

SCIENTIFIC DISCUSSION

1. Introduction

Pompe disease is a rare autosomal recessive disease caused by the deficiency of acid α -glucosidase (GAA), which degrades lysosomal glycogen through the hydrolysis of α -1,4- and α -1,6- glycosidic linkages. Other names for Pompe disease include Glycogen Storage Disease type II, Acid Maltase Deficiency, and Glycogenosis type II. The disease is characterized by organelle bound (lysosomal) accumulation of glycogen, as opposed to the exclusively cytoplasmic accumulation of glycogen that occurs in other glycogen storage disorders.

The absence, or almost complete absence, of GAA in Pompe disease leads to the accumulation of high levels of glycogen in various tissues, particularly cardiac and skeletal muscle, as well as respiratory muscles, leading to generalised myopathy, cardiomyopathy and respiratory failure. Pompe disease can be considered as a spectrum of disease as the clinical presentation of GAA deficiency ranges from a rapidly fatal, usually infantile disease (the classic infantile form) characterized by profound muscle weakness and flaccidity (often referred to as floppy baby) and by a progressive cardiomyopathy, to a slowly progressive late onset myopathy (juvenile and adult forms) where involvement of skeletal muscles dominates the clinical picture and respiratory insufficiency is frequent. In general, there is an inverse correlation between the amount of residual GAA activity and the severity of the disease. In addition to the two forms described above, a second milder subtype of the infantile form with less severe cardiomyopathy, absence of left ventricular outflow obstruction, and traces (less than 5%) of residual acid maltase activity has been described; most of these children had longer survival with assisted ventilation and intubation.

Since there is currently no authorised medicinal product available in the EU for the treatment of Pompe disease, palliative and supportive care provides the mainstay of management.

About the product

Myozyme is a recombinant human acid alpha-glucosidase (rhGAA; INN: alglucosidase alfa) developed for an intravenous enzyme replacement therapy (ERT) for the treatment of both early- and late-onset Pompe disease. It is postulated that Myozyme will restore lysosomal GAA activity resulting in stabilisation or restoration of cardiac and skeletal muscle (including muscles of the respiratory system). Infused rhGAA is only biologically active after lysosomal uptake. Myozyme is provided as a lyophilized powder for solution for injection; see 3.2. for details. The recommended dosage regimen of Myozyme is 20 mg/kg of body weight administered once every 2 weeks as an intravenous infusion.

Genzyme has been actively involved in developing an ERT for Pompe disease since 1998. During development, different sources of rhGAA have been used, and finally using the current CHO cell line and rhGAA purification process (Myozyme). Myozyme has been used in clinical trials in patients with Pompe disease since early 2003. Since this time, the safety and efficacy of Myozyme was studied in two main clinical studies in patients with infantile-onset Pompe disease (≥ 6 months and ≤ 36 months of age in AGLU01702, and ≤ 6 months of age in AGLU01602). In addition, Myozyme was used for the treatment of both infantile and late-onset patients via expanded access mechanisms.

This was a stand-alone application for a new active substance, which will be subject to medical prescription. No scientific advice was given by the CHMP, but the applicant had met several times with Belgian and French authorities. Clinical trials were performed in children, and in a few young adults, due to the nature of the disease. An Orphan Drug Designation was granted to Myozyme on 14 February 2001; the calculated prevalence of this condition was 0.137 per 10.000 EU population.

The applicant submitted an EU-risk management plan (including parts on Safety specification, Pharmacovigilance plan, Assessment of the need for risk minimisation activities).

2. Quality aspects

Introduction

The drug Substance of Myozyme is recombinant human acid alpha-glucosidase (rhGAA), a hydrolase that degrades lysosomal glycogen to glucose. This glycoprotein is produced by recombinant DNA technology on Chinese Hamster Ovary (CHO) cell line according to a continuous harvest cell culture process. Following collection of cell culture harvests, the enzyme is purified by several chromatographic steps.

Myozyme is provided as a lyophilized powder for solution for injection. The finished product is provided in a 20 mL vial containing 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate and 31.2 mg sodium phosphate monobasic monohydrate. The contents of the vial should be reconstituted with 10.3 mL Water for Injection. The reconstituted product contains 5 mg/mL alglucosidase alfa.

Initially, Genzyme entered into partnership with Pharming N.V. (Geel, Belgium) to develop rhGAA purified from the milk of transgenic rabbits (referred to as Pharming rhGAA). In 2000, due to concerns over process scalability and supply issues, rhGAA was produced in Chinese Hamster Ovary (CHO) cell line by Synpac North Carolina Inc. (referred to as Synpac rhGAA). However, concerns about the scalability, productivity and culture process lead Genzyme to develop its own production process using an independently derived CHO cell line (referred to as Myozyme and Genzyme rhGAA), which has been used in clinical trials in patients with Pompe disease since early 2003.

During early development Genzyme also manufactured preclinical and clinical trial materials at the 30L/60L scales using CHO cells cultivated in microcarrier-based continuous perfusion process bioreactors. The drug substance was later produced in CHO cells cultivated in a microcarrier-based continuous perfusion process bioreactor, at two larger bioreactor scales at different sites: Genzyme was requesting marketing authorization for both the 160 L and 2000 L production scales

There were major concerns with regard to the potential levels of process impurities (host cell proteins, HCP and DNA) and possible immunogenicity of CHO cell impurities for the 160L scale.

Initially, there was insufficient data to demonstrate the consistency of the 2000L process and product. However, the impurity profile of the 2000L process (process related impurities, i.e. Host Cell Proteins / DNA) seems to be improved compared to the 160L process and it was recommended to review this, once: i) consistency is demonstrated for the 2000L process and derived product, ii) lower protein impurity content is confirmed by appropriate validation and process-specific detection kit and iii) clinical experience on product derived from the 2000L process is acquired. These major objections were lifted at later stages of the review procedure. Only the 2000L process was recommended for marketing authorisation.

Active Substance

- Manufacture

The 160 L manufacturing process was adequately validated. In contrast, no process validation data were available for the 2000 L process and this was considered as a major objection. During the procedure the required validation data have been provided and the 2000 L scale process was considered satisfactory.

- Specification

Satisfactory specifications and validation of analytical methodology have been provided for control of the active substance. Each batch of active substance is tested for identity, purity and potency. The specifications according to which the tests are performed are justified by batch data as well as data obtained for batches used in preclinical studies and clinical trials. All routine methods used as control

or release tests of starting materials, process intermediate, drug product and stability samples were validated when appropriate. No compendial reference standard of rhGAA is currently available. The company has developed its own reference standards for product testing purposes.

- **Stability**

Based on the stability data provided, a 4 weeks storage period for drug substance stored at 6-10°C may be recommended.

Stability studies demonstrate stability of the Formulated Drug Substance, stored in stainless steel containers during 6 months at 2 – 10°C.

Medicinal Product

Myozyme is a sterile lyophilized dosage powder for injection after reconstitution with WFI.

Myozyme is supplied in a container closure system consisting of a 20cc Type I glass tubing vial, a siliconized 20 mm gray butyl lyophilization stopper and a 20 mm six bridge aluminium seal. The nominal content of the 20 cc vial is 50 mg of active ingredient, alglucosidase alfa. Prior to lyophilization, each vial is filled with 10.5 ml of a buffered solution containing 5 mg/ml drug substance. A 0.5 ml overfill is included to provide a sufficient volume upon reconstitution for withdrawal of 50 mg reconstituted Myozyme. Each vial is intended for single use administration only.

- **Pharmaceutical Development**

Thermal screening studies were initially conducted to evaluate the effects of buffer species, ionic strength, pH, and pharmaceutical excipients on the solution behaviour of rhGAA. Additional buffer/pH screening studies indicated that Genzyme rhGAA would be stable at pH 6.2. Sucrose and mannitol synergistically contribute to the stability of formulated drug substance and facilitate lyophilization of the drug product.

During the scale-up and optimisation of the production batches, three changes were made to the final product formulation:

- The ionic strength of the formulated drug substance buffer was increased from 20 mM to 25 mM
- Addition of polysorbate 80 at a nominal concentration of 0.005%
- Sucrose was removed from the formulation, which did not negatively impact the stability of the formulated drug substance, the lyophilization process, the cake quality, product recovery following reconstitution and the stability of the finished product.

The specifications and stability data resulting from the development of the formulation are satisfactory.

Manufacture of the Product

The manufacture of rhGAA Drug Product consists of three major steps:

1. rhGAA formulation
2. Filling, lyophilization and capping
3. Labelling and packaging

The rhGAA Formulated Drug Substance is aseptically processed and sterilized by filtration through a 0.22 µm filter. This method of sterilization is chosen due to the inability of protein products to withstand terminal sterilization. Product is filled into previously depyrogenated final containers, stoppered with pre-sterilized stoppers and sealed. Sterile filtration and lyophilization of bulk rhGAA in glass vials have been validated.

The rhGAA Formulated Drug Substance is not compounded with a preservative and therefore each vial is intended for single use only.

- **Product Specification**

Specifications have been chosen to conform to ICH Q6B. Specification limits were developed from historical batch release data, as well as stability data, for Drug Product lots derived from Drug Substance lots manufactured at three different scales (30 L/60 L, 160 L and 2000 L). These lots were used clinically, in process validation and biochemical comparability studies.

In general the proposed commercial specification limits are consistent with those established for process validations, and were developed based on Pharmacopeial requirements, targeted or theoretical values \pm range, mean \pm confidence limits and observed or expected stability trends.

The specifications and validation of analytical methodology for control of the finished product are considered to be satisfactory.

- **Stability of the Product**

The data provided support the following:

1. An expiration date of 18 months for Myozyme when stored at 2 – 8°C
2. Storage of Myozyme, reconstituted and diluted for infusion with 0.9% sodium chloride, USP/EP, for up to 24 hours at 2 – 8°C

Discussion on chemical, pharmaceutical and biological aspects

Two proposed commercial manufacturing scales, displaying some differences, were described, i.e. the 160 L and 2000 L processes. Major objections were raised regarding the comparability and the consistency of these 160 L and 2000 L processes.

Based on the data provided, the protein impurities could not be directly correlated to the immunogenicity of the product and it was considered that rhGAA itself may play an important role. Nevertheless protein impurities are considered qualitatively and quantitatively "product and process specific", and are considered as a potential risk factor that should be avoided as much as possible.

Consequently, it was stressed to the applicant that further efforts to reduce this impurity level and to tighten the protein impurities acceptance limit according to batch results should be pursued. In addition, the high protein impurity level was brought to the attention of clinical assessors.

Process validation of the 2000 L scale manufacturing process has been completed and demonstrates acceptable consistency.

The applicant has addressed concerns regarding stability and particulates.

Five biological reagents have been used in the production of Myozyme: donor bovine serum, foetal bovine serum, porcine derived trypsin/EDTA, salmon derived protamine sulfate and salmon derived 2-deoxycytidine. Questions raised to confirm the TSE status of these materials have been satisfactorily addressed.

The viral safety of rhGAA was well addressed. The MCB, MWCB and EOP cells were assayed for adventitious and endogenous agents. No viral particles were observed other than retroviral-like particles normally seen in the MCB and EOP cell types. The starting material does not include any human material and the material of animal origin used is well characterized. Virus validation studies have been performed to meet the CPMP/BWP/268/95 guideline.

Overall, the applicant provided clear and informative responses to most issues raised during the assessment of the marketing authorisation application for Myozyme and points raised in the Day 120 List of Questions. All major objections were adequately addressed although some recommendations regarding the level of impurities as well as the specific protein impurities assay are maintained as outstanding issues and commitments.

In conclusion, from a quality perspective, the 2000L production process may be recommended for approval.

3. Non-clinical aspects

Pharmacology

- Primary pharmacodynamics (in vitro/in vivo)

Results from all non-clinical pharmacology studies of Myozyme suggest effective depletion of glycogen when administered to an animal model of Pompe disease – acid alpha-glucosidase (GAA) knockout mouse.

The time course of the disease progression in the GAA knockout mice used by the applicant shares features with that of infantile and late-onset Pompe patients; however, if the life span of mice was considered, the model resembled more closely a late in life disease progression. Despite the lack of early clinical symptoms, the applicant considered that GAA knockout mice provide a valuable tool for non-clinical studies. The mice lack GAA enzyme activity; therefore they can be used to evaluate the pharmacokinetics and biodistribution of GAA activity following administration of clinically relevant doses of Myozyme. Moreover, since the heart and skeletal muscle of GAA knockout mice contain accumulated glycogen, they can also be used to evaluate the pharmacodynamic effects of Myozyme administration on glycogen depletion. Nonclinical studies performed in these mice provided insight into the appropriate dose and dosing regimen required to produce the desired clinical results. The majority of the pharmacodynamic studies were conducted using mice less than 6 months of age which did not display obvious signs of muscle weakness; therefore, the ability of Myozyme to reverse or stabilize the clinical phenotype was not assessed in these studies.

Almost complete depletion of substrate could be seen in the heart following a single dose of 100 mg/kg of Myozyme. This same efficacy was not noted in the skeletal muscles following a single 100 mg/kg dose which suggested that multiple dosing intervals may be necessary to effectively clear substrate in this tissue. With repeated dosing at 100 mg/kg for 4 weekly doses, all tissues were effectively depleted of glycogen. Long-term efficacy was not studied at the 100 mg/kg dose, but at lower dose levels.

The most appropriate dosing interval was determined by assessing the re-accumulation of substrate over time following a single dose. The data show re-accumulation of substrate beginning >21 days in the heart following a single dose. Based upon these data, comparative studies were conducted to examine efficacy of Myozyme administered once weekly or every other week. A dose range of 10-40 mg/kg of Myozyme was evaluated over a period of weeks for the ability to clear substrate from target tissues (heart and skeletal muscle specifically). In general, the results showed that the total cumulative dose administered over the dosing interval showed similar reductions in glycogen in the target organs (i.e., 20 mg/kg weekly was comparable to 40 mg/kg every other week). Additional studies were conducted to determine if an initial high dose of Myozyme could be administered, followed by repeated low doses, in order to decrease substrate more effectively. These studies were unable to show that an initial high dose followed by repeated lower doses was an effective strategy in this mouse model.

In vitro studies showed differences in affinity for the mannose- 6- phosphate receptor and uptake into Pompe fibroblasts between different sources of rhGAA. However, there were no significant pharmacodynamic differences noted in glycogen depletion across any of the CHO derived rhGAAs

evaluated in the GAA knockout mice, probably due to the complex involvement of other mechanisms in the process of uptake of rhGAA into the muscle.

A study was conducted to evaluate glycogen depletion in 3-month-old mice as compared to 12-month-old mice. Mice were treated according to established dosing regimens from previous studies. Depletion of glycogen from skeletal muscle was more efficient in 3-month-old mice when compared to 12-month-old mice. Furthermore, the tissue distribution of enzyme following dosing also varied with age; with increased levels of Myozyme detected in the heart and decreased levels detected in the skeletal muscles of the 12 month old mice as compared to the 3 month old mice. Although a direct extrapolation to human is not possible, these results supported an early treatment in the clinical situation.

- Secondary pharmacodynamics

Histamine and significant IgE and IgG1 antibody titers were consistent with a hypersensitivity response to a human protein in knockout mice. Similar findings were noted in wild type mice (C57Bl/6) and rats. However, in clinical trials, there was no correlation between Cross-Reacting Immunologic Material (CRIM) status, time to seroconversion, magnitude of antibody titer or occurrence of infusion associated reactions (IARs). This suggests that the observation of severe hypersensitivity in rodents was not predictive of the response seen in the clinic.

- Safety pharmacology

A study was conducted to evaluate the safety pharmacology of Myozyme in Beagle dogs after a single bolus IV administration. Administration of Myozyme at 1, 10, and 100 mg/kg did not show any effects on general condition, blood pressure, heart rate, respiration rate, or rectal body temperature. There was no indication of adverse effects on the respiratory or cardiovascular system from this study.

In order to evaluate potential effects on the cardiac conduction, the applicant initiated a new study to assess the effect of Myozyme on the cardiovascular system of the cynomolgus monkey. This study showed that no qualitative ECG abnormalities were associated with the intravenous administration of 100 mg/kg Myozyme.

No additional safety pharmacology studies were conducted with Myozyme to evaluate the effect on the central nervous system, as the protein is unlikely to cross the blood- brain barrier and therefore neurological toxicity is not expected.

- Pharmacodynamic drug interactions

Pharmacodynamics drug interaction studies were not performed. Myozyme is a protein and is expected to be metabolically degraded through peptide hydrolysis. Based on its expected metabolism, Myozyme is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

Pharmacokinetics

During the development of Myozyme, changes in formulation and manufacturing scale were evaluated for comparability. In addition, pharmacokinetics were evaluated across multiple species including the GAA knockout mouse model, following single and repeat administration and at multiple dose levels. Several bioanalytical methods were used during the development of Myozyme. All assays used for analysis were qualified and appropriate technical reports were provided.

Repeat dose pharmacokinetics were conducted in Sprague-Dawley rats as part of a 28 day subchronic toxicology study, and in Cynomolgus monkeys as part of a 6 month chronic toxicology study.

- Absorption- Bioavailability

When the AUC was plotted from rat, dog and monkey against dose a linear relationship was seen across all species and doses with exposures at all doses similar. The one exception was seen in male monkeys where the AUC was significantly higher than in female monkeys. This suggested an increased exposure in male monkeys; however this was not correlated to any findings in histopathology or clinical pathology parameters. Additionally, these AUC differences between sexes were not noted in the rat or dog.

When an evaluation was made across the species (excluding the male monkeys) the highest dose administered (100 mg/ kg) resulted in an AUC ranging from 176,441-276,563 $\mu\text{g}\cdot\text{min}/\text{mL}$. The highest dose administered in the AGLU01702 clinical study (20 mg/kg) resulted in an average AUC of 54,060 $\mu\text{g}\cdot\text{min}/\text{mL}$ (901,074 h x ng/mL). Therefore exposure achieved across multiple species was 5 times that achieved in the AGLU01702 clinical trial of Myozyme. Further calculations using relevant PK models to compare the PK in monkeys and humans, showed that the exposure in non-human primates with a 200 mg/kg dose was approximately 6 times higher than a 40 mg/kg dose in humans. In the absence of clear toxic effects this safety margin was considered acceptable.

The data also showed a very good linearity across species, which allowed for a solid evaluation of safety at higher doses and an establishment of an accurate safety margin based upon exposure. The pharmacokinetic analysis comparing multiple formulations and scales showed slight differences in AUC on some occasions.

There was a difference observed in the AUC at doses of 20 mg/kg when the pharmacokinetic parameters were compared in the GAA knockout mouse as compared to the normal mouse. Comparisons showed that there was a consistently higher exposure in the knockout animal (average AUC across multiple studies of 46,607 min x $\mu\text{g}/\text{mL}$) as compared to the normal animal. (28,982 min x $\mu\text{g}/\text{mL}$ from normal CD:1 mice). However, as the exposures determined for normal mice were at the lower end of the range of AUCs determined in the knockout mice in different studies, the use of normal mice for the toxicology studies was considered acceptable.

- Distribution

Biodistribution studies conducted in normal and knockout mouse and following administration of different formulations and scales showed very little difference in their distribution. The majority of the material distributed to the liver with smaller amounts distributing to other organs (heart, spleen, lung and kidney). Only a small amount of material was measured in the skeletal muscles collected.

- Metabolism (in vitro/in vivo)

There were no studies of metabolism performed with Myozyme. Myozyme is a protein and is expected to be metabolically degraded through peptide hydrolysis.

- Excretion

There were no excretion studies with myozyme, which is acceptable for such a product.

Toxicology

The toxicology evaluation was done in accordance with the guidance in ICH S6 and with ICH M3. The safety of Myozyme was evaluated in different normal animal species (mouse, rat, dog, monkey), at multiple dose levels (1-200 mg/ kg;) and following acute and chronic administration. Two single dose acute toxicity studies in rats and dogs, two repeat dose subchronic toxicity studies in rats, one repeat dose subchronic toxicity study in mice and two repeat dose chronic toxicity study in Cynomolgus monkeys were performed to evaluate the safety of Myozyme administered IV. Furthermore, 2 reproductive toxicity studies were conducted in mice to assess the effect of Myozyme on embryo-foetal development and on fertility and early embryonic development. All studies were conducted in compliance with the GLP regulations.

- Single dose toxicity

In the single dose acute toxicity studies in rats and dogs, Myozyme was generally well tolerated up to 100 mg/kg IV. In 2 of 6 dogs administered Myozyme at 10 mg/ kg, and 3 of 6 dogs administered Myozyme at 100 mg/ kg, tremors were observed 60 minutes post- dose.

- Repeat dose toxicity (with toxicokinetics)

An overview of the conducted repeat-dose toxicity studies is provided in the following table.

Table 1: An overview of repeat-dose toxicity studies

Species	Dose/Route	Duration	NOAEL (mg/kg/day)	Animal:Human Exposure Multiple (low, mid, high doses)	
				♂	♀
SD rats	0, 1, 10, 100 mg/kg Myozyme IV (5 mg/kg diphenhydramine on D15 & D22)	4 weeks (once weekly dosing)	F: >10 mg/kg M: 1 mg/kg	0.03 0.38 5.22	0.04 0.43 4.94
SD rats	0, 5, 10, 50 mg/kg Myozyme IV	4 weeks (once weekly dosing)	No NOAEL	-	-
C57Bl/6 Mice	0, 1, 10, 100 mg/kg Myozyme IV	4 weeks (once weekly dosing)	100 mg/kg Myozyme	-	-
Cynomolgus monkey	0, 4, 20, 100 mg/kg Myozyme IV	26 weeks (6-hr infusion every other week dosing)	100 mg/kg	♂ 0.04 1.00 5.62	♀ 0.04 0.76 3.84
Cynomolgus monkey	0, 200 mg/kg Myozyme IV	13 weeks (12-hr infusion every other week dosing)	n.a.		

*AGLU01702 clinical study 20 mg/kg: AUC of 54,060 min x μ g/ mL (901,074 h x ng/ mL)

In the first repeat dose subchronic toxicity study conducted in rats an anaphylactic response was observed in two of 10 animals administered Myozyme at the third dose of 100 mg/kg. Animals in all dose groups were then administered diphenhydramine following the third and fourth dose of Myozyme to counteract potential anaphylactic responses. Following administration of Myozyme at 10 and 100 mg/ kg and diphenhydramine at 5 mg/ kg, some animals still demonstrated clinical responses. Decreases in body weight and body weight changes were noted in males administered 10 and 100 mg/kg of Myozyme. There were no test article-related effects on macroscopic pathology.

In a second repeat dose subchronic toxicity study in rats pronounced clinical signs consistent with a hypersensitivity response were observed in many animals following the third dose of Myozyme despite pretreatment with diphenhydramine. The majority of animals returned to normal by one hour post- dose, however, two female animal deaths were observed within 2 hours of the third dose administration of Myozyme (one from the 10 mg/ kg group and the other from the 50 mg/ kg group). This mortality also appeared to be related to a hypersensitivity reaction to the administered protein. Based on these results, it was not possible to assign a NOEL for any of the test articles as all dose groups showed signs of a hypersensitive reaction to the respective test articles administered.

From the two rat studies, it was concluded that this species appeared to be particularly sensitive to repeated administration of Myozyme.

In the study conducted using C57Bl/ 6 mice no significant clinical signs were observed. In addition, there were no biologically relevant clinical pathology findings with the exception of two female mice with mildly elevated liver enzymes. All microscopic lesions seen were common in mice and were considered incidental to test article administration. Therefore, based on these results, there were no adverse toxic results when Myozyme was administered IV for 4 weekly doses up to 100 mg/ kg in mice.

To further evaluate the dosing intended for humans, Myozyme was administered by a 6 hour IV infusion to Cynomolgus monkeys in the chronic toxicity study. Clinical observations were unaffected by treatment. There were no observations of any tremor-like activity as had been seen in the single

dose toxicity study in dog. No toxicologically relevant test-article related changes occurred in clinical pathology parameters, terminal body and organ weight values and there were no histopathologic findings attributable directly to the test article itself. All monkeys administered Myozyme developed circulating rhGAA-specific IgG antibodies (See below: Other toxicity studies/ Antigenicity). However, there were no signs consistent with a hypersensitivity response. Similarly, there were no clinical observations associated with dose administration, no findings in any clinical chemistry parameters and no findings noted in histopathology review of all tissues. Therefore, it is likely that those findings considered to be significant in the rat and dog may be related to the administration of a recombinant human protein as a rapid bolus injection. In the determination of the true NOAEL consideration must be given to the effect that administration (including dose and dosing regimen) of a recombinant human protein has on other species. The toxicokinetic analysis suggested that the systemic exposure was not compromised by the presence of circulating antibodies. In addition to the above, liver rhGAA activity levels were determined to investigate the possibility of liver accumulation over time. There was a dose response with respect to the levels of rhGAA recovered in the liver. At day 14 post-dose in the 100 mg/ kg group, the rhGAA levels declined significantly from that observed 24 hours post dose; however, levels above background were still detectable suggesting that chronic administration may result in liver accumulation over time. In conclusion, the NOEL for Myozyme when administered as a 6-hour intravenous infusion once every other week to Cynomolgus monkeys for at least 13 treatments is >100 mg/ kg/ dose.

Due to the lack of observed toxicity in Cynomolgus monkeys upon administration of up to 100 mg/kg Myozyme, a second study was initiated in which monkeys received 200 mg/kg Myozyme every other week for 3 months. The results demonstrated that there were no treatment-related clinical observations, laboratory or pathology findings. All catheter and infusion site-related microscopic changes were considered to be within anticipated limits and not test article-related. All monkeys administered Myozyme developed circulating rhGAA-specific IgG antibodies. The toxicokinetic analysis suggested that the systemic exposure was not compromised by the presence of circulating antibodies. The toxicokinetic parameters indicated that sufficient exposure was reached in the toxicology portion of the study to draw conclusions of safety following repeated administration of Myozyme up to 200 mg/kg. Liver Myozyme activity levels were also determined: at day 22 post-dose in the 200 mg/ kg group, the Myozyme levels declined significantly from that observed 8 days post dose; however, levels above background were still detectable suggesting that chronic administration may result in liver accumulation over time. It should be noted that in both chronic toxicity studies, Myozyme accumulation in the liver was not associated with any adverse clinical pathology or histopathology in the recovery animals.

- Genotoxicity in vitro and in vivo (with toxicokinetics)

Studies to assess the mutagenic potential of Myozyme were not conducted. Mutagenic potential would not be anticipated with Myozyme based on the structure of the drug substance (a recombinant human glycoprotein), its impurity profile and the excipients in the final product (mannitol, polysorbate 80 and sodium phosphate). In addition, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology- derived pharmaceuticals and therefore are generally not required. This is also acceptable in accordance with ICH S6 (Preclinical safety evaluation of biotechnology-derived pharmaceuticals).

- Carcinogenicity (with toxicokinetics)

No carcinogenicity studies were conducted with Myozyme, although this therapeutic is intended for long-term treatment with a total exposure over a lifetime greater than 6 months.

Carcinogenic potential would not be anticipated with Myozyme based on the structure of the drug substance (a recombinant human glycoprotein), its impurity profile, and the excipients in the final product (mannitol, polysorbate 80 and sodium phosphate). The biochemical properties of Myozyme are well characterized, and there are no known interactions with DNA. According to ICH S6 standard carcinogenicity studies are not required for biotechnology-derived pharmaceuticals except when there is a concern about the carcinogenic potential; the CHMP agreed that a carcinogenic potential is not suspected for Myozyme.

- Reproductive and developmental studies

Two reproductive toxicity studies were initiated to evaluate the effects of Myozyme in mice.

The effect of Myozyme on embryo-foetal development was evaluated in mice. There were no treatment related mortality or remarkable clinical observations during the study. The mean post implantation loss values were similar among the groups.

There were no foetal external variations. The foetal and litter incidences of total external malformations were similar across groups. The foetal soft tissue variations noted were common for the strain of mouse used. There was a slightly increased incidence of malrotated limbs in high dose fetuses. However, the biological significance of this finding is doubtful. In conclusion, the NOEL for maternal toxicity and for embryo-foetal viability, growth and foetal development (teratogenicity) in mice is considered to be 40 mg/kg/day, corresponding to exposures similar to 40 mg/kg/dose in humans.

The second study evaluated the fertility and embryonic development in mice at doses of 0, 10, 20 and 40 mg/kg. There were 3 unscheduled deaths during the study attributed to an anaphylactic-type reaction resulting from repeated administration of a recombinant human protein and not to direct toxicity associated with the test article. Treatment had no effect on mean body weight gain, food consumption or on selected male reproductive organs (testes, seminal vesicles, prostate, and epididymides). The estrous cycle was unaffected. A decreased fertility index was observed in all groups (including controls). Based upon these conclusions, a subsequent study was initiated to investigate the effect of the vehicle, the IP administration of diphenhydramine and the stress of handling on female fertility. Results from this study are expected in the post authorisation phase (as a follow-up measure).

Cesarean section data from the pregnant mice were unremarkable. There were no abortions or early deliveries. All pregnant dams had litters with viable fetuses. Of the mice that were pregnant, mean pre-implantation loss was unaffected by Myozyme. Myozyme had no effect on embryo/ fetal viability. However, it is recommended that Myozyme should not be used during pregnancy unless clearly necessary (see SPC 4.6). The sperm analysis report showed a treatment-related reduction in epididymal sperm count in the mid and high dose group and an increase in abnormal sperm morphology in the high dose group after 9 weeks of treatment with rhGAA. The lack of correlation with pregnancy outcome could be due to the relatively short 3- to 4-week pre-treatment period of the males before mating.

No other reproductive toxicology studies were carried out. At the request of the CHMP, the applicant committed to perform an embryo-fetal study in rabbits during the post authorisation phase (as a follow-up measure).

- Local tolerance

Local tolerance studies were not performed because Myozyme is administered by intravenous infusion following reconstitution and dilution and does not include concentrations of irritants or corrosive components that are likely to lead to serious reactions at the injection site. In non-clinical toxicity studies there was no evidence of injection site reactions.

- Other toxicity studies

Antigenicity

A secondary objective of the chronic toxicity study in Cynomolgus monkeys was to determine the antibody response during the 26 week repeat administration study of Myozyme. The antibody response to repeat administration of Myozyme in monkeys was evaluated using an ELISA method.

All monkeys administered Myozyme developed circulating rhGAA-specific IgG antibodies. Generally, the titers observed in all groups peaked at Day 85 and remained high out to Day 169. The observed antibody titers were not dose related. The toxicokinetic analysis suggested that the systemic exposure was not compromised by the presence of circulating antibodies.

The presence of circulating antibodies did not appear to have an effect on the activity of Myozyme as measured by the 4-MUG activity assay. Since the exposure was equivalent in the presence of antibodies the safety of Myozyme could be assessed in the repeat dose non-human primate study.

Impurities

Various formulations of Myozyme were tested during the nonclinical development program. Different formulations were evaluated for their pharmacokinetic equivalence and similar biodistribution characteristics to the formulation intended for commercialization. The formulations tested were shown to have pharmacokinetic equivalence and all ingredients in the formulation buffers are described in a recognized pharmacopoeia or equivalent.

Ecotoxicity/environmental risk assessment

Myozyme does not contain or consist of genetically modified organisms within the meaning of Directive 90/220/EC.

The active drug substance of Myozyme is a recombinant version of a naturally occurring human enzyme, which would have the same metabolites or degradation products as the non-recombinant version. In addition, the concentration or distribution of the substance itself and therefore, its metabolites and degradation products, would not alter significantly the concentration in the environment.

No novel excipients are used in the formulation of Myozyme. The excipients that are in the drug product (i.e. mannitol, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate and polysorbate 80) also do not alter significantly the concentration in the environment. Therefore a risk to the environment is not expected.

Discussion on the non-clinical aspects

Results of pharmacodynamic studies suggested effective depletion of glycogen when administered to an animal model of Pompe disease (GAA knockout mouse). A dose range of 10-40 mg/kg of Myozyme was evaluated over a period of weeks for ability to clear glycogen from target tissues (heart and skeletal muscles). Histamine and significant IgG and IgG1 antibody titers were consistent with a hypersensitivity response in mice. Safety pharmacology studies showed no undesirable pharmacodynamic effects on physiological functions in relation to exposure in the therapeutic range.

The pharmacokinetic data showed a good linearity across species.

There were no toxic findings that were consistent across all species tested. The only finding of significance following a single administration was seen in the dog study. This finding consisted of tremors seen at 10 and 100 mg/kg. This finding could not exclude a test article effect.

It is clear from the data presented that there is a consistent finding of hypersensitivity in many of the animal models evaluated. With the exception of the non-human primate study, all species administered Myozyme showed some kind of hypersensitivity response. This hypersensitivity response was not included in the consideration of the NOAEL which was justified as this rodent finding did not appear to be predictive of the response seen in the clinic.

For Myozyme administered repeatedly as a slow infusion, the NOEL is > 100 mg/kg. The exposure assessed at this dose level identifies a 5X safety margin over the recommended dose (20 mg/kg every other week). Further calculations using relevant PK models to compare the PK in monkeys and humans, showed that the exposure in non-human primates with a 200 mg/kg dose was approximately 6 times higher than a 40 mg/kg dose in humans. In the absence of clear toxic effects this safety margin was considered acceptable.

Slight embryo-fetal effects were seen in the mouse at high dose (malrotated limbs), and a study in rabbits will be available in post-authorisation (as a follow-up measure). Small effects on male and female fertility were also observed and the results of further investigations will be available in post-authorisation (as a follow-up measure). A warning in pregnancy is included in the SPC (4.6).

No genotoxicity or carcinogenicity studies were performed, which was acceptable as no such potential is expected for this product.

No impact on the environment is expected from a protein.

4. Clinical aspects

Introduction

Efficacy of Myozyme in the treatment of Pompe disease was studied in two main clinical studies (AGLU01602 and AGLU01702). Several other supportive studies with earlier rhGAA products or data from expanded access programs, using Myozyme, were also submitted as supportive data. All studies with Myozyme are listed in Table 2 below.

Table 2: Clinical Studies with Myozyme

Study Number	Study Design	No./ Location of Enrolling Centers	No. of Subjects Enrolled /Treated Planned	Dose Range & Frequency	Mean Age \pm SD at Study Start
NATURAL HISTORY STUDY ¹					
AGLU-004-00	Natural History Study	33/ 9 countries	168/0	NA	NA
MYOZYME INFANTILE-ONSET STUDIES and EXPANDED ACCESS PROGRAMS					
AGLU01602	Randomized, Open-label, Multicenter Safety, Efficacy, Pharmacokinetic and Pharmacodynamic, Dose Ranging Study of Myozyme	7/ USA, Europe, Israel, Taiwan	19/18 ²	20 or 40 mg/kg qow	4.6 \pm 1.67 months ³
AGLU01702	Open-label Multicenter Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of Myozyme	6/ USA, Europe, Israel	16/15 ⁴ (21)	20 mg/kg qow	17.9 \pm 12.1 months
AGLU02203 (US)	Open-label, Expanded Access Study of Myozyme	5/ USA	5/5 ⁵	20 mg/kg qow	10.3 \pm 3.6 years
AGLU02203 (Europe)	Open-label, Expanded Access Program of Myozyme	20/ Europe, Israel	8/8 ⁶	20 mg/kg qow	3.7 \pm 3.4 years
AGLU02003	Open-label, Extension Study of Myozyme	6/ USA, Europe, South Africa	7/7	10 or 20 mg/kg/wk, or 20 or 40 mg/kg qow	Synpac rhGAA: 21.7 \pm 30.1 months ⁷ Myozyme: 41.2 \pm 20.5 months
Expanded Access	Per Patient Expanded Access program	3/ Europe, Taiwan	3/3 ⁸	10 mg/kg/wk to 40 mg/kg/wk	15.3 \pm 14.4 months
MYOZYME LATE-ONSET STUDIES and EXPANDED ACCESS PROGRAMS					
AGLU02804	Open-label, Single Center Safety, Efficacy, and Pharmacokinetic Study of Myozyme	1/ Europe	5/5	20 mg/kg qow	11.1 \pm 3.7 years
AGLU02103	Open-label, Extension Study of	1/ USA	1/1	30 mg/kg qow	Pharming/ Synpac

	Myozyme				rhGAA: 16.4 years Myozyme: 20.2 years
AGLU02503	Open-label, European Expanded Access Program of Myozyme	2/ Europe	3/2	20 mg/kg qow	9.2 – 19.8 years
AGLU02603 (Europe)	Open-label, Expanded Access Program of Myozyme	7/ Europe	10/10 ¹⁰	20 mg/kg qow	37.7 ± 4.2 years
Expanded Access	Per Patient Expanded Access Program	1/ Europe	1/1	10 mg/kg/wk to 30 mg/kg qow	32.3 years
AGLU02604	Expanded Access Program	1/ USA	2/2	20 mg/kg qow	19 – 39 years
AGLU01202	Late-Onset International (Rotterdam EAP)	2/ Europe	2/2	20 mg/kg qow	15.4 – 36.5 years

¹ AGLU-004-00 was a retrospective chart review study of 168 untreated patients with infantile-onset Pompe disease. Historical reference groups for the AGLU01602 and AGLU01702 studies were derived from this study.

² Nineteen patients enrolled, but 1 patient required invasive ventilation prior to initiation of treatment and was therefore discontinued from the study.

³ Age at first infusion was adjusted for gestational age.

⁴ Sixteen patients enrolled, but 1 patient died before initiating treatment. Note that a total of 21 patients have been treated under this protocol; interim results were obtained from the first 15 patients who had received up to 52 weeks of treatment.

⁵ A total of 15 patients were being treated under this protocol; data from the first 5 patients enrolled and treated for at least 26 weeks were provided.

⁶ 22 patients were being treated under this protocol; data were available from physician narratives received on 8 patients treated for at least 6 months.

⁷ Patients only received Myozyme under these protocols but age at initiation of first ERT is also shown.

⁸ Efficacy data for 2 of the 3 infantile-onset patients were available.

¹⁰ Efficacy data were available from physician narratives on 10 patients treated for at least 6 months.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The Applicant stated that the clinical studies were carried out according to GCP.

Pharmacokinetics

The rhGAA in human plasma was measured using a 4-methylumbelliferyl- α -D-glucoside (4-MUG) substrate. This was a fluorometric assay with a lowest limit of quantification in plasma of 12.5 ng/ml.

- Absorption and distribution

In the clinical trial (AGLU01602) including 18 patients, the pharmacokinetics of Myozyme were evaluated in 15 patients with infantile-onset Pompe disease (all aged less than 6 months at treatment-onset) who received doses of 20 mg/kg or 40 mg/kg Myozyme as an approximate 4 to 6.5-hour infusion, respectively. Pharmacokinetics were dose proportional and did not change over time. After the first and sixth infusion of Myozyme, mean maximum plasma concentrations (C_{max}) ranged from 178.2 to 263.7 μ g/mL for the 20 mg/kg and 40 mg/kg dose groups respectively. The mean area under the plasma concentration-time curve (AUC_{∞}) ranged from 977.5 to 1,872.5 μ g•hr/mL for the 20 mg/kg and 40 mg/kg dose groups. Mean plasma clearance (CL) was 21.9 mL/h/kg and mean volume of distribution at steady state (V_{ss}) was 66.2 mL/kg for both dose groups with small between-subject variability of 15% and 11%, respectively. Mean plasma elimination half-life ($t_{1/2}$) was 2.75 hours for the two dose groups.

The pharmacokinetics of Myozyme were also evaluated in a separate trial (AGLU01702) in 21 patients with infantile-onset Pompe disease (all aged between 6 months and 3.5 years at treatment-onset) who received doses of 20 mg/kg of Myozyme. In 12 patients with available data the AUC_∞ and C_{max} were approximately equivalent to those observed for the 20 mg/kg dose group in the above other main trial. The t_{1/2} of approximately 2-3 hours was also similar in this group of patients.

The pharmacokinetics of Myozyme were evaluated in a trial (AGLU02804) in 5 patients with late-onset Pompe disease aged 6-15 years who received 20 mg/kg Myozyme every 2 weeks. There was no difference in the PK profile of Myozyme in late-onset patients compared to infantile-onset patients.

- Elimination

Excretion, metabolism or genetic polymorphism were not specifically studied. No studies were performed in special populations (e.g. in patients with impaired renal or hepatic function, or in relation to gender, race, weight, elderly).

- Interactions

No pharmacokinetic interaction studies were performed.

Pharmacodynamics

- Mechanism of action

Pompe disease is caused by a deficiency of acid alpha glucosidase (GAA), which degrades lysosomal glycogen. Myozyme is recombinant human acid alpha-glycosidase (rhGAA). Infused rhGAA should restore lysosomal GAA activity resulting in decrease of muscle glycogen accumulation.

- Primary pharmacology

The activity of rhGAA in tissue samples was measured using a 4-methylumbelliferyl- α -D-glucoside (4-MUG) substrate in a fluorometric assay. The glycogen content in tissue samples was measured both by biochemical and histomorphological determination, and in some studies, the presence of glycogen in light microscopic sections was confirmed by electron microscopy.

Quadriceps skeletal muscle biopsies were obtained and muscle glycogen content studied up until week 52 in the main studies AGLU01602 and AGLU01702. The results demonstrated that the majority of patients in both studies had either stable or decreasing muscle glycogen content at weeks 12 and 52. The results from a population pharmacokinetic-pharmacodynamic analysis (including data from patients in study AGLU01602 and AGLU01702) demonstrated a significant correlation between Myozyme plasma AUC and change in biochemical glycogen content of muscle biopsies (Spearman's r: -0.48, p = 0.0075) and between dose and change in GAA activity (Spearman's r: 0.67, p < 0.0001) after 12 weeks treatment. However, the change in muscle glycogen content at weeks 12 and 52 was not entirely predictive of clinical motor response at week 26 in AGLU01602 and at week 52 in AGLU01702.

- Secondary pharmacology

No secondary pharmacology studies were performed. No pharmacodynamic interaction studies were performed.

Clinical efficacy

The studies on clinical efficacy are presented below in the following order: 1) Epidemiological study of the natural history of infantile Pompe disease, 2) Studies in patients with infantile-onset Pompe disease and 3) Studies in patients with late-onset Pompe disease.

Epidemiological study of the natural history of infantile Pompe disease

- *Selection of historical control groups: Epidemiological study of the natural history of infantile Pompe disease (Study AGLU-004-00)*

This was a multinational, multicentre (32 sites from 9 countries, including one center in Austria, Italy, France, UK, and NL), historical cohort study to characterise the natural disease progression in untreated patients diagnosed with infantile Pompe disease. Historical data were retrieved retrospectively from patients medical records and transcribed onto Case Report Forms. The first data abstraction visit or baseline visit was followed by quarterly follow-up visits for living patients to assess the time course of the natural history of the disease. Information was collected from both living and deceased patients.

METHODS

Study participants

Medical records were collected from all patients with clinical diagnosis of infantile Pompe disease as defined by documented GAA-enzyme deficiency or GAA gene mutation and onset of symptoms by 12 months of age corrected for gestation if necessary. The protocol was revised in 2001 at the FDA's request to collect as many records as possible, and include data from all infantile patients, regardless of the phenotype, classical or non-typical. The patients who had been administered ERT with GAA from any source were excluded.

Objectives

The primary study objectives were to 1) characterise the natural history of disease progression in untreated infantile Pompe disease, and identify prognostic factors of improved survival to distinguish between classical and non-classical form of infantile disease, and 2) to collect data to serve as historical control in other clinical studies of efficacy, where appropriate.

Outcomes/ endpoints

Primary endpoints were the % of patients alive and ventilator-free at 12 months from birth, from the date of onset of first symptoms, and from the diagnosis date.

Secondary endpoints included:

- overall ventilator-free survival
- time to death or to first ventilator dependence from birth, from first symptoms and from diagnosis.
- physical growth assessment based on evolution of weight, length and head circumference at birth and at the most recent assessment
- developmental assessment
- assessment of cardiomegaly and/or cardiomyopathy, echocardiogram and electrocardiogram results
- gastrointestinal symptoms and related age at first episode
- respiratory assessment

Follow-up: All patients living at the time of entry in the study were to be followed up quarterly until one of the following events occurred: death, patient received ERT with GAA, or study termination.

Statistical analyses

All statistical comparisons were conducted as two-sided tests. Time to event outcomes were analysed using Kaplan-Meier method. A stepwise model regression was used to identify the most important prognosis variables with regard to the occurrence of an event (death and/or ventilation). Relative risks of an event and corresponding 95% CI were estimated by Cox proportional hazards regression models.

Log-rank tests were used to test the difference in survival distributions whether cardiomegaly was present ≤ 6 months of age or not. In the analysis of multiple recurrences of ventilation episodes, the marginal analysis approach of Wei, Lin and Weissfeld (WLW analysis) was used. t-tests or Wilcoxon Rank Sum tests were used to analyse differences in non-censored continuous variable, e.g. number of hospitalisations or of pneumonias, between 2 groups of patients differing by a specific potential prognosis factor.

RESULTS

300 patients who presented with signs and symptoms of Pompe disease within their first year of life were screened. 168 (83 males and 85 females) were eligible and analysed. The median patient age was 2.0 months at first symptoms (n = 166; range: 0-12 months), 4.7 months at confirmed diagnosis of Pompe disease (n = 165; range: prenatal to 84.2 months), 5.9 months at first ventilator support (n = 49; range: 0.1-39.1 months), and 8.7 months of age at death (n = 163; 95% CI 8.2-9.4 months). The Kaplan-Meier survival rates at 12 and 18 months of age were 25.7% and 14.4%, respectively, while ventilator-free survival rates at 12 and 18 months of age were 16.9% and 8.5%, respectively. Cardiomegaly (92%), hypotonia (88%), cardiomyopathy (88%), respiratory distress (78%), muscle weakness (63%), feeding difficulties (57%), and failure to thrive (53%) were the most frequent presenting signs and symptoms of the disease. Each was first noticed after a median age of approximately 4 months.

These data indicated that patients with infantile-onset Pompe disease present early with a wide array of signs and symptoms suggestive of multi-organ involvement. Patients were treated aggressively with 95.8% of patients receiving at least one palliative therapeutic intervention, most commonly symptomatic drug therapy with cardiac medications and/or antibiotics. Nutritional support and other modalities including respiratory and physical therapy, were also commonly used. 93.5% of patients required hospitalization. It was not possible to readily distinguish classical from atypical Pompe disease in this study, supporting the hypothesis that infantile-onset Pompe disease exists as a spectrum of disease. However, the data supported the concept that patients with the most severe form of infantile-onset Pompe disease are likely to present with clinically important signs and symptoms of the disease within the first 6 months of life and are at greater risk of dying at earlier ages than those who present with symptoms after 6 months of age.

On analysis with multiple covariates, early age at first symptoms and early age at diagnosis were associated with a significantly increased risk of death. Also, a younger median age at death was noted for patients born 1985-1989 and 1990-1994, which could reflect advances with time in the management of critically ill patients with life-threatening conditions such as congestive heart failure and respiratory distress. This was further confirmed by the results of an univariate analysis for the risk of death, indicating a statistically significantly lower risk of death for patients with a year of birth > 1995 , when compared to those born < 1955 (RR 0.71, $p=0.042$).

Studies in patients with infantile-onset Pompe disease

- *Main studies*

A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging Study of the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of Recombinant Human Acid alpha- Glucosidase (rhGAA) Treatment in Patients ≤ 6 Months Old with Infantile-Onset Pompe Disease (Glycogen Storage Disease Type II) (AGLU01602; 26-Week interim report; including survival data up to 18 months of age)

METHODS

Objectives and study design

AGLU 1602 was an on-going phase II/III uncontrolled multicentre multinational (3 centres in the US, 1 in the UK, 1 in France, 1 in Israel and 1 in Taiwan) randomised study of the safety, efficacy, pharmacokinetics and pharmacodynamics of 2 doses of Myozyme (20 and 40 mg/kg/qow = every other week) during 52 weeks in the treatment 18 infantile-onset Pompe disease patients aged ≤ 6 months. Upon completion, patients could be eligible for an open-label extension (AGLU02403)

provided no safety concern had emerged. An interim analysis of data obtained in the 18 patients after a first 6-month treatment period was planned and results presented in the marketing authorisation application. Survival data were presented up to 18 months of age.

Study participants

The main inclusion criteria were:

- Patients aged ≤ 26 weeks adjusted for gestation at the time of the first dose of rhGAA.
- Clinical diagnosis of infantile Pompe disease as defined by both documented clinical symptoms compatible with Pompe disease and documented endogenous GAA deficiency in peripheral blood mononuclear cells. Patients had to have confirmed cardiomyopathy as measured by left ventricular mass index (LVMI) ≥ 65 g/m², as assessed by a cardiologist with 2D echocardiography.

Main exclusion criteria were :

- Symptoms of respiratory insufficiency including O₂ saturation $< 90\%$ on room air (pulse oxymetry) and venous PCO₂ > 55 mmHg or arterial PCO₂ > 40 mmHg on room air.
- Major congenital abnormality or clinically significant signs of organic disease other than those related to Pompe disease
- Any ventilation use at enrolment
- Patient already receiving ERT

Treatment

Patients were randomly assigned to receive intravenous (IV) infusions of rhGAA at a dose of 20 or 40 mg/kg qow. The dose was further adjusted monthly based on changes in body weight. Infusions were administered in the morning following an overnight fast of at least 4 hours. The rate of infusion was increased incrementally to prevent infusion-associated reactions (IAR): initially 1 mg/kg/hr rate, which was gradually increased by 2 mg/kg/hr every 30 minutes if no signs of IAR appeared; maximum rate was 7 mg/kg/hr. Dosing regimen could be reduced at any time by decrements of 10 mg/kg/week in case of liver toxicity or other toxicity, symptoms of immune complex disease or IAR not responding to pre-treatment, rate reduction or treatment.

Outcomes and endpoints

Primary efficacy endpoint at the 26-week interim analysis was percentage of patients alive and free of invasive ventilator support (endotracheal tube) at 12 months of age (both dose groups combined), when compared to a comparable historical untreated cohort derived from the Natural History study. The primary efficacy analysis was later amended to be the Kaplan-Meier estimate of the % of patients alive and free of invasive ventilator support at 18 months of age.

Secondary efficacy endpoints at the 26-week interim analysis were 1) Percentage of patients alive and free of any ventilator support at 12 months of age (both dose groups combined), when compared to the corresponding Historical Reference Subgroup, 2) Assessment of changes in cardiomyopathy between baseline and week 26, as measured by echocardiography to determine LVMI, and 3) Assessment of changes in growth as measured by changes in weight, length and head circumference from baseline to week 26.

Other efficacy endpoints included 1) Percentage of patients alive at 12 months of age, 2) Percentage of patients with signs and symptoms of cardiac failure, 3) Assessment of motor function by Alberta Infant Motor Scale (AIMS) from birth to the age of independent walking (≤ 18 months of age), and by corresponding number of development milestones achieved, 4) Assessment of cognitive function by BSID-II = modified Bayley Scales of Infant Development assessing cognitive, physical, language and speech, and psychosocial development of children from birth to 42 months of age and 5) Assessment of functional status and disability by Paediatric Evaluation of Disability Inventory (PEDI) and Pompe PEDI.

Statistical methods

Interim analysis was planned after the 18th patient enrolled had completed 26 weeks of treatment. Non-completers were considered as failures.

The % of patients alive and free of invasive ventilator support at the milestone of 12 and 18 months of age and the corresponding 95% 2-sided CI were estimated based on a Kaplan-Meier estimate from data on time to death or first ventilator use. The survival curve of time to event (death or invasive ventilatory support) from birth and diagnosis was estimated. The % of patients alive and free of invasive ventilation were compared between the AGLU1602 patients population and a corresponding historical reference population extracted from the Natural History study. (However, the invasive ventilator-free survival was not recorded in the historical population and therefore no final comparison was possible.) The same methodology of analysis was applied to “any ventilator-free survival” and to “survival”. For each secondary parameter, change from baseline was assessed.

As reference subgroup, an untreated historical cohort of patients fulfilling the inclusion/exclusion criteria of AGLU1602 was selected among the 168 subjects of the Natural History study AGLU 004-00, using mainly the following criteria: age at first symptoms and age at diagnosis < 6 months, documented cardiomyopathy with LVMI < 65g/m², and no ventilator use between 0 and 6 months of age.

RESULTS

Results/disposition of patients, demographics and baseline characteristics

Nineteen patients were enrolled and 18 treated (the 19th patient experienced an adverse event that required ventilation during the baseline period before treatment initiation).

Median age at first symptoms, at diagnosis and at first infusion were 1 ± 1.8 (range 0.0-5.4), 4.4 ± 2.2 (0.2-6.8), and 5.3 ± 1.7 (6.3-43.1) months, respectively.

Survival results are given in the Tables 3-6 below.

After 52-weeks of treatment, all 18 patients treated with Myozyme were alive and 15 of these 18 patients were alive and free of invasive ventilatory support, whereas 1 of 42 patients in historical control group was alive at 18 months of age. Comparison of survival curve from diagnosis versus the historical control population was made using a Cox proportional hazards regression analysis. After 52 weeks, patients treated with Myozyme demonstrated prolonged survival as compared to survival in an untreated historical cohort (see Table 3 below).

Table 3: Results for study endpoints using the Cox regression model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=18	N=42	Survival	0.01	(0.00, 0.10)	<0.0001

Note: Results are from a Cox proportional hazards regression analysis which includes treatment as a time-varying covariate, and also includes age of diagnosis and age at symptom onset. Subjects in the historical reference group were born in 1993 or later.

Table 4: Proportion of Treated Patients Alive and Free of Invasive Ventilator Support at 18 months of Age

Dose	N	Proportion Estimate and 95% CI ¹
Overall	18	83.3% (66.1, 100)
20 mg/kg	9	88.9% (68.4, 100)
40 mg/kg	9	77.8% (50.6, 100)

Proportion of untreated Patients Alive at 18 months of Age in Historical Control

N	Number of Patients Alive	Proportion Estimate and 95% CI ²
61	1	1.9% (0.0, 5.5)

1 Kaplan-Meier analysis of time to invasive ventilation or death
2 Kaplan-Meier analysis of time to death

Table 5: Invasive ventilator-free survival at 12 months of age

		Alive and ventilator-free in 1602			
Patients populations		Alive and invasive ventilator-free	censored	Failed	% estimate (95%CI)
Dose	N				
Overall	18	14	3	1	93.8%(81.9, 100)
20 mg	9	8	1	0	100% (N/A)
40 mg	9	6	2	1	87.5% (64.6, 100)

Table 6: Proportion of Patients Who were Alive and Free of Any Ventilator Support at 12 Months of Age

Dose Group	N	Number of Patients Alive and Free of Any Ventilation	Number Censored	Number of Failures	Estimate (%)	95% CI
Overall	18	12	3	3	80.4	(60.4, 100)
20 mg/kg	9	7	1	1	87.5	(64.6, 100)
40 mg/kg	9	5	2	2	72.9	(40.6, 100)

Other clinical endpoints

In table 7 below results on other than survival-endpoints are given.

Table 7: Clinical Response According to Dose Group Following 26 Weeks of Treatment with Myozyme

Parameter Evaluated	20 mg/kg dose	40 mg/kg dose
Patients with decrease in left ventricular mass index from baseline during 26 weeks of treatment	7 of 7	7 of 7
Patients with normal weight at week 26	7 of 9	6 of 9
Patients with motor gains at week 26 as assessed by AIMS Age-Equivalent Scores	7 of 9	6 of 9
Patients with motor gains at week 26 as assessed by Developmental Motor Milestones	7 of 9	8 of 9
Patients with gains in functional skills at week 26 as assessed by Pompe PEDI Mobility Scaled Scores	7 of 9	8 of 9

No difference between the two dose groups were found with respect to survival, invasive ventilator-free survival or any ventilator-free survival, nor in cardiomyopathy, growth, motor development or functional status.

- An Open-Label, Multicenter, Multinational Study of the Safety, Efficacy, Pharmacokinetics, and pharmacodynamics of Recombinant Human Acid alpha-Glucosidase (rhGAA) Treatment in Patients ≥ 6 and ≤ 36 Months Old with Infantile-Onset Pompe Disease (Glycogen Storage Disease Type II) (AGLU01702; 52-week interim report)

Study design and objectives

AGLU 1702 was an on-going phase II uncontrolled multicentre multinational (3 centres in the US, 1 in the UK, 1 in France and 1 in Israel) study of the safety, efficacy, pharmacokinetics and pharmacodynamics of Myozyme in infantile-onset Pompe disease patients during 52-week modules (initial 52-week treatment period followed by a 52-week maintenance module).

Interim analyses were done when the first 15 patients had completed 26 weeks of treatment, and when these 15 patients had completed 52 weeks of treatment.

Study participants

Main inclusion criteria

- Patients aged ≥ 6 months and ≤ 36 months adjusted for gestation at the time of the first dose of rhGAA and clinical diagnosis of infantile Pompe disease as defined by both documented onset of symptoms compatible with Pompe disease by 12 months of age (adjusted for gestation) and documented endogenous GAA deficiency.
- LVMI as assessed by a cardiologist with 2D echocardiography ≥ 65 g/m² in patients ≤ 12 months of age or > 79 g/m² in patients > 12 months of age.

Main exclusion criteria

- Signs and symptoms of cardiac failure and ejection fraction $< 40\%$
- Clinically significant signs of organic disease other than those related to Pompe disease
- Patient already receiving ERT

Treatments

Patients were administered IV infusions of rhGAA at a dose of 20 mg/kg qow initially. The dose could be further adjusted monthly based on changes in body weight. The rate of infusion was increased incrementally to prevent IARs: initially 1 mg/kg/hr rate, which was gradually increased by 2 mg/kg/hr every 30 minutes if no signs of IAR appeared; maximum was 7 mg/kg/hr. Dosing regimen was changed to 10 mg/kg/week in case of liver toxicity, symptoms of immune complex disease, or IAR not responding to pre-treatment, rate reduction or treatment.

Objectives

The objective was to study efficacy, safety, pharmacokinetics and pharmacodynamics. No placebo group was included into the study, but comparison to a historical control group was done.

Outcomes/ endpoints

Primary efficacy endpoint was survival: estimation of survival from birth (all causes mortality), expressed as the % of patients alive over the course of treatment, in comparison with data from the Natural History study.

Secondary efficacy endpoints included the following:

-The effect on respiratory function. This was measured as follows: (a) for patients who were ventilator-free at the onset of the study, the proportion of patients who were alive and ventilator-free over the course of treatment and the ventilator-free survival time (time to first ventilator use or death); (b) for patients who required ventilator use at the onset of the study, the overall duration of ventilator support and the number of hours of ventilator use (in the 24 hours preceding each infusion visit, measured qow).

-The effect of treatment on cardiac status. This was measured by echocardiography (LVMI and left ventricular posterior wall thickness, LVPWT), by radiography (thoracic ratio >0.5) and by the presence of any signs and/or symptoms of cardiac failure.

-The effect of treatment on motor development. This was measured by the Alberta Infant Motor Scale (AIMS) from birth to the age of independent walking (≤ 18 months of age) and, for children aged >18 months, by the Peabody developmental Motor Scale (PDMS-2), a skill-based measure of motor development in children aged 6 to 72 months. The patient's ability to achieve and maintain clinically relevant motor milestones was also assessed.

-Additional efficacy outcomes included the effect of treatment on: (1) the maintenance of cognitive function from baseline as measured by the MDI of the BSID-II; (2) physical growth by body length, weight, and head circumference; (3) change in disability index from baseline as measured by the PEDI; and (4) change in disability index from baseline as measured by the Pompe PEDI.

Sample size

Protocol AGLU01702 was designed to enrol up to 20 patients with infantile-onset Pompe disease (21 were included).

Randomisation, blinding,

None

Statistical methods

Interim analysis was done after the 15th patient enrolled had completed 26 weeks of treatment, and when these 15 patients had completed 52 weeks of treatment.

Non completers were considered as failures.

Primary endpoint/Survival: Patients were stratified by age at first infusion, and survival was analysed for all treated patients and separately depending on patients being aged ≤ 12 months or > 12 months at the time of first infusion. Survival data were compared 1) to those observed in a subgroup of the Natural History study population (called Historical reference subgroup) who met the inclusion criteria of study 1702 (n=86 out of 168), and 2) to an Historical reference subgroup subset of 16 patients from the reference subgroup who survived past 15 months, i.e. the median age at first infusion for patients in AGLU-1702. A Cox proportional hazards regression analysis was also used.

Secondary endpoints: For each secondary parameter, change from baseline was assessed.

RESULTS

Twenty-two patients were enrolled and 21 received treatment. One patient died prior to receiving treatment. The interim analysis results reflected results from 15 patients treated for 52 weeks. After 52 weeks of treatment with Myozyme, the survival rate was 73% (95% CI: 44.9, 92.2) compared to the corresponding survival figure of 37% (95% CI: 13.8, 61.2) in an untreated reference group. None of the deaths were assessed as treatment-related.

Table 8: Results for survival using the Cox regression model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=21	N=48	Survival	0.29	(0.11, 0.81)	0.018

Note: Results are from a Cox proportional hazards regression analysis which includes treatment as a time-varying covariate, and also includes age of diagnosis and age at symptom onset. Subjects in the historical reference group were born in 1995 or later.

Eighty-seven percent of patients demonstrated a reduction in LVMI from baseline to last evaluation. LVMI at baseline declined by an average of 43% at week 26 and 48% at week 52. Echocardiographic measurements of cardiac function (ejection fraction [EF] and shortening fraction [SF]) demonstrated a trend toward normalization through the 52-week treatment period: mean improvements of 33% and 19% in EF and SF, respectively, were observed after 52 weeks of treatment. Maintenance or improvement was seen in 80% of patients in weight-for-age percentiles; in 93% of patients in length-for-age percentiles; and 92% of patients in head circumference-for-age percentiles. Six of 15 patients (40%) had measurable gains in motor assessments (AIMS and/or PDMS-2 gross and fine motor skills), as determined by increases in raw scores and age-equivalent scores from baseline to last assessment. The remaining patients did not demonstrate measurable gains across these motor assessments. All patients with repeat evaluations (n=13, 100%) had gains in BSID-II Mental Scale age-equivalent scores from baseline to the last study assessment, indicating the continued acquisition of cognitive, language, and personal/ social development skills.

- Supportive phase II studies/ Infantile onset Pompe disease

In studies in infantile-onset Pompe disease with earlier rhGAA-products treatment with rhGAA resulted in improvements in cardiomyopathy and global muscular function in all patients. When the results of all these patients were pooled, the median age at survival was 51.4 months. 12 out of 16 patients who were not ventilator-dependent at baseline had become ventilator-dependent (i.e. placed on invasive ventilator support) or died as of 1 July 2004. The median age of ventilator-free survival for those 16 patients was 28.7 months with a 95% CI of 13.8, 38.7. All this data indicated that rhGAA affects mortality; however, determination of the effect size was not possible.

The results from the expanded access programs (see Table 2 above) with Myozyme were in line with the other studies in patients with infantile onset Pompe disease.

Studies in patients with late-onset Pompe disease

Overall data from two clinical studies and expanded access programs were included in the MAA so that in the original MAA 15 late-onset patients (aged 6 to 54 years at onset of therapy; disease severity ranging from those patients who were relatively early in their disease progression, i.e. able to ambulate freely, not requiring ventilator support, to relatively late in their disease progression, i.e. wheelchair-bound, ventilator-dependent) were treated with rhGAA for 6 months to 5 years (duration on Myozyme ranging from 6 months to 2.5 years). (See Table 2 above.)

The open-label clinical trial AGLU02804 assessed the safety and efficacy of Myozyme in 5 patients with late-onset Pompe disease who ranged in age from 5 to 15 years at initiation of treatment. Patients received 20 mg/kg Myozyme every other week for 26 weeks. All patients were freely ambulatory and

all but one patient did not require any form of ventilator support (1 patient required nocturnal non-invasive ventilation). Two patients out of 3 with pulmonary involvement (FVC 58-67% of predicted values) had significant improvement in FVC (+11.5% and +16%, respectively); the third did not. The two patients with improved pulmonary function had increases in Manual Muscle Testing of strength, but not in Hand-Held Dynamometric values or in Energy Expenditure Index. Only one of these two patients improved on the 6-min Walk Test. Thus, the effects of Myozyme in patients with mild to moderate (treated relatively early) late-onset Pompe disease were uncertain.

Data was also submitted on 10 patients with advanced late-onset Pompe disease treated with Myozyme at 20 mg/kg qow to 40 mg/kg qw for 6 months to 2.5 years (including 3 patients treated with different forms of rhGAA for a total of 5 years). At baseline, all but one of the 10 patients required invasive or noninvasive ventilatory support for most of the day and all 10 were wheelchair-dependent. Therefore, tests of pulmonary function and muscle strength were very difficult to perform and assessment of the clinical status of these patients relied exclusively on physician's narrative. Only one patient had cardiomyopathy. One 11-year-old boy who was not ventilator-dependent but was using a wheelchair since the age of 9 started treatment (not with Myozyme) and, 72 weeks later, he could stand with difficulty; at 84 weeks he could walk and at 108 weeks he could abandon his wheelchair; he has lived normally thereafter. The nine other patients remained ventilator-dependent, but had different signs of possible improvements in their lung or muscle functions, and in their well-being.

After the oral explanation the CHMP requested the applicant to submit any further data on patients with late-onset Pompe disease: the applicant submitted physicians' narratives on 10 patients treated with Myozyme for more than 6 months, 2 of whom had been included with preliminary data in the previous list, and 8 of whom were new patients from Expanded Access Program AGLU02603 (see Table 2). The preliminary results of these patients were in line with the earlier submitted data. Overall, 5/18 late-onset Pompe disease patients who could only be evaluated through physicians' narratives showed clinically significant decreases in the number of hours of non invasive ventilation (from approximately 20 h/day to 10 h/day); 4/18 had increased ambulation, including one who fell and broke her femur; and many gained weight or had declared improvements in their quality of life.

Discussion on clinical efficacy

The study AGLU01602 showed that treatment with Myozyme of patients with infantile-onset Pompe disease aged less than 6 months significantly prolonged survival and ventilator-free survival at 18-months of age compared to a historical control subgroup. Thus, patients experienced prevention or delay of the use of invasive and noninvasive ventilator support providing them with increased mobility and freedom from mechanical supports during their survival time. Significant clinical benefit was also observed in the majority of the patients in terms of improvements in cardiomyopathy, growth, motor function, as well as in functional skills/status. These conclusions did not change when additional analyses, requested by the CHMP during the procedure, were employed (including a Cox analysis after controlling for e.g. age at diagnosis, age at first symptoms, and birth year).

During the procedure CHMP requested the applicant to analyse whether patients who were already ventilator-dependent should be treated with Myozyme, since many of them would not derive any benefit in terms of pulmonary function, and other clinical benefits had not been quantified in these patients. However, the number of these ventilator-dependent patients with early-onset Pompe disease was limited and thus no conclusions could be made. The applicant will address this aspect in their planned clinical study in late-onset Pompe disease patients.

There were no differences between 20 mg/kg and 40 mg/kg doses in study AGLU1602 in any of the studied endpoints. In addition, patients receiving 40 mg/kg tended to develop a more robust antibody response and more IARs compared to those receiving 20 mg/kg. Further, skeletal muscle GAA activity increased and skeletal muscle glycogen content decreased only slightly more with 40 mg/kg dose compared to the 20 mg/kg dose. Therefore, the CHMP recommended marketing authorisation only for the 20 mg/kg dose.

Further, the CHMP requested the applicant to study prognostic factors for good or poor response to Myozyme-treatment, e.g. muscle biopsies at different time points. No such prognostic factors could yet be identified. The applicant committed to search for such factors as a follow-up measure.

One main question was whether results obtained in infantile-onset Pompe disease patients treated before the age of 6 months could be extrapolated to late-onset disease patients, as late-onset Pompe disease is also a progressive disease, but its course differs significantly from that of the infantile-onset form of the disease. It was recognised that some of the late-onset disease patients treated with Myozyme had shown positive clinical responses. However, these data remained difficult to interpret in the absence of clear endpoints, including for quality of life assessment, and due to the lack of a valid control group. It is also known that some patients with late-onset Pompe disease may experience a rapid deterioration in skeletal and respiratory muscle function leading to loss of ambulation and respiratory failure, while others progress less rapidly, and yet others present with a dissociation in the progression of skeletal and respiratory muscle involvement. Thus, complete extrapolation of the results from infantile-onset to late-onset disease was not considered a valid approach in general. This is expressed in the SPC in 4.1 and 5.1. The applicant committed to carry out a randomised, double-blind, placebo-controlled study in patients with mild to moderate late-onset Pompe disease in order to quantify the effect of Myozyme in this population. The applicant also committed to submit the final results of two other ongoing clinical studies in these late-onset Pompe disease patients (i.e. AGLU02804, an open-label study on safety, PK and efficacy in five patients; and AGLU03105, an open-label study on safety and efficacy in five patients who are receiving respiratory support) as follow-up measures.

Clinical safety

- Patient exposure

As of March 2005, a total of 61 patients from clinical studies and Expanded Access programme have received from 1 to 110 weeks (median 56 weeks) of Myozyme treatment primarily at doses of 20 mg/kg qow and 40 mg/kg qow (but ranging from 10 mg/kg qw up to 40 mg/kg qw). Eleven (11) patients have received Myozyme for ≤ 26 weeks, while 15 patients have received Myozyme for > 26 weeks but < 52 weeks, and 35 patients have received Myozyme for > 52 weeks.

- Adverse events

Most adverse events reported in 39 infantile-onset Pompe patients treated with Myozyme up to more than one year (76 weeks) during the two main clinical studies were consistent with the natural course of Pompe disease. Adverse Drug Reactions (ADRs) related to Myozyme reported in more than one patient are listed in Table 9 by System Organ Class. The ADRs listed are shown as percentage of patients experiencing the ADR with the absolute number of patients in brackets. ADRs were mostly mild to moderate in intensity and 82% were assessed as IARs (occurred during the infusion or during the 2 hours following the infusion).

Table 9: Adverse drug reactions related to Myozyme

System Organ Class	Preferred term	Frequency (no. of patients) N = 39
Psychiatric disorders	Agitation	5% (2 pts)
Nervous system disorders	Tremor	5% (2 pts)
Cardiac disorders	Tachycardia	8% (3 pts)
	Cyanosis	5% (2 pts)
Vascular disorders	Flushing	13% (5 pts)
	Hypertension	5% (2 pts)
	Pallor	5% (2 pts)
Respiratory, thoracic and mediastinal disorders	Cough	8% (3 pts)
	Tachypnoea	8% (3 pts)
Gastrointestinal disorders	Vomiting	5% (2 pts)
Skin and subcutaneous tissue disorders	Urticaria	13% (5 pts)
	Rash	10% (4 pts)
	Rash macular	5% (2 pts)
	Erythema	5% (2 pts)
	Rash maculo-papular	5% (2 pts)
General disorders and administration site conditions	Pyrexia	15% (6 pts)
	Rigors	5% (2 pts)
Investigations	Oxygen saturation decreased	8% (3 pts)
	Blood creatine phosphokinase MB increased	5% (2 pts)
	Blood pressure increased	5% (2 pts)

A limited number of patients with late-onset Pompe disease were treated with Myozyme. ADRs related to Myozyme reported in 2 of 9 late-onset patients treated with Myozyme for up to 1 year in 3 different studies included increased heart rate, hypertension, headache, peripheral coldness, paresthesia, flushing, infusion site pain, infusion site reaction, increased blood pressure and dizziness. All ADRs were seen in a single patient, mild in intensity and assessed as an IARs.

In general, the adverse drug reaction profiles were similar in infantile-onset and in late-onset patients.

Adverse events of particular interest

Pyrexia was the most frequently reported AE in patients with infantile-onset Pompe disease. Pyrexia was often associated with underlying infection, predominantly upper respiratory tract infections, which are commonly observed in patients with Pompe disease. In the Infantile-onset pooled population (AGLU01602 and AGLU01702), 89.7% of the patients experienced 139 events of pyrexia. The majority of the events of pyrexia were assessed as mild and not related to Myozyme. In the majority of patients, pyrexia assessed as related to Myozyme occurred during the infusion, was transient and episodic in nature, and resolved with intervention (antipyretics and/or temporary interruption of the infusion). All patients recovered without sequelae from the event of pyrexia. No correlation was observed between the occurrence of pyrexia and duration of treatment.

Infusion associated reactions (IARs) were defined as those AEs which occurred following the initiation of the infusion up to and including the 2 hour post-infusion observation period and that were assessed by the Investigator as related to Myozyme administration. They were reported for 18 of the 39 patients treated with Myozyme in the infantile-onset pooled population (AGLU01602 and AGLU01702), 2 of the 5 patients in Study AGLU02203, 2 of the 7 patients in Study AGLU02003, 1 of the 3 patients in the AGLU02503 Programme, and the single patient in Study AGLU02103. IARs were generally well tolerated, and were managed with rate reduction and/or an interruption of the

Myozyme infusion. There were no dose reductions required due to IARs and no patients discontinued due to IARs. The onset of IARs did not correlate with IgG titer or time of seroconversion. No patient experienced IgE-mediated acute-type hypersensitivity reaction.

In AGLU01602 there were 31 IARs in 4 patients with 40 mg/kg dose, compared to 11 IARs in 4 patients with 20 mg/kg dose.

- Serious adverse events (SAEs)/ deaths/ other significant events

Overall, the majority of the patients treated with Myozyme experienced at least one SAE, most of which were assessed as not related to treatment with Myozyme and some also reported at baseline. SAEs involved predominantly infections, respiratory related complications, and cardiac disorders. In the infantile-onset pooled population (AGLU01602 and AGLU01702) 33 of 39 (84.5%) patients experienced at least one SAE for a total of 213 SAEs after initiation of treatment. The most common SAEs were respiratory failure (9 patients [23.1%], 23 events [10.8%]), pneumonia (7 patients [17.9%], 18 events [8.5%]), catheter related infection (7 patients [17.9%], 9 events [4.2%]), and respiratory distress (7 patients [17.9%], 9 events [4.2%]), pyrexia (5 patients [12.8%], 6 events [2.8%]), pneumonia aspiration (4 patients [10.3%], 15 events [7.0%]), bronchiolitis (4 patients [10.3%], 5 events [2.3%]), and oxygen saturation decreased (4 patients [10.3%], 4 events [1.9%]). Twenty (51.3%) of 39 patients experienced at least one serious respiratory related event.

Seventy percent (70%) of the treatment-emergent SAEs (151 of 213 events) were mild to moderate in severity. Fifteen (15) patients experienced 62 SAEs assessed as severe, none of which was assessed as related to Myozyme. Eleven (11) of the 213 (5.2%) SAEs were assessed as related to treatment (IARs). SAEs generally resolved without sequelae after medication, non-drug therapy, and/or hospitalisation.

Overall, 9 of 61 patients in the total population who received treatment with Myozyme through a clinical trial and/or expanded access programme died. Median exposure to Myozyme in these 9 patients was 4.3 months (range 0.1 to 14 months). The deaths were due to cardiorespiratory causes consistent with complications of the underlying Pompe disease. None of these deaths were assessed as related to Myozyme by the Investigator.

- Laboratory findings

No significant abnormalities in laboratory tests were detected. Most patients with Pompe disease had elevated AST, ALT or CK levels prior to the initiation of the treatment; no consistent changes in these values were observed in clinical studies following initiation of Myozyme treatment.

Immunological responses

Immunologic responses are expected in patients who are treated with recombinant human proteins. Anti-rhGAA antibody assessment consisted of a 2-step process: an ELISA screening assessment followed by a confirmatory radioimmunoprecipitation assay. Further ELISA assays were used to determine the titer of anti-rhGAA antibodies. All IgG seropositive patients were tested for the presence of IgG inhibitory antibodies to rhGAA. The majority of the patients developed anti-rhGAA antibodies within three months of Myozyme treatment. One patient treated with Myozyme at a dose of 40 mg/kg qow developed extremely high titres of IgG antibodies ($>1.5 \times 10^6$); inhibitory antibodies were detected while a clinical decline was observed. In addition, one patient developed a positive inhibitory antibody response after 2.5 years of treatment while being treated with rhGAA obtained from a different source at a dose of 10 mg/kg qd 5x/week. This patient developed nephrotic syndrome and immune complex deposition.

- Safety in special populations

No studies in special populations were carried out.

- Safety related to drug-drug interactions and other interactions

No drug-interaction studies were performed.

- Discontinuation due to adverse events

No patient discontinued treatment due to an adverse event, with the exception of the observed deaths.

- Post marketing experience

Not applicable.

- Readability testing

The applicant committed to provide readability testing (“user consultation”) report as a follow-up measure.

- Discussion on clinical safety

Myozyme treatment was generally well tolerated. The most common adverse reactions were pyrexia (probably due to Pompe disease), flushing, urticaria and rash – the majority were assessed as IARs. When IARs occurred, the events were typically managed with infusion rate reductions and/or pretreatment, when necessary. Pretreatment medications were not routinely administered to all patients. No patients discontinued treatment due to IARs. The only real concern with Myozyme treatment was the systematic development of rhGAA IgG antibodies. One patient treated with Myozyme developed inhibitory antibodies; another patient who was treated with earlier rhGAA-product also developed inhibitory antibodies. This patient who received frequent dosing of rhGAA over extended time also developed circulating immune complexes with immune complex disposition and nephrotic syndrome. The applicant committed to monitor closely the immunological response of patients treated with Myozyme in the post-marketing phase (see the Risk Management Plan below).

5. Pharmacovigilance

▪ Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

▪ Risk Management Plan

The MAA submitted a risk management plan (RMP). In the plan the applicant committed to carry out an immunosurveillance programme to monitor immunological response (including possible formation of inhibitory antibodies) to Myozyme treatment. In addition, the applicant committed to amend the existing Pompe registry of untreated Pompe disease patients to include collection of data for patients treated with Myozyme to facilitate the evaluation of long-term efficacy and safety through the registry. Further, the applicant will also introduce an educational programme for the prevention and treatment of infusion associated reactions and development of antibodies. Educational material will be also provided for physicians on the risks of the drug if used during pregnancy. The applicant also committed to monitor liver function tests through the clinical programme, although disturbances of liver function tests observed in the clinical studies were most probably the result of the underlying disease.

Table 10: Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Infusion Associated Reactions (IAR)	<p>Registry information and global manual for physicians at treatment sites will encourage reporting of IAR. Adverse event collection forms will be provided to all registry sites.</p> <p>Independent data safety monitoring board (for the ongoing clinical studies) and allergic reaction review board</p>	<p>Mentioned in sections 4.2, 4.4, 4.8 of the SPC:</p> <ul style="list-style-type: none"> - Advice on infusion rate in section 4.2 - Warning on IAR, the need to monitor patients and treatment in section 4.4 <p>IAR management guidelines</p>
Development of antibodies	Immunosurveillance program (with regular IgG antibody level monitoring, including inhibitory antibodies)	<p>Warning on development of antibodies and monitoring in section 4.4 of the SPC.</p> <p>Educational material will be provided.</p>
Possibility for teratogenic effect	The company committed to provide: fertility and embryofetal development study involving a 10-week pre-treatment for the male, and an embryofetal development study using a non-rodent species (e.g. rabbit).	<p>Warning in section 4.6 of the SPC, that it should not be used in pregnancy unless clearly necessary.</p> <p>Educational material will be provided.</p> <p>Inconclusive data and lack of full characterisation of these effects mentioned in section 5.3 of the SPC.</p>
Elevated liver function tests (accumulation in liver seen in Cynomolgus monkeys)	Liver function tests will be monitored throughout the clinical programme and through spontaneously reported adverse events.	
Potential for medical errors		<p>The product will be administered by physicians experienced in the management of patients with Pompe disease or similar diseases.</p> <p>Special instructions on preparation and administration in the section 6.6 of the SPC. Separate guidelines. Global pharmacy manual.</p>
Long-term effects	Pompe registry (mentioned in SPC 5.1), with specific HRQoL-questionnaire based on Pompe patients' neuromuscular and respiratory problems and specific follow-up of growth disturbances in children. Annual reports to be submitted.	
Use in renal or hepatic insufficiency	Data to be collected in these patients through Pompe registry and clinical trials. Annual reports to be submitted.	Lack of data mentioned in section 4.2.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of this medicinal product: The company will provide educational material regarding the IARs, development of antibodies and on the risks of the drug when used during pregnancy. Given that the product will be used by special physicians experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases, the CHMP considered that there is no need to further specify the content in the opinion. Different safety issues in the RMP should be reviewed in the updates to the EU-RMP.

6. Overall conclusions, benefit/risk assessment and recommendation

Quality

Myozyme was demonstrated to have satisfactory quality attributes and product manufactured by the 2000 L process (only) was recommended for approval.

Since a high dose of rhGAA is administered to patients, a relatively high level of protein impurities (host cell proteins) will also be administered. Therefore, this should be considered from a clinical perspective with regard to potential antibody formation.

Non-clinical pharmacology and toxicology

Results of pharmacodynamic studies suggested effective depletion of glycogen when Myozyme was administered to GAA-knockout mice in an animal model of Pompe disease. A dose range of 10-40 mg/kg of Myozyme was evaluated over a period of weeks for ability to clear glycogen from target tissues (heart and skeletal muscles).

Histamine and significant IgG and IgG1 antibody titers were consistent with a hypersensitivity response in mice.

The pharmacokinetic data showed a good linearity across species.

There were no toxic findings that were consistent across all species tested. Slight embryo-fetal effects were seen in the mouse at high dose (malrotated limbs), and a study in rabbits will be available in post-authorisation (as a follow-up measure). Small effects on male and female fertility were also observed and the results of further investigations will be available in post-authorisation (as a follow-up measure). A warning in pregnancy is included in the SPC (4.6).

It is clear from the data presented that there was a consistent finding of hypersensitivity in many of the animal models evaluated. With the exception of the non-human primate study, all species administered Myozyme showed some kind of hypersensitivity response. This hypersensitivity response was not included in the consideration of the NOAEL.

Clinical Efficacy

Myozyme is a recombinant GAA thus restoring lysosomal GAA activity resulting in decrease of muscle glycogen accumulation. Treatment with Myozyme increased survival and ventilator free survival in patients with infantile-onset Pompe disease treated before 6 months of age. It also improved cardiac, motor and respiratory function, as well as growth and functional skills/ status in these patients.

In patients with late-onset Pompe disease the benefits of Myozyme could be evaluated in a 5-patient observational study where 2/3 patients with pulmonary involvement had increases in forced vital capacity after 6 months of treatment. Physicians' narratives were available in another 18 patients treated under open access programs. The effects of Myozyme were highly variable and its efficacy could not be quantified, although some patients showed clinically significant decreases in the number of hours of non invasive ventilation, had increased ambulation, or gained weight.

The applicant committed to carry out a randomised, double-blind, placebo-controlled study in late-onset Pompe disease patients with mild to moderate disease in order to quantify the efficacy of Myozyme. The applicant also committed to submit the final results of two other ongoing clinical studies in these late-onset Pompe disease patients. (i.e. AGLU02804, an open-label study on safety, PK and efficacy in five patients; and AGLU03105, an open-label study on safety and efficacy in five patients who are receiving respiratory support).

Clinical Safety

Myozyme treatment was well tolerated. The most common adverse reactions were pyrexia, flushing, urticaria and rash (usually as infusion associated reactions). The only real concern was systematic development of IgG rhGAA antibodies; inhibitory antibodies were detected in two patients (one with Myozyme, one with Synpac rhGAA) during the development. The applicant committed to carry out a post-marketing immunosurveillance programme.

Benefit/risk assessment

Infantile-onset Pompe disease is a serious disease usually resulting in death before the age of 12 months. No medicinal product has been authorised for the treatment of Pompe disease in the EU before Myozyme. Myozyme increases, robustly, survival and ventilator free survival in these patients. It also improves cardiac, motor and respiratory function, as well as growth and functional status/skills. Myozyme treatment is generally well tolerated. The only concern is systematic development of IgG rhGAA antibodies; the applicant has committed to post-marketing immunosurveillance programme.

In late-onset Pompe disease patients the benefits of Myozyme remained uncertain. The applicant committed to carry out a randomised, double-blind, placebo-controlled study in these patients in order to confirm the encouraging preliminary findings.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that some pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some safety concerns (see the Risk management Table 10 above). The following additional risk minimisation activity was required: Educational material will be provided to physicians on infusion associated reactions, development of antibodies and on the risks of the drug if used during pregnancy.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Myozyme in the treatment of Pompe disease was favourable and therefore recommended the granting of the marketing authorisation in the following indication:

“Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α -glucosidase deficiency).

The benefits of Myozyme in patients with late-onset Pompe disease have not been established (see SPC section 5.1).”