NEW ZEALAND DATA SHEET

1 MYOZYME 50 MG/10 ML POWDER FOR INFUSION CONCENTRATE

MYOZYME 50 mg/10 mL powder for concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mg vial contains 52.5 mg alglucosidase alfa.

Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5.0 mg/mL alglucosidase alfa.

Alglucosidase alfa-rch is produced by recombinant DNA technology in a Chinese hamster ovary cell line.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

MYOZYME does not contain preservatives.

Each vial is for single use only.

Each reconstituted vial must be diluted prior to administration in 0.9% sodium chloride for injection

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MYOZYME is indicated for the long-term treatment of patients with a confirmed diagnosis of Pompe disease (acid alfa-glucosidase deficiency).

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

The recommended dosage regimen of MYOZYME is 20 mg/kg of body weight administered once every 2 weeks as an intravenous infusion.

Elderly population

Clinical studies did not include any subjects aged 65 years and older. It is not known whether they respond differently than younger subjects.

Paediatric population

There is no evidence for special considerations when MYOZYME is administered to paediatric patients of all ages.

Method of administration

Each reconstituted vial must be diluted prior to administration in 0.9% sodium chloride for injection.

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6 Special precautions for disposal and other handling.

Infusions should be administered incrementally. MYOZYME should be administered at an initial infusion rate of no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Appropriate medical support measures should be readily available when MYOZYME is administered because of the potential for severe infusion reactions. The infusion rate may be slowed and/or temporarily stopped in the event of Infusion Associated Reactions (IARs).

4.3 CONTRAINDICATIONS

Hypersensitivity (anaphylactic reaction) to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Risk of Hypersensitivity Reactions

Serious hypersensitivity reactions, including life-threatening anaphylactic reactions, have been observed in infantile and late-onset Pompe patients during MYOZYME infusion, some of which were IgE-mediated. A small number of patients (<1%) in clinical trials and in the commercial

setting developed anaphylactic shock and/or cardiac arrest during MYOZYME infusion that required life-support measures. Reactions included bronchospasm, wheezing, respiratory arrest, respiratory distress, apnoea, stridor, dyspnoea, oxygen saturation decreased, cardiac arrest, hypotension, bradycardia, tachycardia, cyanosis, vasoconstriction, flushing, chest pain, chest discomfort, throat tightness, angioedema, pharyngeal oedema, face oedema, peripheral oedema, urticaria, and rash.

If severe hypersensitivity or anaphylactic reactions occur, immediate discontinuation of the administration of MYOZYME should be considered and appropriate medical treatment should be initiated. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when MYOZYME is administered because of the potential for severe infusion reactions.

The risks and benefits of re-administering alglucosidase alfa following an anaphylactic or severe hypersensitivity reaction should be considered. Some patients have been rechallenged and have continued to receive alglucosidase alfa under close clinical supervision. Extreme caution should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

Immunogenicity

There are no marketed tests for antibodies against alglucosidase alfa. It is recommended that patients be monitored for IgG antibody formation every 3 months. If testing is warranted, contact Sanofi Genzyme at 0800 283 684 for information on testing and to obtain a sample collection box.

The effects of IgG antibody formation on safety and efficacy has been evaluated in clinical trials and post-marketing experience. In clinical studies, the majority of patients i.e. 89% (34/38) developed IgG antibodies to alglucosidase alfa and seroconversion typically occurred within 3 months of treatment. Thus, development of IgG antibodies is expected to occur in most patients treated with alglucosidase alfa. Patients treated with higher doses of MYOZYME tended to develop a more robust antibody response and experienced more IARs. Overall, a correlation was not observed between the onset of IARs and the time of IgG antibody formation. IARs can occur across all levels of antibody titres, however a trend was observed for more frequent IARs with higher titres of IgG antibody. The clinical impact on efficacy is multifactorial, however the development of high and sustained IgG antibody titres is a contributing factor.

With regard to infantile-onset Pompe disease (IOPD), a tendency was observed for patients treated with a higher dose (40 mg/kg) to develop higher titres of IgG antibodies. Furthermore, Cross Reactive Immunologic Material (CRIM) status has been shown to be associated with immunogenicity and patients' responses to enzyme replacement therapies. Negative CRIM status, indicating no endogenous enzyme is detected, is a risk factor to develop high and sustained IgG antibody titres. This risk is higher among CRIM negative patients versus CRIM-positive patients and is a contributing factor to a poor outcome. However, high and sustained IgG antibody titres has also occurred in a limited number of CRIM-positive patients, generally with very low endogenous enzyme.

With respect to late-onset Pompe disease (LOPD) patients, the majority showed either stabilising or decreasing antibody titres over time. The development of high and sustained IgG antibody titres is infrequent in LOPD patients. Thus, the impact of IgG antibodies is more limited for LOPD patients.

A small number of patients who were IgG positive also tested positive for inhibition of enzyme effects in an in vitro assay. There is evidence to suggest that patients developing sustained titres ≥ 12,800 of anti-alglucosidase alfa antibodies may have a poorer clinical response to treatment, or may lose motor function as antibody titres increase. Treated patients who experience a decrease in motor function should be tested for neutralisation of enzyme uptake or activity.

A small number of patients tested positive for alglucosidase alfa - specific IgE antibodies, 1 of whom experienced an anaphylactic reaction. Testing was typically performed for IARs, especially moderate to severe or recurrent reactions. Some patients have been successfully re-challenged using slower rates and/or lower initial doses and continued to receive treatment with alglucosidase alfa under close clinical supervision.

The effect of antibody development on the long - term efficacy of MYOZYME is not fully understood. Some IgG-positive patients in clinical trials and on commercial therapy who were evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in in vitro assays. However, the clinical relevance of this in vitro inhibition is unclear.

IgG antibody titres should be monitored based on clinical phenotype. Baseline serum sample collection prior to the first infusion is strongly encouraged. For IOPD patients, regular monitoring during first year of treatment (example: every 3 months) is suggested and subsequent monitoring depending on clinical outcomes and antibody titres level. For LOPD patients, antibody development should be assessed within 6 months and subsequent monitoring as clinically warranted based on safety and efficacy considerations.

Infusion reactions were reported in 20 of 39 patients (51%) treated with MYOZYME in clinical studies and appear to be more common in antibody-positive patients: 8 of 15 patients with high antibody titres experienced infusion reactions whereas none of 3 antibody-negative patients experienced infusion reactions.

Patients in clinical trials, expanded access programs and on commercial therapy have undergone testing for MYOZYME-specific IgE antibodies. Testing was performed for infusion reactions, especially moderate to severe or recurrent reactions, for which mast - cell activation was suspected. A small number of these patients tested positive for MYOZYME specific IgE binding antibodies, some of whom experienced an anaphylactic reaction (see section 4.4: Special Warnings and Precautions for Use, Risk of Hypersensitivity Reactions). Some patients have been successfully rechallenged using a slower infusion rate at lower initial doses and have continued to receive treatment with MYOZYME under close clinical supervision.

Immune-mediated reactions

Severe cutaneous and possibly immune-mediated reactions have been reported with alglucosidase alfa including ulcerative and necrotizing skin lesions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion.

Nephrotic syndrome was observed in a few Pompe patients treated with alglucosidase alfa and who had high IgG antibody titres (≥ 102, 400). In these patients renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis among patients with high IgG antibody titres.

Patients should be monitored for signs and symptoms of systemic immune complex-mediated reactions involving skin and other organs while receiving alglucosidase alfa. If immune mediated reactions occur, discontinuation of the administration of alglucosidase alfa should be considered, and appropriate medical treatment initiated. The risks and benefits of re-administering alglucosidase alfa following an immune mediated reaction should be considered. Some patients have been successfully rechallenged and continued to receive alglucosidase alfa under close clinical supervision.

Immunomodulation

Immunogenicity data from clinical trials and published literature in CRIM-negative infantile-onset patients (IOPD) suggests that the administration of immune tolerance induction (ITI) regimens given to alglucosidase alfa naive patients (prophylactic ITI) may be effective in preventing or reducing the development of High Sustained Antibody Titre (HSAT) against alglucosidase alfa. Data from a small number of patients who developed HSAT with or without inhibitory activity following treatment with MYOZYME, showed limited effect of ITI. Data from a limited number of patients from clinical studies suggest that prophylactic ITI, younger age at treatment (before the development of HSAT), and less advanced disease may contribute to better responses to MYOZYME which suggests that early initiation of ITI can result in improved clinical outcomes. ITI regimens may need to be tailored to individual patient needs. (see Section 5.1 – Pharmacodynamic Properties, Clinical Trials.

Pompe patients are at increased risk of respiratory infections due to the progressive effects of the disease on the respiratory muscles. Pompe patients treated with immunosuppressive agents may be at further increased risk of developing severe infections and vigilance is recommended. Fatal and life-threatening respiratory infections have been observed in some of these patients.

Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anaesthesia for Central Venous Catheter Placement

Cardiac arrhythmia, including ventricular fibrillation, ventricular tachycardia and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been observed in infantile-onset Pompe disease patients with cardiac hypertrophy, associated with the use of general anaesthesia for the placement of a central venous catheter intended for MYOZYME infusion. Caution should be used when administering general anaesthesia for the placement of a central venous catheter in infantile-onset Pompe disease patients with cardiac hypertrophy.

Risk of Acute Cardiorespiratory Failure

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed after infusion with MYOZYME in a few infantile-onset Pompe disease patient with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of MYOZYME. (See section 6.6 Preparation and Administration Instructions: Use Aseptic Techniques)

Infusion Associated Reactions (IARs)

In clinical trials and expanded access programs with MYOZYME, 38 of 280 (approximately 14%) patients treated with MYOZYME have developed infusion reactions that involved at least 2 of 3 body systems: cutaneous, respiratory or cardiovascular systems. These events included: Cardiovascular: hypotension, cyanosis, hypertension, tachycardia, ventricular extrasystoles, bradycardia, pallor, flushing, nodal rhythm, peripheral coldness; Respiratory: tachypnoea, wheezing/bronchospasm, rales, throat tightness, hypoxia, dyspnoea, cough, respiratory tract irritation, oxygen saturation decreased; Cutaneous: angioneurotic oedema, urticaria, rash, erythema, periorbital oedema, pruritus, hyperhidrosis, cold sweat, livedo reticularis (see section 4.8- Adverse Effects). Of these cases, 8 patients experienced severe or significant hypersensitivity reactions.

Additional IARs reported from worldwide post-marketing sources after marketing approval (including ongoing clinical programs) included: cardiac arrest, bradycardia, angioneurotic oedema, pharyngeal oedema, oedema peripheral, chest pain, chest discomfort, dyspnoea, muscle spasm, fatigue and conjunctivitis. Those IARs assessed as severe included cardiac arrest, bradycardia, chest pain, and dyspnoea.

Infusion associated reactions (IARs) occurred in 51% (20/39) of patients treated with MYOZYME in two infantile - onset clinical studies for 52 weeks. In a randomized, double-blind, placebo-controlled trial of patients with late-onset Pompe disease, 28% of patients in the alglucosidase alfa treatment group experienced IARs. IARs occur at any time during and mostly up to 2 hours after the infusion of MYOZYME. They are more likely to occur with higher infusion rates. The majority of reactions were assessed as mild to moderate, some reactions were severe. Some patients were pre-treated with antihistamines, antipyretics and/or steroids. IARs may occur in patients after receiving antipyretics, antihistamines or steroids.

If an IAR occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion and/or administration of antihistamines and/or antipyretics may ameliorate the symptoms. If severe infusion reactions occur, immediate discontinuation of the administration of MYOZYME should be considered and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reaction and cardiac arrest, epinephrine and/or cardiopulmonary resuscitation measures have been administered. Early detection of signs and symptoms of hypersensitivity or anaphylactic reactions may assist in effective management of patients and prevent possible significant or irreversible outcomes. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when MYOZYME is administered because of the potential

for severe hypersensitivity reactions. Patients who have experienced IARs should be treated with caution when re-administered MYOZYME.

Severe infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included pyrexia, decreased oxygen saturation, tachycardia, cyanosis, and hypotension. Other infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnoea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face oedema, feeling hot, headache, hyperhidrosis, lacrimation increased, livedo reticularis, nausea, periorbital oedema, restlessness, and wheezing.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion reactions. These patients should be monitored more closely when administering MYOZYME.

There were no differences between the 20mg/kg and 40mg/kg doses in any of the studied endpoints; however there was an increase in infusion related reaction with the 40 mg/kg dose (see section 4.8 Undesirable effects).

Patients who experience IARs suggestive of hypersensitivity reactions may also be tested for IgE antibodies to alglucosidase alfa.

Paediatric Use

Paediatric patients from 1 month up to 3.5 years of age at time of first infusion have been treated with MYOZYME in clinical trials. Other open-label clinical trials of MYOZYME have been performed in older paediatric patients ranging from 2 to 16 years at the initiation of treatment. Two of the 3 major trials investigating the efficacy of MYOZYME have focused on Infantile-onset Pompe Disease. AGLU1602 included 18 patients (mean age 4.6 months with a range of 1.2 – 6.1 months) and AGLU17012 included 21 patients (mean age 15.7 months with a range of 3.7 – 43.1 months. Two paediatric patients (<18 years old) have also been included in Study AGLU02704 in Late-onset Pompe patients. In addition, paediatric patients have been included in the following trials: AGLU02203 (33 patients commenced, 20 patients completed), AGLU03707 (4 patients in an immune tolerance induction study) and AGLU3807 (4 patients in a study to evaluate a prophylactic immunomodulatory regimen given prior to MYOZYME).

Use in the Elderly

Clinical studies did not include any subjects aged 65 years and older. It is not known whether they respond differently than younger subjects.

Use in Hepatic Impairment

The safety and efficacy of MYOZYME in patients with hepatic impairment have not been evaluated and no specific dose regimen can be recommended for these patients.

Use in Renal Impairment

The safety and efficacy of MYOZYME in patients with renal impairment have not been evaluated and no specific dose regimen can be recommended for these patients..

Effects on Laboratory tests

Overall, there were few clinically significant abnormal clinical laboratory evaluations in patients treated with MYOZYME. However, assessment of clinical significance varied across investigators based upon individual standards of clinical practice. In general, changes in laboratory parameters during the conduct of the studies of patients treated with MYOZYME were consistent with the evolving clinical status of individual patients and were not considered treatment related.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

No drug interaction studies have been conducted with MYOZYME.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The limited data from clinical studies, post-marketing reports and published case reports with the use of MYOZYME in male and female patients have not identified a MYOZYME - associated risk on fertility and reproductive performance.

Alglucosidase alfa at intravenous doses up to 40 mg/kg, administered every other day (plasma AUC 5 times the human steady-state exposure at the recommended biweekly dose) had no effect on fertility or reproductive performance in mice.

Use in pregnancy

Category B1

The limited data from post-marketing reports and published case reports with the use of alglucosidase alfa in pregnant women have not identified a MYOZYME - associated risk of miscarriage, or adverse maternal or fetal outcomes. There have been reports of diaphragmatic hernia, atrial septal defect and truncus arteriosus persistent in post-marketing experience, however the relationship of MYOZYME to these events is unknown.

Myozyme should not be used during pregnancy unless clearly necessary. The continuation of treatment for Pompe disease during pregnancy should be individualised to the pregnant woman. Untreated Pompe disease may result in worsening disease symptoms in pregnant women.

Developmental studies performed in pregnant mice and rabbits at IV doses up to 40 mg/kg/day during the period of organogenesis (9.5 and 13 times the expected human exposure, based on AUC values) revealed no evidence of embryofetal developmental toxicity due to alglucosidase alfa.

Use in lactation

Alglucosidase alfa may be excreted in breast milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MYOZYME and any potential adverse effects on the breastfed child from MYOZYME or from the underlying maternal condition.

A lactating woman may consider interrupting breastfeeding, pumping and discarding breast milk during MYOZYME administration and for 24 hours thereafter in order to minimise drug exposure to a breastfed infant.

In a pre- and post-natal study in mice, survival of the offspring was reduced during days 15-21 of lactation at the highest dose evaluated (40 mg/kg IV every other day; 5 times the expected human exposure based on AUC values). However, the relationship of this finding to MYOZYME was unclear since this observation was not dose or time dependent, and there were no other effects on any other parameter evaluated in the high dose group. Furthermore, when the data was analysed on a per litter basis, the litter loss was not significantly different between the control group and the highest dose tested. MYOZYME should be given to a breastfeeding woman only if clearly needed and after a careful risk/benefit analysis has been conducted for both the mother and child.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the ability to drive and handle machines have been conducted with alglucosidase alfa. Because dizziness has been reported as an infusion associated reaction, this may affect the ability to drive and use machines on the day of the infusion.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

Infantile-onset Pompe disease

The most common serious treatment-emergent adverse events (regardless of relationship) observed in clinical studies with MYOZYME were pneumonia, respiratory failure, respiratory distress, catheter related infection, respiratory syncytial virus infection, gastroenteritis, and fever. The most common treatment-emergent adverse events (regardless of relationship) were fever, diarrhoea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation.

Table 1 - Treatment - emergent adverse events (regardless of relationship) that occurred in at least 20% of patients treated with MYOZYME® in clinical trials described above. (Reported frequencies of adverse events have been classified by MedDRA terms.)

System Organ Class	Number of Patients	Number of
Preferred Term	(N=39)	Adverse Events
	n (%)	n
Any Adverse Events =	**39 (100)**	**1859**
General disorders and administration site conditions	**38 (97)**	
Pyrexia	36 (92)	169
Respiratory, thoracic and mediastinal disorders	**38 (97)**	
Cough	18 (46)	69
Respiratory distress	13 (33)	18
Respiratory failure	12 (31)	24
Rhinorrhoea	11 (28)	16
Tachypnoea	9 (23)	15
Infections and infestations	**37 (95)**	
Pneumonia	18 (46)	43
Otitis media	17 (44)	35
Upper respiratory tract infection	17 (44)	39
Gastroenteritis	16 (41)	17
Pharyngitis	14 (36)	26
Ear Infection	13 (33)	23
Oral candidiasis	12 (31)	20
Catheter related infection	11 (28)	15
Bronchiolitis	9 (23)	10
Nasopharyngitis	9 (23)	25
Gastrointestinal disorders	**32 (82)**	
Diarrhoea	24 (62)	62
Vomiting	19 (49)	62
Gastroesophageal reflux disease	10 (26)	13
Constipation	9 (23)	14
Skin and subcutaneous tissue disorders	**32 (82)**	
Rash	21 (54)	72
Diaper dermatitis	14 (36)	34
Urticaria	8 (21)	25
Investigations	**28 (72)**	
Oxygen saturation decreased	16 (41)	44

System Organ Class	Number of Patients	Number of
Cardiac disorders	**24 (62)**	
Tachycardia	9 (23)	31
Bradycardia	8 (21)	18
Injury, poisoning and procedural complications	**22 (56)**	
Post procedural pain	10 (26)	20
Blood and lymphatic system disorders	**17 (44)**	
Anaemia	12 (31)	23
Vascular disorders	**14 (36)**	
Flushing	8 (21)	15

Five additional juvenile-onset Pompe disease patients were evaluated in a single-centre, open label, non-randomised, uncontrolled clinical trial. Patients were aged 5 to 15 years, ambulatory (able to walk at least 10 metres in 6 minutes), and not receiving invasive ventilatory support at study entry. All 5 patients received treatment with 20 mg/kg MYOZYME for 26 weeks. The most common treatment-emergent adverse events (regardless of causality) observed with MYOZYME treatment in this study were headache, pharyngitis, upper abdominal pain, malaise, and rhinitis.

Adverse Drug Reactions

The most common adverse drug reactions (ADRs) were infusion associated reactions (IARs). Infusion reactions occurred in approximately 50% of patients treated with MYOZYME in two infantile-onset clinical studies for 52 weeks. The majority of these reactions were mild to moderate. IARs which were reported in more than 1 patient in clinical studies and the expanded access program included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnoea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face oedema, feeling hot, headache, hyperhidrosis, lacrimation increased, livedo reticularis, nausea, periorbital oedema, restlessness and wheezing. Severe infusion reactions reported in more than 1 patient included pyrexia, decreased oxygen saturation, tachycardia, cyanosis and hypotension.

If severe infusion reactions occur, immediate discontinuation of the administration of MYOZYME should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when MYOZYME is administered. Most infusion related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion and/or administration of antipyretics, antihistamines or steroids.

Late-onset Pompe disease

The most common adverse reactions observed in a randomized, double-blind, placebo controlled study of 90 patients with late-onset Pompe disease (aged 10 to 70 years) were infusion reactions. Patients were treated with 20 mg/kg alglucosidase alfa or placebo (randomized in a 2:1 ratio) once

every two weeks for 78 weeks. Infusion reactions occurred in approximately 28% of patients treated with alglucosidase alfa, compared to 23% of placebo-treated patients. The majority of these reactions was mild to moderate and resolved spontaneously. Infusion reactions which were reported in ≥ 5% of alglucosidase alfa-treated patients included headache, nausea, dizziness, urticaria, rash, chest discomfort, anaphylaxis, vomiting, hyperhidrosis, flushing and blood pressure increased.

Serious adverse reactions reported in 4 patients treated with alglucosidase alfa were: angioedema, chest discomfort, throat tightness, non-cardiac chest pain and supraventricular tachycardia. Reactions in 2 of these patients were IgE-mediated anaphylactic reactions.

Adverse Events reported in at least 5% of patients treated with alglucosidase alfa or placebo in a clinical study of patients with Late Onset Pompe Disease are listed in Table 2:

Table 2 Summary of Treatment Emergent AEs Occurring in at Least 5% of Alglucosidase alfa or Placebo-Treated Patients by Treatment Group

System Organ Class Preferred Term	Alglucosidase alfa Patients		Placebo Patients	
	Number of patients[1] n (%)	Number of adverse events[2] n (%)	Number of patients[1] n (%)	Number of adverse events[2] n (%)
Any adverse event	60 (100.0)	1445 (100.0)	30 (100.0)	851 (100.0)
Infections and Infestations	49 (81.7)	131 (9.1)	26 (86.7)	75 (8.8)
Nasopharyngitis	25 (41.7)	45 (3.1)	16 (53.3)	25 (2.9)
Upper respiratory tract infection	11 (18.3)	16 (1.1)	3 (10.0)	3 (0.4)
Influenza	5 (8.3)	8 (0.6)	7 (23.3)	8 (0.9)
Urinary tract infection	5 (8.3)	6 (0.4)	4 (13.3)	7 (0.8)
Sinusitis	4 (6.7)	5 (0.3)	4 (13.3)	5 (0.6)
Herpes simplex	4 (6.7)	6 (0.4)	3 (10.0)	4 (0.5)
Gastroenteritis viral	3 (5.0)	5 (0.3)	3 (10.0)	3 (0.4)
Gastroenteritis	6 (10.0)	6 (0.4)	1 (3.3)	1 (0.1)
Viral infection	2 (3.3)	2 (0.1)	2 (6.7)	2 (0.2)
Gastrointestinal infection	0	0	2 (6.7)	2 (0.2)
Rhinitis	0	0	2 (6.7)	2 (0.2)
Respiratory tract infection	3 (5.0)	3 (0.2.)	0	0
Injury, poisoning and procedural complications	46 (76.7)	209 (14.5)	23 (76.7)	160 (18.8)
Fall	39 (65.0)	155 (10.7)	20 (66.7)	121 (14.2)

System Organ Class Preferred Term	Alglucosidase alfa Patients		Placebo Patients	
	Number of patients[1] n (%)	Number of adverse events[2] n (%)	Number of patients[1] n (%)	Number of adverse events[2] n (%)
Contusion	4 (6.7)	6 (0.4)	6 (20.0)	7 (0.8)
Procedural pain	9 (15.0)	11 (0.8)	3 (10.0)	6 (0.7)
Muscle strain	4 (6.7)	5 (0.3)	4 (13.3)	5 (0.6)
Excoriation	0	0	3 (10.0)	4 (0.5)
Injury	4 (6.7)	4 (0.3)	1 (3.3)	1 (0.1)
Skin laceration	4 (6.7)	5 (0.3)	1 (3.3)	1 (0.1)
Joint sprain	1 (1.7)	1 (0.1)	2 (6.7)	2 (0.2)
Musculoskeletal and connective tissue disorders	44 (73.3)	222 (15.4)	22 (73.3)	118 (13.9)
Arthralgia	18 (30.0)	27 (1.9)	9 (30.0)	21 (2.5)
Pain in extremity	15 (25.0)	27 (1.9)	7 (23.3)	25 (2.9)
Back pain	14 (23.3)	22 (1.5)	7 (23.3)	15 (1.8)
Muscle spasms	14 (23.3)	18 (1.2)	6 (20.0)	7 (0.8)
Myalgia	12 (20.0)	40 (2.8)	5 (16.7)	14 (1.6)
Neck pain	7 (11.7)	9 (0.6)	5 (16.7)	11 (1.3)
Musculoskeletal pain	8 (13.3)	14 (1.0)	2 (6.7)	3 (0.4)
Musculoskeletal stiffness	8 (13.3)	11 (0.8)	1 (3.3)	1 (0.1)
Muscular weakness	6 (10.0)	8 (0.6)	3 (10.0)	4 (0.5)
Muscle twitching	5 (8.3)	7 (0.5)	1 (3.3)	1 (0.1)
Musculoskeletal chest pain	5 (8.3)	6 (0.4)	1 (3.3)	1 (0.1)
Buttock pain	3 (5.0)	4 (0.3)	1 (3.3)	1 (0.1)
Gastrointestinal disorders	39 (65.0)	283 (11.9)	20 (66.7)	100 (11.8)
Diarrhoea	18 (30.0)	43 (3.0)	13 (43.3)	20 (2.4)
Nausea	11 (18.3)	38 (2.6)	10 (33.3)	49 (5.8)
Vomiting	13 (21.7)	16 (1.1)	3 (10.0)	5 (0.6)
Toothache	1 (1.7)	1 (0.1)	4 (13.3)	6 (0.7)
Abdominal pain	4 (6.7)	5 (0.3)	3 (10.0)	3 (0.4)
Abdominal pain upper	6 (10.0)	23 (1.6)	2 (6.7)	4 (0.5)
Constipation	6 (10.0)	8 (0.6)	0	0

System Organ Class Preferred Term	Alglucosidase alfa Patients		Placebo Patients	
	Number of patients[1] n (%)	Number of adverse events[2] n (%)	Number of patients[1] n (%)	Number of adverse events[2] n (%)
Dyspepsia	5 (8.3)	8 (0.6)	0	0
Abdominal discomfort	2 (3.3)	2 (0.1)	2 (6.7)	2 (0.2)
Abdominal distention	1 (1.7)	1 (0.1)	2 (6.7)	2 (0.2)
Oral mucosal blistering	0	0	2 (6.7)	2 (0.2)
Nervous system disorders	37 (61.7)	180 (12.5)	20 (66.7)	194 (22.8)
Headache	24 (40.0)	91 (6.3)	15 (50.0)	130 (15.3)
Dizziness	14 (23.3)	31 (2.1)	6 (20.0)	14 (1.6)
Paraesthesia	6 (10.0)	16 (1.1)	4 (13.3)	10 (1.2)
Hypoaesthesia	2 (3.3)	2 (0.1)	2 (6.7)	3 (1.4)
Tremor	4 (6.7)	4 (0.3)	0	0
Areflexia	3 (5.0)	4 (0.3)	2 (6.7)	2 (0.2)
Migraine	3 (5.0)	5 (0.3)	1 (3.3)	4 (0.5)
Somnolence	3 (5.0)	5 (0.3)	0	0
General disorders and administration site conditions	39 (65.0)	119 (8.2)	19 (63.3)	65 (7.6)
Pyrexia	8 (13.3)	8 (0.6)	8 (26.7)	11 (1.3)
Fatigue	7 (11.7)	9 (0.6)	6 (20.0)	14 (1.6)
Oedema peripheral	10 (16.7)	12 (0.8)	3 (10.0)	5 (0.6)
Asthenia	3 (5.0)	3 (0.2)	4 (13.3)	8 (0.9)
Influenza like illness	2 (3.3)	2 (0.1)	4 (13.3)	5 (0.6)
Chest discomfort	7 (11.7)	16 (1.1)	1 (3.3)	1 (0.1)
Pain	5 (8.3)	8 (0.6)	1 (3.3)	1 (0.1)
Infusion site reaction	5 (8.3)	6 (0.4)	0	0
Feeling hot	3 (5.0)	4 (0.3)	2 (6.7)	3 (0.4)
Pitting oedema	2 (3.3)	2 (0.1)	2 (6.7)	2 (0.2)
Chest pain	4 (6.7)	4 (0.3)	1 (3.3)	1 (0.1)
Chills	3 (5.0)	3 (0.2)	1 (3.3)	4 (0.5)
Malaise	3 (5.0)	3 (0.2)	0	0
Respiratory, thoracic and	34 (56.7)	72 (5.0)	17 (56.7)	43 (5.1)

System Organ Class Preferred Term	Alglucosidase alfa Patients		Placebo Patients	
	Number of patients[1] n (%)	Number of adverse events[2] n (%)	Number of patients[1] n (%)	Number of adverse events[2] n (%)
mediastinal disorders				
Pharyngolaryngeal pain	12 (20.0)	19 (1.3)	5 (16.7)	9 (1.1)
Cough	6 (10.0)	6 (0.4)	5 (16.7)	5 (0.6)
Dyspnoea	7 (11.7)	10 (0.7)	4 (13.3)	6 (0.7)
Sinus congestion	2 (3.3)	2 (0.1)	3 (10.0)	3 (0.4)
Nasal congestion	2 (3.3)	2 (0.1)	2 (6.7)	3 (0.4)
Dyspnoea exertional	4 (6.7)	5 (0.3)	0	0
Epistaxis	3 (5.0)	8 (0.6)	0	0
Ear and labyrinth disorders	30 (50.0)	59 (4.1)	10 (33.3)	16 (1.9)
Hypoacusis	20 (33.3)	22 (1.5)	7 (23.3)	7 (0.8)
Ear discomfort	4 (6.7)	23 (1.6)	1 (3.3)	1 (0.1)
Vertigo	4 (6.7)	6 (0.4)	0	0
Ear pain	3 (5.0)	3 (0.2)	1 (3.3)	4 (0.5)
Skin and subcutaneous tissue disorders	25 (41.7)	110 (7.6)	9 (30.0)	23 (2.7)
Rash	6 (10.0)	10 (0.7)	3 (10.0)	5 (0.6)
Pruritis	6 (10.0)	15 (1.0)	1 (3.3)	1 (0.1)
Urticaria	6 (10.0)	15 (1.0)	0	0
Hyperhidrosis	5 (8.3)	10 (0.7)	0	0
Rash pruritic	4 (6.7)	7 (0.5)	1 (3.3)	3 (0.4)
Eczema	0	0	2 (6.7)	2 (0.2)
Erythema	3 (5.0)	5 (0.3)	1 (3.3)	1 (0.1)
Rash popular	3 (5.0)	4 (0.3)	0	0
Investigations	9 (15.0)	21 (1.5)	10 (33.3)	20 (2.4)
Blood pressure increased	3 (5.0)	3 (0.2)	1 (3.3)	2 (0.2)
Psychiatric disorders	7 (11.7)	23 (1.6)	8 (26.7)	10 (1.2)
Insomnia	6 (10.0)	7 (0.5)	2 (6.7)	2 (0.2)
Anxiety	2 (3.3)	4 (0.3)	3 (10.0)	3 (0.4)

System Organ Class Preferred Term	Alglucosidase alfa Patients		Placebo Patients	
	Number of patients[1] n (%)	Number of adverse events[2] n (%)	Number of patients[1] n (%)	Number of adverse events[2] n (%)
Depression	1 (1.7)	3 (0.2)	2 (6.7)	2 (0.2)
Vascular disorders	13 (21.7)	19 (1.3)	5 (16.7)	7 (0.8)
Flushing	3 (5.0)	5 (0.3)	2 (6.7)	2 (0.2)
Hypertension	3 (5.0)	3 (0.2)	1 (3.3)	1 (0.1)
Eye disorders	13 (21.7)	20 (1.4)	3 (10.0)	3 (0.4)
Cataract	4 (6.7)	4 (0.3)	2 (6.7)	2 (0.2)
Blurred vision	3 (5.0)	3 (0.2)	0	0
Renal and urinary disorders	12 (20.0)	16 (1.1)	5 (16.7)	6 (0.7)
Pyuria	1 (1.7)	1 (0.1)	2 (6.7)	2 (0.2)
Haematuria	3 (5.0)	4 (0.3)	1 (3.3)	1 (0.1)
Nephrolithiasis	3 (5.0)	4 (0.3)	0	0
Reproductive system and breast disorders	5 (8.3)	7 (0.5)	5 (16.7)	6 (0.7)
Dysmenorrhoea	0	0	2 (6.7)	3 (0.4)
Cardiac disorders	9 (15.0)	20 (1.4)	1 (3.3)	1 (0.1)
Palpitations	3 (5.0)	9 (0.6)	1 (3.3)	1 (0.1)
Metabolism and nutrition disorders	7 (11.7)	10 (0.7)	2 (6.7)	2 (0.2)
hypokaleamia	3 (5.0)	5 (0.3)	0	0
Blood and lymphatic system disorders	7 (11.7)	9 (0.6)	1 (3.3)	1 (0.1)
lymphadenopathy	5 (8.3)	6 (0.4)	0	0
Immune system disorders	3 (5.0)	26 (1.8)	0	0
Hypersensitivity	3 (5.0)	26 (1.8)	0	0

[1] Percentages are based on the total number of patients treated in the study group. A patient experiencing more than 1 AE within an SOC or preferred term is counted once within that SOC or preferred term. Events occurring in 5% of patients in either treatment group are presented; corresponding percentage of patients in alternate treatment group is presented which may represent less than 5% of patients.

[2] Percentages are based on the total number of AEs experienced by patients in the study group during treatment.

Adverse Drug Reactions– IOPD and LOPD

Of the serious ADRs reported with MYOZYME, the most significant were cardiorespiratory failure, anaphylactic reactions and cardiac arrest. Cardiorespiratory failure, possibly associated with fluid overload, was reported in a few infantile - onset Pompe disease patient and pre - existing cardiac hypertrophy likely contributed to the severity of the reaction (see section 4.4: Special Warnings and Precautions for Use, Risk of Acute Cardiorespiratory Failure).

Other ADRs, listed by System Organ Class are listed below:

Immune system disorders: hypersensitivity

Psychiatric disorders: agitation, restlessness

Nervous system disorders: tremor, dizziness, paraesthesia, headache

Eye disorders: conjunctivitis

Cardiac disorders: tachycardia, cyanosis, cardiac arrest, bradycardia

Vascular disorders: flushing, hypertension, flushing, pallor, hypotension, vasoconstriction

Respiratory, thoracic and mediastinal disorders: tachypnoea, cough, throat tightness, respiratory arrest, apnea, respiratory distress, bronchospasm, wheezing, pharyngeal oedema, dyspnoea, stridor

Gastrointestinal disorders: vomiting, retching, nausea, diarrhoea, nausea, abdominal pain
Skin and subcutaneous tissue disorders: urticaria, rash, erythema, rash-maculopapular, rash-papular, pruritus, hyperhidrosis, periorbital edema, livedo reticularis, lacrimation increased

Musculoskeletal and connective tissue disorders: muscle spasms, muscle twitching, myalgia, arthralgia

Renal and urinary disorders: nephrotic syndrome, proteinuria

General disorders and administration site conditions: pyrexia, irritability, chills, chest discomfort, peripheral oedema, local swelling, fatigue, feeling hot, peripheral coldness, infusion site pain, infusion site reaction, infusion site swelling, infusion site induration, infusion site extravasation

Investigations: oxygen saturation decreased, heart rate increased, blood pressure increased, body temperature increased

Post-Marketing Experience

Infusion-associated reactions (IARs) reported from worldwide post-marketing sources have included cardiac arrest, bradycardia, angioneurotic oedema, pharyngeal oedema, oedema peripheral, chest pain, chest discomfort, dyspnoea, muscle spasm, fatigue, respiratory distress, throat tightness and conjunctivitis. Those IARs assessed as severe included cardiac arrest, bradycardia, chest pain, and dyspnoea. The majority of patients continued to receive treatment with MYOZYME, some under close clinical supervision.

A review of the safety information revealed a total of 5 patients experienced significant infusion associated reactions. In addition, a patient who experienced non-serious recurrent generalised urticaria was IgE positive. In total, 11 patients treated in either clinical studies or with commercial MYOZYME have tested positive for IgE antibodies. In total, (up until March 2008) 178 patients treated with MYOZYME in clinical trials and/or the commercial setting were evaluated for *in vitro* inhibition of enzyme activity. Of these, 137 patients were also evaluated for inhibition of uptake. A total of 32 of 178 (18.0%) patients tested positive for *in vitro* inhibition by inhibition of enzyme activity and/or inhibition of uptake assay at one or more time points.

Four of the 32 patients tested for inhibition of enzyme activity and all 32 patients tested positive for inhibition of uptake at one or more time points. Nineteen of the 32 (59%) patients were classified as positive for uptake inhibition and 13 (41%) patients were classified as borderline. The majority of infantile-onset patients who developed inhibitory antibodies were Cross Reactive Immunologic Material (CRIM) negative, developed peak antibody titres ≥ 102,400 and showed signs of clinical decline. In late-onset patients who tested positive for inhibition of cellular uptake in study AGLU02704 there was no clear effect of IgG antibodies or inhibitory antibodies on safety or efficacy endpoints at study conclusion.

In addition to infusion reactions reported in clinical trials and expanded access program, the following infusion reactions have been reported from worldwide sources after marketing approval, including ongoing clinical programs: peripheral/local edema, abdominal pain, arthralgia, syncope and somnolence. Additional adverse drug reactions included proteinuria and nephrotic syndrome in patients with high IgG antibody titres (≥ 102,400).

Recurrent reactions consisting of flu-like illness or a combination of events such as fever, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and lasting usually for a few days have been observed in some patients treated with alglucosidase alfa. The majority of patients were successfully rechallenged with alglucosidase alfa using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and have continued to receive treatment under close clinical supervision.

Significant skin lesions (necrotising inflammation) were reported in 1 patient following MYOZYME treatment in a post-marketing setting. After temporary discontinuation of MYOZYME treatment, lesions resolved and the patient was able to continue on therapy.

Severe cutaneous and possibly immune-mediated reactions have been reported with alglucosidase alfa including ulcerative and necrotizing skin lesions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion.

Nephrotic syndrome was observed in a few Pompe patients treated with alglucosidase alfa and who had high IgG antibody titres (≥ 102,400). In these patients renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis among patients with high IgG antibody titres.

Hypersensitivity

Significant hypersensitivity reactions have been reported from worldwide post-marketing sources in patients treated with MYOZYME. Some of these patients experienced life-threatening anaphylactic reactions, including anaphylactic shock, some of which were IgE-mediated. Reactions generally occurred shortly after initiation of the infusion. Patients presented with a constellation of signs and symptoms, primarily respiratory, cardiovascular, oedematous and/or cutaneous in nature. Reactions included bronchospasm, wheezing, respiratory arrest, respiratory distress, apnea, stridor, dyspnea, oxygen saturation decreased, cardiac arrest, hypotension, bradycardia, tachycardia, cyanosis, vasoconstriction, flushing, chest pain, chest discomfort, throat tightness, angioedema, pharyngeal edema, face edema, peripheral edema, urticaria, and rash.

In approximately 280 patients treated with MYOZYME, some patients experienced severe or significant hypersensitivity reactions, including a life-threatening anaphylactic shock (see section 4.4: Risk of Hypersensitivity Reactions). One patient developed an anaphylactic shock, which consisted of bronchoconstriction, hypotension, cyanosis, hypoxia, pallor and oxygen desaturation, during MYOZYME infusion that required life-support measures.

The majority of adverse reactions received during the current reporting period were consistent with the manifestation of the underlying Pompe disease or disease progression.

Physicians should monitor hypersensitivity reactions, drug–induced skin reactions, clinical decline or plateau of treatment and consider the risks and benefits of continued treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

In clinical trials, patients received doses up to 40 mg/kg of body weight. IARs are more likely to occur with higher doses or infusion rates, than recommended. See section 4.4 Special Warnings and Precautions - Infusion Associated Reactions (IARs).

For risk assessment and advice on the management of overdose, contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes, ATC code: A16AB07.

MYOZYME is a purified form of the lysosomal enzyme acid alfa - glucosidase (GAA). Alglucosidase alfa - rch is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa - rch is a 896 amino acid glycoprotein with 7 asparagine - linked glycosylation sites that are occupied by a mixture of complex, oligomannose and phosphorylated oligomannose structures. Alglucosidase alfa - rch has a molecular weight of approximately 110 kD.

Mechanism of Action

Pompe disease (glycogen storage disease type II, GSD II, glycogenosis type II, acid maltase deficiency) is a rare autosomal recessive disease caused by the deficiency of lysosomal acid alfa-glucosidase (GAA). GAA degrades lysosomal glycogen by catalysing the hydrolysis of the α-1, 4- and α-1,6-glycosidic linkages. Pompe disease results in intralysosomal accumulation of glycogen in various tissues, particularly cardiac and skeletal muscles, leading to the development of cardiomyopathy, progressive muscle weakness, and impairment of respiratory function.

Treatment of Pompe disease with MYOZYME provides an exogenous source of GAA.

Intracellular trafficking of the 110 kD form of rhGAA to the lysosome occurs via a cation independent mannose-6-phosphate receptor dependent mechanism. This receptor is present on the surface of many cell types and may play a role in uptake of exogenous lysosomal enzymes. During internalisation and trafficking to the lysosome, rhGAA undergoes proteolytic and N-glycan processing resulting in the formation of a mature form, which degrades lysosomal glycogen at low pH.

Clinical efficacy and safety

The efficacy of MYOZYME has been evaluated in 3 clinical trials of patient's naïve to enzyme replacement therapy (ERT) at the initiation of treatment and are detailed below. In addition, several other studies and expanded access programs were conducted. Other supportive studies and expanded access programmes have been conducted.

In a retrospective natural history study in patients with infantile-onset Pompe disease (n=168), the median age at onset of symptoms was 2.0 months and the median age of death was 9.0 months. Kaplan-Meier survival rates at 12, 24 and 36 months of age were 26%, 9% and 7%, respectively.

Paediatric Population

Infantile - Onset Pompe Disease

The pivotal study, AGLU01602, was an international, multicentre, historically - controlled clinical trial of 18 non-ventilated infantile-onset Pompe disease patients aged 7 months or less at first infusion.

Patients were randomised equally to receive either 20 mg/kg or 40 mg/kg MYOZYME every 2 weeks for the duration of the study. The primary endpoint was the proportion of patients alive and/or free of invasive ventilation at 18 months of age (time to event). An untreated historical cohort (n = 42), derived from a retrospective natural history study discussed above, served as a comparator group for assessment of the primary endpoint. Given the limited data on invasive ventilator use in the historical population, a comparison to overall survival in the historical cohort was made.

The primary efficacy endpoint for pivotal study AGLU01602 was achieved. At the 18-month milestone, 13 of the 18 patients in AGLU01602 were alive and invasive ventilator-free, 3 were receiving invasive ventilator support, and 2 patients who had not reached the age of 18 months by the end of the study were censored from the analysis, though they were alive and free of invasive ventilator support at that time. By contrast only one of 42 patients in the historical cohort group was alive at 18 months of age. Comparison of survival curves from time of 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 2). Results from the Cox analysis indicate that in this study MYOZYME reduced the risk of death and/or allowed the patient to be free of invasive ventilation at 18 months of age by 99% (hazard ratio 0.01), which is also highly significant. Results for the primary endpoint are detailed in Table 2.

Table 2 - 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.

Treatment with MYOZYME greatly increased patient survival as assessed at 18 months of age.

Cardiac status and motor function were assessed as secondary endpoints.

Changes from baseline to Month 12 in left ventricular mass index (LVMI) were measured by echocardiography. For the 14 patients with both baseline and Month 12 echocardiograms, all had decreases from baseline in LVMI (mean decrease 118 g/m2, range 45 to 193 g/m2). 13 patients (72%, 13/18) made gains in motor function over baseline as measured by motor performance age-equivalent scores of the Alberta Infant Motor Scale (AIMS).

There were no differences between the 20mg/kg and 40mg/kg doses in any of the studied endpoints; however there was an increase in infusion related reactions with the 40mg/kg dose (see section 4.8 Undesirable effects).

Sixteen of the 18 patients who participated in Study AGLU01602 were enrolled in an extension study (AGLU02403) for up to 150 weeks. One patient died and did not enter into the extension study. A second patient continued treatment under an international expanded access program. At the end of the study, 14 of 16 patients (87.5%) were alive and 9 of 16 patients (56.3%) were alive and free of invasive ventilatory support. The two patients who died were aged 2 years 6 months and 3 years 5 months respectively. One additional patient died after study end and another one after withdrawal from the study.

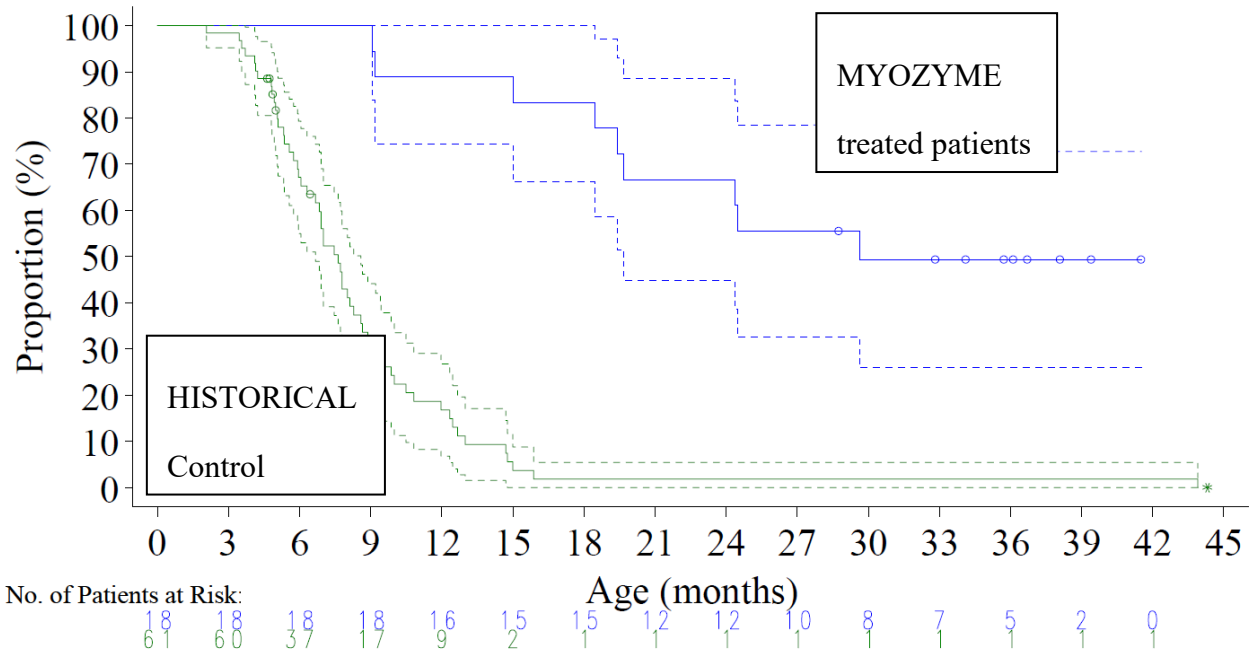
Table 4 - Cox Regression Model Analysis: Estimation of the Effect of alglucosidase alfa on Invasive Ventilator-Free Survival, Ventilator-Free Survival, and Overall Survival using AGLU01602/AGLU02403 and Historical Control Group Patients4641

Number of Treated Patients	Number of Historical control Comparator patients	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N = 18	N = 61	Invasive ventilator-free survival	0.09	0.038, 0.215	<0.0001
		Any ventilator free survival	0.13	0.059, 0.294	<0.0001
		Survival	0.05	0.016, 0.141	<0.0001

Note: Results are from a Cox proportional hazards regression analysis which includes treatment as a time-varying covariate, and also adjusts for age of diagnosis and age at symptom onset. Data through the end of Study AGLU02403 (June 12, 2006) are included in the models.

At their last evaluation, 7 patients (38.9%) had a left ventricular mass within normal limits, and mean LVMI had decreased 40%. By the end of the extension study, a total of 11 patients (61%) acquired new motor skills while on treatment with alglucosidase alfa, including the achievement of independent ambulation, as assessed by AIMS and motor milestone scores. The remaining 7 patients (38.9%) were classified as motor non responders at the end of study and had minimal or no significant gross motor skills. Three patients made significant motor gains during the study that were not maintained by the end of the study.

Figure 1 - Kaplan-Meier Estimate of Time to Invasive Ventilation or Death from Date of Birth to End of Study AGLU2403 (Comparison to Historical Control MYOZYME treated patients Group



For primary endpoint of Kaplan-Meier Estimate, for the untreated historical cohort n=61

Study AGLU01702 was an international, multicentre, open-label clinical trial of 21 infantile-onset patients who were 3 months to 3.5 years old at first treatment. All patients received 20 mg/kg MYOZYME every other week for up to 168 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion.

The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the end of the study, 15 (71.4%) 21 patients were alive. None of the deaths were assessed as related to alglucosidase alfa treatment. The effect of MYOZYME treatment on survival was further assessed using a Cox proportional hazards model to fit time-to-event from time of disease diagnosis. Survival data were compared firstly to these observed in a subgroup of the Natural History study population (called the Historical Reference Sub-group) (n = 86) and secondly to a subset of 16 patients belonging to the Historical Reference Sub-group who had survived past 15 months. Results from the Cox analysis (Table 5) indicate that in this study MYOZYME reduced the risk of death by 78% (hazard ratio 0.209), which is also highly significant.

Table 5 - Survival Results for Study AGLU01702 using the Cox Regression Model

Treated Patients	Historical Reference Comparator	Endpoint	Treatment Effect Hazard Ratio	95% Confidence Interval	p-value
N=21	N=84	Survival	0.209	(0.083, 0.524)	0.0009

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. Analysis is from time of diagnosis through to the end of the study (July 14, 2006)

16 patients were free of invasive ventilatory support at the time of first infusion: At the end of the study, 7 (43.8%) patients remained free of invasive ventilation, 5 patients died, and 4 patients were invasive ventilator dependent.

Fifteen of 21 patients (71%) showed improvement in cardiomyopathy as measured by a decrease in left ventricular mass (LMV) from first to last study evaluation. Two additional patients maintained normal LVM throughout the study. Thirteen of 21 patients (61.9%) had measurable gains in motor function as determined by increases in age-equivalent scores from baseline in the AIMS and/or Peabody Development Motor Scale. The remaining patients (8 of 21, 38.9%) did not demonstrate measurable gains across these motor assessments.

Late - Onset Pompe Disease

AGLU02804 was a single-centre, open-label clinical trial which assessed the 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 1 patient did not require any form of ventilator support. Of the 3 patients with significant pulmonary involvement at baseline (percentage predicted forced vital capacity (FVC) in the sitting position ranging from 58 - 67%), 2 demonstrated clinically meaningful improvements in FVC (+11.5 and +16%) in the sitting position by week 26. Motor function was evaluated using the 6 - Minute Walk Test (6MWT). Three of the patients demonstrated a clinically meaningful improvement (ranging from 41-118 m) in 6MWT at fast speed by week 26. 1 patient experienced a clinically meaningful improvement in the 6MWT at comfortable speed.

Study AGLU02704 was a randomized, double-blind, placebo-controlled study of 90 patients (45 male, 45 female) with late-onset Pompe disease who ranged in age from 10 to 70 years at initiation of treatment. All patients were naïve to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for 78 weeks (18 months). At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 metres in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded from the study.

The co-primary efficacy outcome assessments were distance walked (metres) in 6 minutes (6-Minute Walk Test, 6MWT) and FVC % predicted in the sitting position. After 78 weeks, patients treated with alglucosidase alfa showed improvement in distance walked as measured by 6MWT and stabilization of pulmonary function as measured by FVC % predicted as compared to placebo-treated patients. The estimated mean distance walked in 6 minutes increased by 25.13 metres for alglucosidase alfa-treated patients and decreased by 2.99 metres for placebo-treated patients, indicating a statistically significant alglucosidase alfa treatment effect compared to placebo of +28.12 metres ($p = 0.0347$). The estimated mean % predicted FVC increased by 1.20% for alglucosidase alfa patients and decreased by 2.20% for placebo-treated patients, for a

statistically significant treatment effect of 3.40% (p=0.0055). The results are shown in Table below:

Table 6 - Change from baseline: efficacy outcomes in the placebo-controlled study

		Alglucosidase alfa (N = 60)	Placebo (N = 30)
6-Minute Walk Test Distance (metres)			
Pre-treatment Baseline	Mean ± s.d.	332.20 ± 126.69	317.93 ± 132.29
Week 78/Last Observation	Mean ± s.d.	357.85 ± 141.32	313.07 ± 144.69
Estimated Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI)	25.13* (10.07, 40.19)	-2.99* (-24.16, 18.18)
Estimated Difference Between Groups in Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI) p-value	28.12* (2.07, 54.17) 0.0347	
Wilcoxon-Mann-Whitney Test	p-value	0.0283	
Forced Vital Capacity (Percent of predicted normal)			
Pre-treatment Baseline	Mean ± s.d.	55.43 ± 14.44	53.00 ± 15.66
Week 78/Last Observation	Mean ± s.d.	56.67 ± 16.17	50.70 ± 14.88
Estimated Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI)	1.20* (-0.16, 2.57)	-2.20* (-4.12, -0.28)
Estimated Difference Between Groups in Change from Baseline to Week 78/Last Observation (ANCOVA)	Mean (95% CI) p-value	3.40* (1.03, 5.77) 0.0055	
Wilcoxon-Mann-Whitney Test	p-value	0.0026	

* Estimates are based on ANCOVA, adjusting for randomization strata and baseline observation

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic profile of MYOZYME was evaluated in studies AGLU01602 and AGLU01702 as part of the clinical development program. In both studies, plasma GAA levels obtained before and after MYOZYME infusions on day 0 and week 12 were evaluated via a GAA activity assay and these data were used to determine various pharmacokinetic parameters. The

pharmacokinetic profile of MYOZYME was also evaluated in AGLU02804 on day 0 and at weeks 12 and 26. Pharmacokinetic parameters from these 3 clinical studies are summarised in Table 7.

Pharmacokinetic data were available from 15 of the 18 patients with infantile-onset Pompe disease treated with MYOZYME in study AGLU01602 at a dosage of 20 mg/kg or 40 mg/kg every 2 weeks. the 20 mg/kg dose was infused over a period of approximately 4 hours and the 40 mg/kg dose was infused over approximately 6.5 hours. The pharmacokinetics of rhGAA were dose proportional and did not change over time.

The pharmacokinetics of MYOZYME were also evaluated in 12 patients with infantile - onset Pompe disease in Study AGLU01702 at a dosage of 20 mg/kg. Patients received 20 mg/kg of MYOZYME as an approximate 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the 20 mg/kg dose group in AGLU01602 study (see Table 7).

The pharmacokinetics of MYOZYME were evaluated in clinical study AGLU02804 in 5 patients with late-onset Pompe disease who received 20 mg/kg MYOZYME every 2 weeks. There was no difference in the pharmacokinetic profile of MYOZYME in late-onset patients compared to infantile onset patients (see Table 7).

Table 7 - Summary of Pharmacokinetic Parameters after IV Infusion of MYOZYME® 20 mg/kg in Studies AGLU01602, AGLU01702, and AGLU02804

		Study AGLU01602 (N=18)		**Study AGLU01702 (N=15)**		**Study AGLU02804 (N=5)**		
Parameter		Day 0 (N=151)	Week 12 (N=151)	Day 0 (N=14)	Week 12 (N=12)	Day 0 (N=4)	Week 12 (N=5)	Week 26 (N=5)
Cmax (ng/mL)		160,910 ± 27,598	195,540 ± 73,190	188,112 ± 83, 402	208, 239 ± 58,612	306,921 ± 104,801	368,904 ± 63,629	310,883 ± 65,866
AUC∞(hr*ng/mL)		937,896 ±199,381	1,017,118 ± 262,278	901,074 ± 313,911	1,103,327 ± 277,549	1,435,034 ± 182,983	1,689,479 ± 252,296	1,471,771 ± 230,970
T½ β (hr)		2.71 ± 0.58	2.80 ± 0.57	2.05 ± 0.49	2.72 ± 0.64	2.71 ± 0.36	2.88 ± 0.61	2.59 ± 0.23
CL	(mL/hr/kg)	22.1 ± 4.2	21.8 ± 5.4	26.1 ± 14.2	19.5 ± 6.24	14.1 ± 1.66	12.1 ± 1.89	13.9 ± 2.30
	(mL/hr)	133 ± 41	154 ± 51	286 ± 248	204 ± 83.3	554 ± 197	455 ± 126	541 ± 160
Vss	(mL/kg)	66.9 ± 10.3	67.0 ± 9.8	84.8 ± 29.6	75.8 ± 20.8	56.0 ± 12.2	47.2 ± 9.66	53.8 ± 10.7
	(mL)	404 ± 116	469 ± 100	914 ± 592	795 ± 304	2,251 ± 1,066	1,774 ± 526	2,111 ± 715

19 of 21 patients who received treatment with MYOZYME and had pharmacokinetics and antibody titre data available at week 12 developed antibodies to alglucosidase alfa. 5 patients with antibody titres ≥ 12,800 at Week 12 had an average increase in clearance of 50% (range 5% to

90%) from week 1 to week 12. The other 14 patients with antibody titres < 12,800 at week 12 had similar average clearance values at week 1 and week 12.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies have been conducted to assess the genotoxic potential of MYOZYME.

Carcinogenicity

No studies have been conducted to assess the carcinogenic potential of MYOZYME.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Polysorbate 80

Dibasic sodium phosphate heptahydrate

Monobasic sodium phosphate monohydrate

6.2 INCOMPATIBILITIES

Myozyme should not be infused in the same intravenous line with other products.

6.3 SHELF LIFE

3 years.

If storage is necessary after reconstitution hold at 2°C - 8°C for no more than 24 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store MYOZYME under refrigeration at 2°C - 8°C. DO NOT FREEZE OR SHAKE. Do not use MYOZYME after the expiration date on the vial.

This product contains no preservatives. To reduce microbial hazard, use as soon as practicable after dilution. For storage conditions after dilution of the medicinal product, see section 6.3 Shelf-life.

The reconstituted and diluted infusion solution should be protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER

It is supplied in single-use, clear Type I glass 20 mL vials. The closure consists of a siliconised butyl stopper and an aluminium seal with a plastic flip-off cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparation and Administration Instructions: Use Aseptic Techniques

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

   Patient weight (kg) x dose (mg/kg) = patient dose (in mg).

   Patient dose (in mg) divided by 50 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number for vials needed to withdraw the calculated volume of MYOZYME required.

   Patient dose (in mg) ÷ 5 mg/mL = total number of mL required of reconstitution MYOZYME solution.

   Example:

   Patient weight (16 kg) x dose (20 mg/kg) = patient dose (320 mg). 320 mg divided by 50 mg/vial = 6.4 vials therefore, 7 vials should be reconstituted.
2. Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes). Reconstitute each vial by slowly injecting 10.3 mL of sterile water for injection to the inside wall of each vial. Each vial will yield 5 mg/mL. The total extractable dose per vial is 50 mg per 10 mL. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilised cake. Tilt and roll each vial gently. Do not invert, swirl, or shake.
3. The reconstituted MYOZYME solution should be protected from light.
4. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discolouration. If upon immediate inspection opaque particles are observed or if the solution is discoloured do not use. The reconstituted solution may occasionally contain some alglucosidase alfa rch particles in the form of thin white strands or translucent fibres

subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa rch and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filtration without having a detectable effect on the purity or strength.

5. Withdraw the calculated volume of MYOZYME from the appropriate number of vials
6. MYOZYME should be diluted in 0.9% sodium chloride for injection immediately after reconstitution to a final concentration of 0.5 to 4 mg/mL.
7. Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.
8. Remove airspace from the infusion bag to minimise particle formation due to the sensitivity of MYOZYME to air - liquid interfaces.
9. Add the reconstituted MYOZYME solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.
10. Gently invert or massage the infusion bag to mix. Do not shake. To reduce microbial hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C - 8°C for no more than 24 hours. Protect from light.

The diluted solution should be filtered through a 0.2 μm, low protein - binding, in - line filter during administration to remove any visible particles.

After reconstitution: **MYOZYME IS FOR SINGLE USE IN ONE PATIENT ONLY.** Remaining MYOZYME left in a vial after withdrawing the patient's calculated dose should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription Only Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

16 April 2009

10 DATE OF REVISION OF THE TEXT

02 July 2025

Summary of changes

Section changed	Summary of new information
4.4	Replacement of Sanofi contact number
	Update to Immunogenicity section regarding IgG antibody formation.
	Editorial change to add Immune-mediated reactions section heading
4.9	Updated information on the management of overdose