HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

16 June 2010

MYOZYME 50 mg, powder for concentrate for solution for infusion
B/1 20-ml glass vial (CIP code: 569 575-1)
B/10 20-ml glass vials (CIP code: 569 576-8)
B/25 20-ml glass vials (CIP code: 569 577-4)

Applicant: GENZYME S.A.S.

alglucosidase alfa
ATC code (2010): A16AB07

List I

Medicinal product for hospital use only
Orphan drug status

Date of Marketing Authorisation: 29 March 2006 (centralised procedure)

Reason for request: Change in conditions of listing, change in wording of indications (inclusion on the list of products approved for hospital use).

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Alglucosidase alfa

1.2. Background
Myozyme is a recombinant form of human acid alfa-glucosidase produced by recombinant DNA technology using Chinese Hamster Ovary (CHO) cell culture. It is used in replacement enzyme therapy.

1.3. Indication
“Myozyme is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid alfa-glucosidase deficiency).
In patients with late-onset Pompe disease the evidence of efficacy is limited”.

1.4. Dosage
“Myozyme treatment should be supervised by a physician experienced in the management of patients with Pompe disease or other inherited metabolic or neuromuscular diseases.
The recommended dosage regimen of alglucosidase alfa is 20 mg/kg of body weight administered once every two weeks as an intravenous infusion.
Infusions should be administered incrementally. It is recommended that the infusion begin at an initial rate of 1 mg/kg/hr and be gradually increased by 2 mg/kg/hr every 30 minutes if there are no signs of infusion-associated reactions (IARs) until a maximum rate of 7 mg/kg/hr is reached. IARs are described in section 4.8.
Posology for children, adolescents, adults and elderly:
There is no evidence for special considerations when Myozyme is administered to children, adolescents, adults or elderly patients.
The tolerance and efficacy of Myozyme in patients with renal or hepatic insufficiency have not been evaluated and no specific dosage regimen can be recommended for these patients.
Patient response to treatment should be routinely evaluated based on a comprehensive evaluation of all clinical manifestations of the disease.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification
A: Alimentary tract and metabolism
A16: Other alimentary tract and metabolism products
A16A: Other alimentary tract and metabolism products
A16AB: Enzymes
A16AB07: alglucosidase alfa

2.2. Medicines in the same therapeutic category
None

2.3. Medicines with a similar therapeutic aim
None

3. ANALYSIS OF AVAILABLE DATA

The company has submitted five reports of clinical studies, one publication, and the 2009 report of the French Pompe disease register.

One of these studies is not included in the discussion below. This is an observational study (AGLU 02303). The main aims of this study were to describe the natural clinical progression of late-onset Pompe disease during a one-year observation period and to identify the most relevant and most reproducible clinical parameters to assess therapeutic efficacy.
The distance walked in the six-minute walk test (6MWT) and the forced vital capacity (FVC) were adopted as the most relevant intermediate parameters to assess the efficacy of therapeutic intervention in the late-onset form of Pompe disease.

3.1. Efficacy

3.1.1 Study AGLU02704 (LOTS)

Method:

Study design:
Randomised (2:1 randomisation), double-blind, placebo-controlled study.

Inclusion criteria:
- Age ≥ 8 years;
- Diagnosis of Pompe disease confirmed by acid alpha-glucosidase (AAG) activity on fibroblast culture ≤ 40% of the normal average and by identification of 2 mutations in the AAG gene;
- Patients able to walk 40 metres in two six-minute walk tests performed on two consecutive days, with or without a walking aid;
- FVC while seated ≥ 30% and < 80% of the predicted value;
- FVC postural drop ≥ 10% when the patient moves from upright to supine position.

Exclusion criteria:
- Use of invasive ventilation fitted to an endotracheal tube;
- Use of a non-invasive ventilation while awake and upright;

Primary efficacy endpoints:
- Change in the distance walked in the six-minute walk test (6MWT) between baseline and the end of the study;
- Change in forced vital capacity (FVC) while seated between baseline and the end of the study.

Secondary endpoints:
- Change in the outcomes of the bilateral quantitative muscle test (QMT) of the knee flexors and extensors between baseline and the end of the study;
- Change in the physical component summary (PCS) score of the MOS-SF-36 (medical outcome score 36-item short form) questionnaire;
- 9-item Rotterdam handicap scale (RIHS-9).

Treatment:
Myozyme: 20 mg/kg every two weeks for 78 weeks (18 months).

Statistics:

- The initial calculation of the number of subjects needed was based on the 6-minute walk test with the following criteria: power of 80%, significance level = 5%, randomisation 2/1, difference between the two groups of 52.5 metres and a standard deviation of 70 metres. Assuming a 10% to 15% drop out rate, 72 patients had to be recruited (48 taking Myozyme and 24 taking placebo).
  As the primary efficacy endpoint would be assessed every three months, the statistical analysis plan was adapted to provide for longitudinal assessment after inclusion of 90 patients and based on a monthly change difference of 3.75 metres and a power of 90%. As it was impossible to recruit more than 90 subjects, the duration of treatment, initially planned to be 52 weeks, was increased to obtain the level of statistical information required.
- The EMA has accepted the Wilcoxon-Mann-Whitney test for two-group comparisons[1], adjusted for randomisation strata (based on the result of the walk test and forced vital capacity), as the main test.

Results:

Patients included:
A total of 90 patients were enrolled: 60 in the Myozyme group and 30 in the placebo group. Forty-two of them had taken part in the observational study AGLU 02303. Their main characteristics can be found in *table 1*.

Table 1: characteristics of patients at baseline (ITT population)

	MYOZYME (n=60)	Placebo (n=30)
Age at start of treatment (years) Mean ± standard deviation Median and range	 45.3 ± 12.4 45 [15.9 ; 70]	 42.6 ± 11.6 43.1 [10.1 ; 68.4]
Age at onset of first symptoms (years) Mean ± standard deviation Median and range	 30.3 ± 12.3 33.6 [5.3 ; 58.6]	 23.9 ± 11 27.8 [2.7 ; 42.6]
Duration of disease (years) Mean ± standard deviation Median and range	 9 ± 6.3 7.5 [0.3 ; 24.8]	 10.1 ± 8.4 7.6 [0.5 ; 31.3]
% AAG activity (fibroblasts) Mean ± standard deviation Median and range	 27.7 ± 21.3 23.4 [0 ; 123.2]	 26.6 ± 19.9 24.8 [0.7 ; 83.7]
Use of walking aid (%, n)	38.3%(23)	53.3% (16)
Use of ventilation support (%, n)	33.3% (20)	36.7% (11)

Primary efficacy endpoints:

- Distance walked in the 6-minute walk test (6MWT): the results are shown in *table 2*.

Table 2: 6-minute walk test (ITT population)

	MYOZYME (n=60)	Placebo (n=30)	P*
6MWT at baseline (metres) Mean ± standard deviation Median and range	 332.3 ± 126.7 360 [77 ; 626]	 317.9 ± 132.3 339 [41 ; 608]	 NS
6MWT : difference between baseline and end of study (metres) † Mean ± standard deviation Median and range	 26.1 ± 64.4 15 [-87 ; 260]	 - 4.9 ± 45.2 - 7.5 [-112 ; 7]	 < 0.03

*: Wilcoxon-Mann-Whitney test for the difference between the groups; †: End of study: week 78 or last available data;

1 MYOZYME EPAR - http://www.ema.europa.eu/humandocs/PDFs/EPAR/myozyme/Myozyme-H-636-II-07-AR.pdf

- Forced vital capacity: the results are presented in *table 3*.

Table 3: forced vital capacity (ITT population)

	MYOZYME (n=60)	Placebo (n=30)	P*
FVC at baseline (% of predicted) Mean ± standard deviation Median and range	 55.4 ± 14.4 53.5 [31 ; 78]	 53 ± 15.7 49 [30 ; 78]	NS
FVC: difference between baseline and end of the study (% of predicted) † Mean ± standard deviation Median and range	 1.25 ± 5.5 0 [-12 ; 14]	 - 2.3 ± 4.3 - 3 [-11 ; 7]	< 0.003

*: Wilcoxon-Mann-Whitney test for the difference between the groups; †: End of study: week 78 or last available data;

Secondary endpoints:

- Bilateral quantitative muscle test of knee flexors and extensors (QMT): the results are shown in *table 4*.

Table 4: bilateral quantitative muscle test of the lower limb (ITT population)

	MYOZYME (n=60)	Placebo (n=30)	P*
QMT at baseline (% of predicted) Mean ± standard deviation Median and range	 37.7 ± 18.9 34.4 [8.8 ; 94.3]	 32.5 ± 18.2 28.6 [6.8 ;80.5]	NS
QMT: difference between baseline and end of the study (% of predicted) † Mean ± standard deviation Median and range	 1.2 ± 9.9 0.5 [-19.3 ; 48.5]	 - 2.1 ± 5.1 - 2.1 [-16.3 ; 14.3]	<0.03

*: Wilcoxon-Mann-Whitney test for the difference between the groups; †: End of study: week 78 or last available data;

- SF-36 questionnaire and Rotterdam handicap scale.
  The comparison of changes in SF-36 questionnaire scores between baseline and the end of the study showed no significant difference between the groups.
  The same was true of the Rotterdam handicap scale scores.

3.1.2 Study AGLU03206

Method

Open-label study, extension of the previous study (AGLU02704).

Inclusion criterion:
Patients who completed study AGLU02704

Primary efficacy endpoints:

- Change in the distance walked in the six-minute walk test (6MWT) between baseline and the end of the study;
- Change in forced vital capacity (FVC) while seated between the start and end of the study.

Secondary endpoints:

- Change in the outcomes of the bilateral quantitative muscle test (QMT) of the knee flexors and extensors between baseline and the end of the study;
- Change in the physical component summary (PCS) score of the MOS-SF-36 (medical outcome score 36-item short form) questionnaire;

Treatment:
Myozyme: 20 mg/kg every 2 weeks.

Patients had to have taken part in the two studies for at least 104 weeks: a minimum of 26 weeks treatment for the placebo group in study AGLU02704 and 104 weeks for the treatment group.

Results:

Patients included:
A total of 81 patients were enrolled in the study: 55 patients treated with Myozyme in the previous study and 26 patients in the placebo group.

Treatment:
All patients completed the 26 weeks of treatment.

Primary efficacy endpoints:

- Change in the distance walked in the 6-minute walk test. The results are shown in *table 5*

Table 5: change in the 6-minute walk test during the extension study

	MYOZYME/MYOZYME (n=52)	Placebo/MYOZYME (n=23)
6MWT: difference between baseline and end of study (Δ S78/S104) (metres) Mean ± standard deviation Median and range	 - 6.9 ± 32.8 -9 [-16.1 ; 2.2]	 4.2 ± 23.8 0 [-26 ; 58]

- Change in vital forced capacity (FVC) while seated. The results are shown in *table 6:*

Table 6: change in vital forced capacity (FVC) while seated in the extension study

	MYOZYME/MYOZYME (n=52)	Placebo/MYOZYME (n=23)
FVC: difference between baseline and end of study (Δ S78/S104) (% of predicted) Mean ± standard deviation Median and range	 -0.7 ± 3.7 -1[-9 ; 11]	 -1 ± 5.4 1 [-12 ; 8]

Secondary endpoints:

- Change in bilateral quantitative muscle test: the results are shown in *table 7*

Table 7: bilateral quantitative muscle test of the lower limb during the extension study

	MYOZYME/MYOZYME (n=52)	Placebo/MYOZYME (n=23)
QMT: difference between baseline and end of study (Δ S78/S104) (% of theoretical value) Mean ± standard deviation Median and range	 1.1 ± 4.8 0.5 [-13.3 ; 20]	 0.2 ± 3.4 0.3 [-9.3 ; 7.3]

3.1.3 Study AGLU03105

Method

Five patients with advanced late-onset Pompe disease were included in this prospective non-comparative study.
They were aged between 28 and 62 years.
The diagnosis was confirmed by low acid alfa-glucosidase (AAG) activity and by genotype.
All the patients enrolled had been on assisted breathing for five or more years. Four of them had been on invasive ventilation for five to 23 years and had been confined to a wheelchair or were bed-bound.
The assessment criteria were respiratory and motor function.
The patients were treated with IV infusion of 20 mg/kg every two weeks for 52 weeks.

Results:

Four patients completed the study (one patient died during the study, but there was no causal relationship to the treatment).
Two patients experienced an improvement in respiratory function, with increases of 20 and 30 minutes in the time they could spend in a seated position without assisted ventilation.
The motor function of two patients improved.

3.1.4 Study AGLU02804

An interim report of this study (after 26 weeks of treatment) had been submitted to the Transparency Committee in 2006.

Method

Five patients aged from 5 to 15 years were enrolled in this prospective non-comparative study.
The diagnosis of Pompe disease was confirmed by low acid alfa-glucosidase (AAG) activity or by identification of a mutation in the AAG gene.
Muscle weakness was defined by manual muscle testing (MMT).
In order to be enrolled, patients had to be able to perform the functional tests and respiratory investigation while supine, and to walk at least 10 metres with or without a walking aid.
Non-inclusion criteria were the use of an invasive breathing device fitted to an endotracheal tube or a non-invasive breathing aid used while awake and upright.

Endpoints:
Change in the six-minute walking test (walking at a comfortable-pace and fast-pace walking) between baseline and the end of the study;
Change in age-adjusted forced vital capacity (FVC) in seated and supine between baseline and the end of the study;
Change in the muscle strength test (total MMT body score).

Treatment: an IV infusion of 20 mg/kg every two weeks for 74 weeks.

Results:

The distance walked in six minutes during the comfortable-pace walking test decreased in three patients (by 5, 48 et 61 m) and increased in the other two (by 22 and 64 m).
The distance walked in six minutes during the fast-pace walking test increased in all five patients (by 27 m to 158 m).
At baseline two patients had a FVC of between 80 and 100% of the predicted value; in one of these patients the figure decreased during the study and in the other patient it increased. Three patients had FVC below 80% of predicted at baseline: the figure increased during the study (6.8 to 21.8% in a seated position).
The MMT score of all five patients increased by between 9 and 79 points (the total scores at baseline were between 243 and 290).

3.1.5 Observational study on 44 patients with late-onset Pompe disease[2].

Method

Inclusion criterion:
Low endogenous AAG activity confirmed by at least two biochemical methods.
Primary efficacy endpoints:
6-minute walk test;
Forced vital capacity (FVC) in a seated position.
Duration of treatment: 12 months.

2 Strothotte S, Strigl-Pill N. Enzyme replacement therapy with alglucosidasealfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. J Neurol 2010; 257: 91-7

Results:

Patients included:
The mean age of the 44 patients was 48.9 ± 12.9 years (21 to 69 years);
40.5% of them had difficulty walking, 21.6% used a walking aid and 18.9% used a wheelchair.
43.2% were on assisted ventilation (invasive in 5.4% of cases and non-invasive (mask) in 37.8% of cases).

Efficacy:
6-minute walk test

Nine out of the 44 patients were unable to perform the test at the start of the study;
Test results are available for 22 patients. The average distance walked increased by 52 metres during the study (mean value at baseline: 341 ± 149.5 metres);

Forced vital capacity (% of predicted):

This was assessed for 33 patients and remained stable during the study: change of 0.5 ± 10.7 (mean value at baseline: 69.6 ± 28.1).

3.1.6 Data taken from the French Pompe disease register (report of September 2009).

This register was created in 2004, initially for epidemiological investigation. Since Myozyme was put on the market it has been recommended that all patients undergoing treatment should be included in the register.
Assessment by a reference centre is recommended every six months for patients undergoing treatment and once a year for patients not receiving treatment.

As of 1 January 2009, 60 out of the 75 patients in the register were being treated with Myozyme. The mean age of patients receiving treatment was 50 ± 15 years.
The length of follow-up of these patients was six to 36 months.
Sixteen out of 60 (27%) were in a wheelchair and 42 out of 60 (70%) used ventilatory support.
Data on their progress is given in *table 8*

Table 8: progress of patients receiving treatment

	VC* (n=52)	6MWT† (n=41)
Average progress	0.042 litres/year, i.e. 2% of the baseline value	20.20 metres/year
Worsening % (n)	29% (15, of which 12 V: 8 IV, 4 NIV)	34% (14)
Improvement % (n)	56% (29, of which 20 V: 6 IV, 14 NIV)	59% (24)
No change % (n)	15% (8, of which 4 V: 1 IV, 3 NIV)	7% (3)

*VC: vital capacity while seated; †: 6-minute walk test; V: on ventilation; IV: invasive ventilation; NIV: non-invasive ventilation

The conclusion of the report as far as efficacy is concerned is: “Preliminary data from the follow-up of patients undergoing treatment shows considerable variation in progress between patients with respect to seated VC and the six-minute walk test. Two-thirds of patients seem to have improved or remained stable. However, a much longer follow-up period for all patients (three to five years) will probably be needed in order to draw significant conclusions about the efficacy of treatment with recombinant enzyme therapy.”

3.1.7 Data obtained from the international Pompe disease register - report issued in February 2009 (data collected between September 2004, the date on which the register was created and October 2008).
The aim of this register is to collect data from patients suffering from Pompe disease, irrespective of whether or not they are being treated with Myozyme. This proprietary medicinal product received marketing authorisation in Europe in March 2006 and in the United States in April 2006.
As of 3 October 2008, 564 patients were in the register.
Patients in the register: their characteristics are given in *table 9*

Table 9: characteristics of patients (data as of 3 October 2008)

	Patients on treatment	Patients not on treatment	Status unknown	Total
Number of patients n (%)	392 (69.5%)	121 (21.5%)	51 (9%)	564
Age at the start of monitoring* (years) n mean ± standard deviation median [range]	392 30.87 ± 23.2 34.0 [0.0 ; 74.7]	92 25.9 ± 21.9 24.33 [0.0 ; 78.1]	35 29.5 ± 18.1 33.17 [0.0 ; 59.6]	519 29.9 ± 22.7 31.46 [0.0 ; 78.1]
Age at first infusion (years) n mean ± standard deviation median [range]	392 30.9 ± 23.2 34 [0 ; 74.7]	_	_	392 30.9 ± 23.2 34 [0 ; 74.7]
Age at most recent entry (years) n mean ± standard deviation median [range]	392 32.2 ± 22.8 35.1 [0.1 ; 76.2]	121 31.1 ± 23.0 32.8 [0.2 ; 78.9]	51 34.8 ± 18.6 36.9 [0.5 ; 65.7]	564 32.2 ± 22.5 34.9 [0.1 ; 78.8]

* the start of monitoring is the date of the first infusion for patients undergoing treatment, and the date of the first data item collected for the other patients. The start of monitoring may be before inclusion in the register, as some data may have been entered retrospectively.

Among patients on treatment, 58.4% (n=229) were aged over one year at the onset of symptoms, 18.9% (n=74) were aged six months or less and 2.8% (n=11) were aged between six months and one year.

Data analysed: the data presented do not come from longitudinal follow-up of patients; patients who have a follow-up at 12 months are not necessarily a sub-group of patients for whom six-month data are available. This complicates the interpretation of changes in this data over time. Longitudinal data for patients on treatment were presented when sufficient information was available.

Treatment: key data are given in *table 10*

Table 10: treatment

	Start	6 months	12 months	18 months	24 months	30 months
Patients on treatment with a known treatment start date - n	392	154	120	87	58	21
Dose (mg/kg) n mean ± standard deviation median [range]	347 20.3 ± 3.4 20 [10 ; 40]	151 20.7 ± 3.8 20 [12 ; 40]	115 20.9 ± 4.1 20 [19; 40]	82 21.2 ± 4.5 20 [20 ; 40]	55 21.7 ± 6.0 20 [10 ; 40]	20 24.6 ± 8.2 20 [20 ; 40]
Changes or discontinuation n (%)						
- death	_	1 (3.8)	0	0	0	0
- adverse event	_	5 (19.2)	2 (10.5)	2 (20)	0	0
- lack of efficacy	_	3 (11.5)	1 (5.3)	1 (10)	0	1 (33.3)
- pregnancy	_	0	1 (5.3)	0	0	0
- compliance difficulties	_	0	1 (5.3)	1 (10)	0	0
- difficulties with reimbursement	_	2 (7.7)	0	0	0	0
- personal reasons	_	0	0	0	1 (20)	0
- other reasons	1 (100)	13 (50)	13 (68.4)	4 (40)	3 (60)	2 (66.7)

Ventilation for patients on treatment. The data are shown in *table 11*

Table 11: data on ventilation for patients on treatment

	Start of treatment	6 months	12 months	24 months	30 months
Patients whose ventilation status is known - n	59	86	68	29	17
Non-invasive ventilation n (%)	21 (35.6)	25 (29.1)	18 (26.5)	29 (37.9)	7 (41.2
Invasive ventilation n (%)	1 (1.7)	5 (5.8)	5 (7.4)	6 (20.7)	2 (11.8)

Ambulatory status of patients on treatment aged 12 months or over at the onset of symptoms

Table 12: ambulatory status of patients

	Start	6 months	12 months	24 months
Patients whose ambulatory status is known - n	54	65	54	19
Able to walk n (%)	43 (79.6)	55 (84.6)	43 (79.6)	10 (52.6)
Unable to walk n (%)	11 (20.4)	9 (13.8)	7 (13)	4 (21.1)
Unknown n (%)	0	1 (1.5)	4 (7.4)	5 (26.3)

Data from the 6-minute walk test is given in *tables 12 and 13*

Table 12: results of the 6-minute walk test for patients aged ≥ 8 years on treatment

	Start	12 months	24 months
Patients for whom a walk test result is available (n)	36	42	15
Distance walked (m) mean ± standard deviation median [range]	 355.9 ± 182.3 346 [71 ; 794]	 365.3 ± 152.7 369.5 [97 ; 684]	 303.2 ± 185.5 298 [0 ; 667]

Table 13: change in distance walked, patients ≥ 8 years on treatment

	12 months (n=22)	24 months (n=5)
Distance walked (m) mean ± standard deviation median [range]	 367.4 ± 181.7 360.5 [75-668]	 406.8 ± 231 405 [157-655]
Change since the start of treatment mean ± standard deviation median [range]	 26.5 ± 116.48 21.5 [-354 ; 296]	 -10.6 ± 22.8 -4 [-39 ; 12]

3.2. Adverse effects

3.2.1 Study AGLU02704

Treatment duration:
The median duration of participation in the study was 78 weeks and the median number of treatment administrations was 39 in both groups. 91.7% of patients in the Myozyme group and 86.7% in the placebo group completed the study, with at least 77 weeks of treatment.
A summary of the adverse events occurring during the study is given in *table 14*:

Table 14: adverse events occurring during study AGLU02704

	MYOZYME (n=60)	Placebo (n=30)
Patients with at least one AE % (n)	100% (60)	100% (30)
Patients with AEs related to treatment % (n)* Of which, infusion-associated reactions % (n)	53.3% (32) 28.3% (17)	56.7% (17) 23.3% (7)
Patients with SAEs % (n)	21.7% (13)	20 % (6)
Withdrawals from the study because of an AE	5% (3)	3.3% (1)
Deaths % (n)	1.7% (1) †	0

AE: adverse event; SAE: serious adverse event; *: relationship possible to certain; †: regarded as not related to the treatment.

The most frequent adverse effects in the Myozyme group (≥ 5% of patients) that were not observed in the placebo group were: urticaria, hyperhidrosis, chest discomfort, muscle contractions, cataract, vasomotor flushes, myalgia, increase in blood pressure and vomiting.
The most common adverse effects (≥ 5% of patients) recorded in the two groups were nausea, headache, vertigo, fatigue.
Most of the adverse effects were infusion reactions in both groups:

- 79.2% of the adverse effects experienced by 28.3% of patients (n=17) in the Myozyme group;
- 50.7% of the adverse effects experienced by 23.3% of patients (n=7) in the placebo group;

Serious adverse effects:

- In the Myozyme group: three anaphylactic reactions regarded as infusion reactions: one with chest discomfort and a feeling of tightness of the throat, one with chest pain of non-cardiac origin, and one case of angioneurotic oedema.
  One case of supraventricular tachycardia;
- In the placebo group: one case of septal hypodermitis and one case of headache.

Study withdrawals:

- Two patients in the Myozyme group stopped treatment because of an adverse effect: one severe hypersensitivity reaction and one case of severe angioneurotic oedema;
- One patient in the placebo group stopped treatment because of severe headaches considered to be infusion-associated reactions.
- Five patients withdrew from the trial for other reasons: four wanted to continue treatment with the commercial form of Myozyme and one withdrew from the trial for personal reasons.
- One death in the Myozyme group was regarded as not related to treatment.

3.2.2 Study AGLU03206

Treatment duration:
This study was an open-label extension of the previous study. The total duration of treatment of patients in the group which had been treated with Myozyme in the previous study was 113 ± 29 weeks (median: 113 weeks).
The total duration of treatment of patients in the group which had been treated with placebo in the previous study was 40 ± 13 weeks (median: 44 weeks).

A summary of the adverse events which occurred during treatment with Myozyme in studies AGLU02704 and AGLU03206 is given in *table 15:*

Table 15: adverse events occurring during treatment with Myozyme

	MYOZYME/MYOZYME (n=60) (median duration of treatment: 113 weeks)	Placebo/MYOZYME (n=26) (median duration of treatment: 44 weeks)
Patients with at least one AE % (n)	100% (60)	96.2% (25)
Patients with AEs related to treatment % (n)* Of which, infusion-related reactions % (n)	61.7% (37) 35% (21)	23.1% (6) 7.7% (2)
Patients with SAEs % (n)	25% (15)	7.7% (2)
Study withdrawals because of an AE	5% (3)	0
Deaths % (n)	1.7% (1)	

AE: adverse event; SAE: serious adverse event; *: relationship possible to certain; †: regarded as not related to the treatment.

3.2.3 Study AGLU03105

Five out of 59 adverse events (8.4%) were considered related to administration of Myozyme: three cases of infusion reaction (two cases of fever and one case of cramps) and two cases of localised erythema at the infusion site.

3.2.4 Study AGLU02804

The five patients completed the course of treatment.
None of the adverse events recorded during the study were considered related to the treatment.

3.2.5 Observational study in 44 patients with late-onset Pompe disease[3].

Three patients regularly received antihistamine treatment before each infusion, and three others received it after suffering allergic reactions regarded as moderate during the infusion or within six hours after the infusion: erythema, tachycardia, fall in oxygen saturation levels, exanthem, feeling of a "lump in the throat" and pruritus.
One patient experienced oedema of the hands, an acute loss of hearing, herpes, pollakiuria, a feeling of "muscle tingling" and a hypertensive crisis.
The 44 patients completed the one-year course of treatment.

3.2.6 Data from the French Pompe disease register[4].

The adverse events referred to in the report for the 60 patients who received treatment include:
one case of laryngeal spasm requiring discontinuation of treatment, one case of weight gain (10 kg), one case of increased blood pressure, one case of skin rash, back pain and nausea, one case of fever, one case of reddening and one case of bronchial obstruction.

3.2.7 Data obtained from the international Pompe disease register - February 2009 (data collected between September 2004, the date on which the register was created, and October 2008).

As reports are made to the adverse events register on a voluntary basis, it is not possible to know whether the adverse events related to the 392 patients receiving treatment who were surveyed, nor if all adverse events were reported. The adverse events are therefore recorded as absolute figures and not as percentages of individuals treated.
The adverse events are shown in *table 16*

Table 16: adverse events in patients receiving treatment

Patients on treatment (n)	392
Patients with an adverse event (n)	90
Patients with an infusion reaction (n)	44
Patients with a serious adverse event	57
Patients with a serious adverse effect* Of which, infusion reactions	27 17

Serious adverse effects reported for 3 or more patients: tachycardia (n=5), decrease in oxygen saturation (n=5), urticaria (n=5), bradycardia (n=4), muscle weakness (n=4), hypersensitivity (n=3), pneumonia (n=3), dyspnoea (n=3), respiratory distress (n=3), hyperhidrosis (n=3), hypotension (n=3).

3 Strothotte S, Strigl-Pill N. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2 : 12-month results of an observational clinical trial. J Neurol 2010; 257: 91-7
4 French Pompe disease register - Report issued in September 2009

Adverse events indicative of a possible allergic/hypersensitivity reaction were reported for nine out of the 392 patients receiving treatment, eight of whom suffered a serious adverse event. Five of these patients had a late-onset form.

Twenty-three deaths were recorded among the patients on treatment, sixteen of whom were children under five. No death was considered to be treatment-related.

3.2.8 The SPC for the product states that "severe and potentially life-threatening anaphylactic reactions, including anaphylactic shock, have been reported in infantile and late-onset patients during Myozyme infusions. Because of the potential for severe infusion associated reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readly available when Myozyme is administered."

3.3. Conclusion

A 78-week study had been carried out to assess the efficacy of Myozyme versus placebo in patients not requiring non-invasive breathing support in the daytime while upright and able to perform the 6-minute walk test. It showed a significant difference in favour of the group receiving treatment with respect to the average change from the start to the end of the study in the distance walked in the 6-minute walk test (26.08 metres versus - 4.87 metres) and forced vital capacity in a seated position (1.25% of predicted versus – 2.3%).
During the 26-week open-label extension of the previous study, the average change in the 6-minute walk test from baseline to the end of the study was -6,9 metres in the group which had already undergone treatment (total of 104 weeks) and 4.2 metres in the placebo/Myozyme group (total of 26 weeks treatment); the change in forced vital capacity was -0.7% in the group which had already received treatment and -1% in the placebo/Myozyme group.

Two non-comparative studies with very small cohorts do not allow any conclusions to be drawn as to the efficacy of treatment.

In one observational study, the results of the 6-minute walk test (22 out of 44 patients) showed an average increase in the distance walked of 52 metres over one year. Forced vital capacity (33 out of 44 patients) remained stable: increase of 0.5% of predicted.

According to the French Pompe disease register (60 patients on treatment followed for 6 to 36 months as of 1 January 2009), the average change in the 6-minute walk test was 20.20 metres a year (worsening for 34% of patients, improvement for 59% and no change for 7%) and the average change in the seated vital capacity was 0.042 litres a year, or 2% of the baseline value (worsening for 29% of patients, improvement for 56% and no change for 15%).

During the controlled study, 53% of patients in the Myozyme group had adverse effects regarded as treatment-related, versus 56.7% in the placebo group. The most frequent adverse effects in both groups were infusion-associated reactions. Three patients in the Myozyme group had severe anaphylactic reactions requiring withdrawal from the trial in two cases.

The most commonly recorded adverse effects in the uncontrolled studies were also allergic reactions to the infusion. The SPC for Myozyme contains a warning with regard to the possibility of serious and potentially life-threatening anaphylactic reactions.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Pompe disease is a metabolic myopathy caused by mutations which lead to a functional deficit of acid alpha 1,4-glucosidase (AAG), which is responsible for hydrolysing glycogen into glucose. This enzyme deficit leads to an excess of intralysosomal glycogen, mainly in striated, skeletal and cardiac muscle. Glycogen deposits cause gradual loss of muscle contractility, which is reflected in impairment of motor, respiratory and cardiac functions. The degree of impairment varies according to the form of the disease and how long the patient has been suffering from it.
The late-onset form can start in early childhood, or at any time until late adulthood. It is characterised by an impairment of the skeletal and respiratory muscles. The condition gradually progresses over several years until the patient becomes wheelchair-bound and reliant on assisted ventilation.

This proprietary medicinal product enters into the context of replacement therapy.

The efficacy/adverse effects ratio is moderate.

Public health benefit:
Pompe disease, in both early-onset and late-onset forms, is a serious condition which can lead to functional disability and loss of autonomy, but it is a minor public health burden because it is so rare.
Improving the management of patients suffering from Pompe disease constitutes a public health need falling within the scope of public health priorities (Public Health Act 2004, Rare diseases plan).
In view of the results of the LOTS study on functional criteria (median gain of 22 metres in the walk test, median gain of 3% in forced vital capacity), and the lack of data indicating the likely impact on the progression of disability (reliance on a wheelchair and invasive ventilation), MYOZYME is not expected to have any impact on the morbidity of patients who receive treatment.
Furthermore, no improvement in quality of life was demonstrated in the LOTS study.
The transposability of the results of this study into clinical practice is acceptable.
No impact on the organisation of the health care system is expected.
MYOZYME is therefore unlikely to offer a response to the identified need.
Consequently, MYOZYME is not expected to have a public health benefit for this indication.

This proprietary product is a first-line treatment.
There is no alternative therapy.

The actual benefit of this proprietary medicinal product is low.

4.2. Improvement in actual benefit (IAB)

Given the minor quantitative effect observed, the lack of data regarding long-term efficacy (especially the effect on the subsequent need for assisted ventilation), and despite the lack of alternative treatment, Myozyme provides a minor improvement in actual benefit (IAB IV) in the management of the late-onset form of Pompe disease.

4.3. Therapeutic use

The usual treatment for late-onset Pompe disease has in the past been symptomatic and palliative depending on the degree of motor or respiratory impairment: need for walking aids (canes, walker) until the patient becomes reliant on a wheelchair, assisted ventilation, initially non-invasive and later on invasive.

MYOZYME administered by the intravenous route is the first enzyme replacement treatment for late-onset Pompe disease.

4.4. Target population

The French Pompe disease register indicates that as of 1 January 2009, 120 cases had been recorded in France.
As the disease may be underdiagnosed, the maximum target population for Myozyme administered to treat late-onset Pompe disease is 150 individuals in France.
This assessment of the target population will be periodically reviewed by the Transparency Committee in the light of data supplied by reference centres and/or French data supplied by the pharmaceutical company.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indications and dosages of the marketing authorisation.

The Committee would like to reassess the proprietary product MYOZYME in two years time, taking account of additional data on the longer-term follow-up of patients and the definition of criteria for treatment discontinuation.
The Committee stresses the need for the Pompe disease register to be maintained.

Packaging: Appropriate for the prescription conditions.