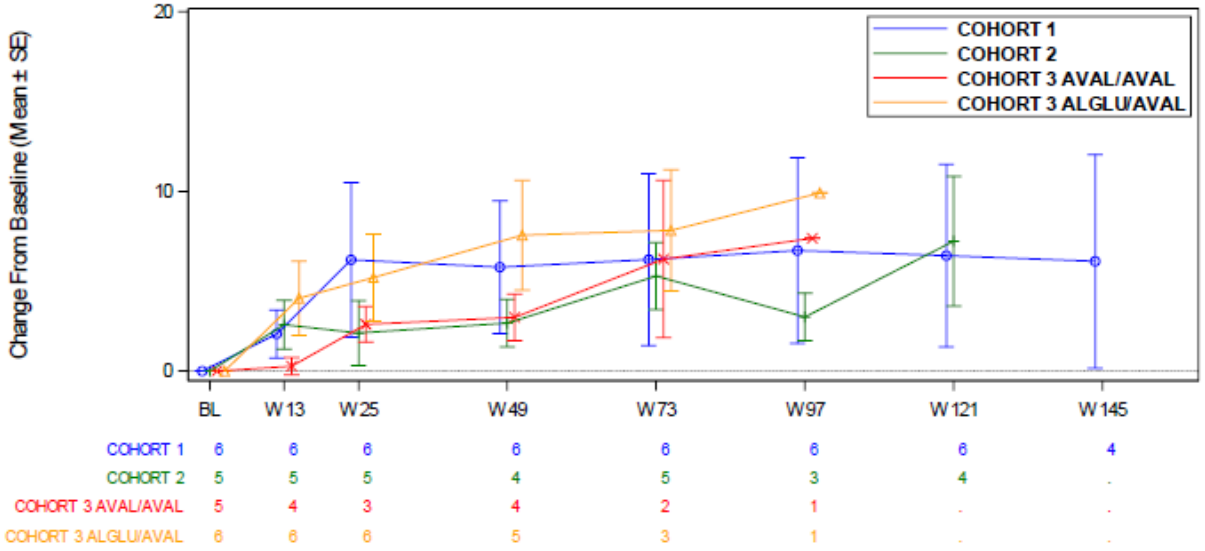
In an open-label, uncontrolled study in LOPD patients, including 11 patients switched from alglucosidase alfa to avalglucosidase alfa, the FVC (% predicted) and 6MWT tended to be stable during long-term treatment with avalglucosidase alfa 20 mg/kg every other week for up to 6 years.

Clinical trial in patients with IOPD

Study 2, ACT14132/mini-COMET, was a multi-stage, phase 2, open-label, multicentre, multinational, repeated ascending dose cohort of avalglucosidase alfa in 22 paediatric IOPD patients (≤12 years of age), who had demonstrated either clinical decline (cohorts 1 and 2) or sub-optimal clinical response (cohort 3) while on treatment with alglucosidase alfa. Cohort 1 had 6 patients who received 20 mg/kg every other week, cohort 2 had 5 patients who received 40 mg/kg every other week, and cohort 3 had 11 patients who received either avalglucosidase alfa at 40 mg/kg every other week (5 patients) or alglucosidase alfa at their stable pre-study dose (ranging between 20 mg/kg every other week and 40 mg/kg weekly) for 25 weeks (6 patients), before switching to avalglucosidase alfa 40 mg/kg every other week.

The primary objective was to evaluate the safety and tolerability of avalglucosidase alfa and the secondary objective was to determine its efficacy. Data showed stabilisation or improvement in efficacy outcomes of GMFM-88, QMFT, Pompe-PEDI (Figure 4), LVMZ score, eyelid position measurements in most patients. Treatment effect was more pronounced with 40 mg/kg every other week compared to 20 mg/kg every other week. Two out of six patients treated with avalglucosidase alfa at 20 mg/kg every other week (cohort 1) demonstrated further clinical decline and had their dose increased from 20 to 40 mg/kg every other week. All patients who received 40 mg/kg every other week maintained this dose throughout the study.

Figure 4 - Mean (SE) change from baseline of Pompe-PEDI Functional Skills Scale: Mobility Domain score over time



Pompe Registry

Medical or healthcare professionals are encouraged to register patients who are diagnosed with Pompe disease at www.registrynxt.com. Patient data will be anonymously collected in this Registry. The objectives of the "Pompe Registry" are to enhance the understanding of Pompe disease and to monitor patients and their response to enzyme replacement therapy over time, with the ultimate goal of improving clinical outcomes for these patients.

5.2 Pharmacokinetic properties

Patients with late-onset Pompe disease (LOPD)

The pharmacokinetics of avalglucosidase alfa was evaluated in a population analysis of 75 LOPD patients aged 16 to 78 years who received 5 to 20 mg/kg of avalglucosidase alfa every other week for up to 5 years. It was described by a 3-compartment model with 2 distinct phases. A first phase lasting between 10 and 18 hours (after start of infusion) was predominantly characterised by the linear clearance. A second phase occurred at very low concentrations and is likely to represent low clearance of avalglucosidase alfa from the third compartment back to the central compartment.

Patients with infantile-onset Pompe disease (IOPD)

The pharmacokinetics of avalglucosidase alfa was characterised in 16 patients aged 1 to 12 years who were treated with avalglucosidase alfa, 6 patients treated with 20 mg/kg and 10 patients treated with 40 mg/kg doses every other week for up to 25 weeks.

Absorption

In LOPD patients, for a 4-hour IV infusion of 20 mg/kg every other week, the mean Cmax and mean AUC2W were 273 µg/mL (24%) and 1220 µg.h/mL (29%), respectively.

In IOPD patients, for a 4-hour IV infusion of 20 mg/kg every other week and 7-hour IV infusion for 40 mg/kg every other week, the mean Cmax ranged from 175 to 189 µg/mL for the 20 mg/kg dose and 205 to 403 µg/mL for 40 mg/kg dose. The mean AUC2W ranged from 805 to 923 µg•hr/mL for the 20 mg/kg dose and 1720 to 2630 µg•hr/mL for 40 mg/kg dose.

Distribution

In LOPD patients, the typical population PK model predicted central compartment volume of distribution of avalglucosidase alfa was 3.4 L.

In IOPD patients treated with avalglucosidase alfa 20 mg/kg and 40 mg/kg every other week, the mean volume of distribution at steady state ranged between 3.5 to 5.4 L.

Elimination

In LOPD patients, the typical population PK model predicted linear clearance was 0.87 L/h. Following 20 mg/kg every other week, the mean plasma elimination half-life was 1.55 hours.

In IOPD patients treated with avalglucosidase alfa 20 mg/kg and 40 mg/kg every other week, mean plasma clearance ranged from 0.53 to 0.70 L/h, and mean plasma elimination half-life from 0.60 to 1.19 hours.

Linearity/non-linearity

The exposure to avalglucosidase alfa increased in a dose-proportional manner between 5 to 20 mg/kg in LOPD patients and between 20 and 40 mg/kg in IOPD patients. No accumulation was observed following every other week dosing.

Immunogenicity

In the study 1, EFC14028/COMET, 96.1% (49 of 51 patients) receiving avalglucosidase alfa developed treatment-emergent ADA. As only 2 patients were ADA-negative, the ADA impact on PK was assessed by categorising the ADA-positive patients into 3 peak titre groups: ≤800, 1,600-6,400, and ≥12,800. Five patients had ≥50% change in the AUC at week 49 from baseline but no obvious pattern in titres. Inter-subject comparison of the AUC at Day 1 or 2 and week 49 supported the overall analysis of percent change in the AUC and ADA positivity categorieed by ADA titres. In vitro evaluation of neutralising antibodies that inhibited enzyme activity or inhibited cellular uptake demonstrated no clear relationship of assay positivity with AUC. The treatment-experienced IOPD patients had titres ≤6,400, and as changes in PK were not observed, the relationship to ADA was not evaluated for this group.

Special populations

Population pharmacokinetic analyses in LOPD patients showed that body weight, age, and gender did not meaningfully influence the pharmacokinetics of avalglucosidase alfa.

Hepatic Impairment
The pharmacokinetics of avalglucosidase alfa has not been studied in patients with hepatic impairment.

Renal Impairment
No formal study of the effect of renal impairment on the pharmacokinetics of avalglucosidase alfa was conducted. On the basis of a population pharmacokinetic analysis of data from 75 LOPD patients receiving 20 mg/kg, including 6 patients with mild renal impairment (glomerular filtration rate: 60 to 89 mL/min; at baseline), no relevant effect of renal impairment on avalglucosidase alfa exposure was observed.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, and developmental and reproductive toxicity. Diphenhydramine (DPH) pretreatment was administered in all mouse studies to prevent or minimize hypersensitivity reaction. DPH was not needed in other species.

Repeated doses of avalglucosidase alfa in mice produced measurable anti-drug antibody titers and signs consistent with hypersensitivity. Therefore, the chronic toxicity of avalglucosidase alfa was evaluated only in monkeys for 26 weeks. The no-observed-adverse-effect-level (NOAEL) in monkeys was the highest dose administered (200 mg/kg avalglucosidase alfa every other week IV).

Avalglucosidase alfa caused no adverse effects in a combined male and female fertility study in mice up to 50 mg/kg IV every other day (see section 4.6).

In an embryo-fetal toxicity study in mice, administration of avalglucosidase alfa on Gestation Days 6 through 15 produced maternal toxicity related to immunologic response (including an anaphylactoid

response) at the highest dose of 50 mg/kg/day (1.7 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD). This dose also produced increased postimplantation loss and mean number of late resorptions. Avalglucosidase alfa does not cross the placenta in mice, suggesting that the embryo-fetal effects were related to maternal toxicity from the immunologic response. No malformations or developmental variations were observed. The developmental NOAEL in mice was 20 mg/kg/day (see section 4.6).

No adverse effects were observed in an embryo-fetal toxicity study in rabbits administered avalglucosidase alfa on Gestation Day 6 through 19 up to 100 mg/kg/day IV (6.4 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for patients with LOPD) (see section 4.6).

There were no adverse effects in a pre- and postnatal developmental toxicity study in mice following administration of avalglucosidase alfa once every other day on Gestation Day 6 through Postpartum Day 20. The NOAEL for reproduction in the dams and for viability and growth in the offspring was 50 mg/kg/dose IV.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
L-Histidine HCl monohydrate
glycine
mannitol
polysorbate 80

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials - 48 months

6.4 Special precautions for storage

Store in a refrigerator between 2°C to 8°C. Do not use avalglucosidase alfa after the expiration date on the vial.

The reconstituted and diluted solution should be administered without delay. The reconstituted product can be stored up to 24 hours when refrigerated at 2°C to 8°C and diluted product can be stored up to 24 hours when refrigerated at 2°C to 8°C and up to 9 hours (including infusion time) when stored at room temperature (up to 27°C).

6.5 Nature and contents of container

Each pack contains 1, 5, 10 or 25 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vials are single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Use aseptic technique during preparation.

1. Determine the number of vials to be reconstituted based on individual patient's weight and the recommended dose of 20 mg/kg or 40 mg/kg.

Patient weight (kg) x dose (mg/kg) = patient dose (in mg). Patient dose (in mg) divided by 100 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.
Example: Patient weight (16 kg) x dose (20 mg/kg) = patient dose (320 mg). 320 mg divided by 100 mg/vial = 3.2 vials; therefore, 4 vials should be reconstituted.
Example: Patient weight (16 kg) x dose (40 mg/kg) = patient dose (640 mg).
640 mg divided by 100 mg/vial = 6.4 vials; therefore, 7 vials should be reconstituted.

2. Remove the required number of vials needed for the infusion from the refrigerator and set aside for approximately 30 minutes to allow them to reach room temperature.
3. Reconstitute each vial by slowly injecting 10 mL of Sterile WFI to each vial. Each vial will yield 100 mg/10 mL (10 mg/mL). Avoid forceful impact of the water for injection on the powder and avoid foaming. This is performed by slow drop-wise addition of the WFI down the inside of the vial and not directly onto the lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl, or shake. Avoid any air introduction into the infusion bag during the dilution of the product.
4. Perform an immediate visual inspection of the reconstituted vials for particulate matter and discolouration. If upon immediate inspection opaque particles are observed or if the solution is discoloured, do not use. Allow the solution to become dissolved.
5. The reconstituted solution should be diluted in 5% dextrose in water to a final concentration of 0.5 mg/mL to 4 mg/mL. See Table 6 for the recommended total infusion volume based on the patient weight.
6. Slowly withdraw the volume of reconstituted solution from each vial (calculated according to patient's weight).
7. Add the reconstituted solution slowly and directly into the 5% dextrose solution. Avoid foaming or agitation of the infusion bag. Avoid air introduction into the infusion bag.
8. Gently invert or massage the infusion bag to mix. Do not shake. The reconstituted and diluted infusion solution should be protected from light.
9. It is recommended to use an in-line, low protein binding, 0.2 µm filter to administer avalglucosidase alfa. After the infusion is complete, flush with dextrose 5% in water bag.
10. Do not infuse avalglucosidase alfa in the same intravenous line with other products.

Table 6: Projected intravenous infusion volumes for avalglucosidase alfa administration by patient weight at 20 and 40 mg/kg Dose

Patient Weight Range (kg)	Total infusion volume for 20 mg/kg (mL)	Total infusion volume for 40 mg/kg (mL)
5.1 to 10	50	100
10.1 to 20	100	200
20.1 to 30	150	300
30.1 to 35	200	400
35.1 to 50	250	500
50.1 to 60	300	600
60.1 to 100	500	1000
100.1 to 120	600	1200
120.1 to 140	700	1400
140.1 to 160	800	1600
160.1 to 180	900	1800
180.1 to 200	1000	2000

7. SCIENTIFIC OPINION HOLDER

Aventis Pharma Ltd t/a Sanofi
410 Thames Valley Park Drive
Reading
Berkshire
RG6 1PT

8. EAMS NUMBER

04425/0004

9. DATE OF SCIENTIFIC OPINION

05/03/2021

Information updated on 04/10/2021

Contact information

Email: GB-EAMS-Pompe@sanofi.com
Tel: 08000 35 25 25.