HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

9 January 2013

The draft opinion adopted by the Transparency Committee on 7 November 2012 was the subject of a hearing on 9 January 2012

MYOZYME 50 mg, powder for concentrate for solution for infusion

B/1 vial (CIP code: 34009 569 575 1 4)
B/10 vials (CIP code: 34009 569 576 8 2)

Applicant: GENZYME S.A.S

INN	Alglucosidase alfa
ATC Code (2012)	A16AB07 (enzyme)
Reason for the review	**Re-assessment of the actual benefit (AB) and the level of improvement in actual benefit (IAB) at the request of the applicant.**
List concerned	**Inclusion for hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). […] In patients with late-onset Pompe disease the evidence of efficacy is limited."**

Actual Benefit	**The actual benefit of MYOZYME remains low in the treatment of late-onset Pompe disease.**
Improvement in Actual Benefit	**The improvement in actual benefit remains minor (level IV) in the treatment of late-onset Pompe disease.**
Therapeutic use	**Currently, MYOZYME is the only enzyme replacement therapy in the treatment of late-onset Pompe disease.**
Recommendations	**The Transparency Committee recommends an annual assessment of all patients treated with MYOZYME for late-onset Pompe disease.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation	29 March 2006 (centralised procedure); RMP
Prescribing and dispensing conditions / special status	List I Additional List Orphan medicinal product. Medicine for hospital use only: initial prescription to be checked by the reference centre or a centre specialising in Pompe disease treatment

ATC Classification	2012 A: Alimentary tract and metabolism A16: Other alimentary tract and metabolism products A16A: Other alimentary tract and metabolism products A16AB: Enzymes A16AB07: alglucosidase alfa

02 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.

In March 2006, MYOZYME was granted Marketing Authorisation (centralised procedure) for enzyme replacement therapy (ERT) in patients with infantile or late-onset Pompe disease, without the benefits in the late-onset form being clearly established.
In its Opinion of 20 September 2006, the Transparency Committee considered that:

- in the infantile form of the disease, the actual benefit was substantial and the IAB (improvement in actual benefit) was level II for treatment;
- in the late-onset form of the disease, the actual benefit was insufficient in the absence of a formal demonstration of efficacy.

In this Opinion, the Committee has stated that it will re-assess MYOZYME for the late-onset form of the disease in view of the results of the comparative study which should be sent to EMA and/or all new data likely to be provided by the applicant.

In light of the new clinical data presented in the treatment of the late-onset form of the disease, the Marketing Authorisation for MYOZYME was amended in October 2009 to state that: "In patients with late-onset Pompe disease the evidence of efficacy is limited". On 16 June 2010, in this indication, the Transparency Committee granted a low actual benefit and a level IV IAB (improvement in actual benefit) for treatment. It also indicated that: "The Committee would like to reassess MYOZYME in two years time, taking account of additional data on the longer-term monitoring of patients and the definition of criteria for treatment suspension. The Committee is stressing the importance of maintaining the Pompe disease register."

This document focuses on the analysis of new clinical data provided by the applicant in response to the request for the Committee to reassess MYOZYME for late-onset Pompe disease.

03 THERAPEUTIC INDICATION

“MYOZYME is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency).
MYOZYME is indicated in adults and paediatric patients of all ages.
In patients with late-onset Pompe disease the evidence of efficacy is limited.”

04 DOSAGE

“MYOZYME should be administered as an intravenous infusion. The recommended dose regimen is 20 mg/kg of body weight administered once every 2 weeks. […] There is no evidence for special considerations when MYOZYME is administered to paediatric patients of all ages or elderly patients. […] The safety and efficacy of MYOZYME in patients with renal or hepatic impairment have not been evaluated and no specific dose regimen can be recommended for these patients.”

05 THERAPEUTIC NEED

Pompe disease (or glycogenosis type II, or glycogen storage disease type II, or acid maltase deficiency) is a rare, autosomal recessive inherited lysosomal disorder. It is a metabolic myopathy caused by a deficiency in a natural hydrolase, acid alfa glucosidase (GAA), which breaks down lysosomal glycogen into glucose. A deficiency in this enzyme leads to an accumulation of glycogen in certain tissues, especially the cardiac, respiratory and skeletal muscles, resulting in hypertrophic cardiomyopathy and progressive muscle weakness affecting the waist and the diaphragm, with changes in the ability to walk and respiratory function.

The age when the first symptoms are seen, the severity of the functional impact as well as the duration and speed of disease progression vary greatly from patient to patient. However, there are two distinct clinical forms:

- the infantile form, which generally occurs before the age of 6 months and progresses rapidly during the first year of life;
- the late-onset form, which manifests during early infancy, childhood, adolescence or even in adulthood and progresses more slowly. Persistence of sufficient residual acid alfa glucosidase activity may explain the absence in the development of cardiomyopathy in this form of the disease.

According to data from a prospective observational study[1] carried out on 268 patients between 2002 and 2009, patients with the late-onset form have a significantly reduced survival compared with the general population, with a median age of death of 55 years. Nearly 50% of these patients have a loss of motor and/or respiratory independence 10 to 15 years after diagnosis.

According to guidelines[2,3], treatment for late-onset Pompe disease combines an ERT with alfa alglucosidase and management of symptoms. It is started from the appearance of the first signs of musculoskeletal or respiratory impairment in patients who have had their diagnosis confirmed through laboratory tests. ERT should be re-assessed annually. Treatment is continued until the annual clinical assessment shows an improvement or stabilisation in musculoskeletal or diaphragm deficiencies.

06 CLINICALLY RELEVANT COMPARATOR

06.1 Medicinal products

There are no comparator medicines available.

06.2 Other health technologies

There are no comparator technologies available.

Conclusion

There are no clinically relevant comparator medicines.

[1] Güngör D, De Vries JM, Hop WCJ et al. Survival and associated factors in 268 adults with Pompe disease prior to treatment with enzyme replacement therapy. Orphanet J Rare Dis 2011; 6: 34.

[2] Annane D, Caillaud C, Desnuelle C et al. Guidelines from the French Pompe Disease evaluation and treatment committee. Methods of use of human recombinant alglucosidase alfa (MYOZYME) and the monitoring of adult patients. http://www.cetl.net/maladies-lysosomales/cetp-maladie-de-pompe/documents-60/article/recommandations-du-cetpompe, referred to on 20 September 2012.

[3] Cupler EJ, Berger KI, Leshner RT et al. Consensus treatment recommendations for late-onset Pompe disease. Muscle Nerve 2012; 45: 319-333.

07 SUMMARY OF PREVIOUS ASSESSMENTS

Date of Opinion	20 September 2006 (inclusion on the list of medicines approved for hospital use)
Indication	ERT in patients with Pompe disease
Actual Benefit	- Substantial in the infantile form - Insufficient in the late-onset form
Improvement in Actual Benefit	Substantial in the infantile form (level II)
Studies requested	The Committee would like patients newly diagnosed with the late-onset form of the disease be included in MYOZYME clinical trials.

Date of Opinion	16 June 2010 (amendments to inclusion conditions)
Indication	ERT in patients with late-onset Pompe disease
Actual Benefit	Low
Improvement in Actual Benefit	Minor (level IV)
Studies requested	The Committee: - would like to receive additional data concerning the longer-term monitoring of patients and the definition of criteria for treatment suspension; - is stressing the importance of maintaining the Pompe disease register.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The only comparative, prospective randomised study (LOTS study)[4] was presented in the previous Transparency Committee opinion of June 2010.[5] The new studies presented by the applicant are observational (prospective cohorts) and open-label:

- one study[6] that aims to compare the survival of patients treated and not treated with MYOZYME;
- four studies[7,8,9,10] aiming in particular to assess the motor and respiratory function of patients treated with MYOZYME;
- one observational study (study AGLU4107 or SLOOS)[11] carried out on a restricted number of participants (n=8) the results from which will not be presented.

8.1.1 Güngör D. et al observational study (not published[6]

The Güngör trial is a prospective observational study with the aim of evaluating the impact of treatment with MYOZYME on the survival of a cohort of adult patients with late-onset Pompe disease.

MYOZYME was administered every two weeks via IV infusion at a dose of 20 mg/kg.

Statistical analysis:
The survival time was evaluated from the start of the trial up to the last follow-up appointment or until death.

The association between the overall survival of patients and ERT was estimated using Cox models, with time dependent co-variants, both for the univariate and multivariate analyses. The following adjustment factors were examined and chosen a priori: age, sex, severity of the disease (on the basis of needing a wheelchair or respiratory assistance) and the country of residence. The results are presented in the form of risk ratios (Hazard Ratio; HR) with 95% confidence intervals (CI).

Two models were applied to describe the relationship between treatment with MYOZYME and patient survival. In the two models, treatment with MYOZYME was considered as a time dependent covariant (value of 0 before starting treatment, changing to a 1 at the start of treatment). During the follow-up period, patients were included into a non-treatment group (control group) and did not receive MYOZYME.

[4] Van der Ploeg AT, Clemens PR, Corzo D et al. A randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease. N Eng J Med 2010; 362: 1396-1406.
[5] Myozyme. Transparency Committee Opinion of 16 June 2010.
[6] Güngör D et al. study, submitted for publication.
[7] de Vries JM, van der Beek NA, Hop WC et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: an open-label single-center study. Orphanet J Rare Dis 2012; 7: 73.
[8] Bembi B, Pisa FE, Confalonieri M et al. Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. J Inherit Metab Dis 2010; 3356: 727-735.
[9] Angelini C, Semplicini C, Ravaglia S et al. Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years. J Neurol 2012; 259: 952-8.
[10] Regnery C, Kornblum C, Hanisch F et al. Months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. J Inherit Metab Dis 2012; 35: 837-845.
[11] SLOOS study. Annane D et al. Unpublished.

Model 1: ERT, age and severity of disease as time dependent covariants
In the first model, in addition to ERT, the categories of age and severity of the disease were also taken into account in the model as time dependent covariants and were thus counted from the start of ERT.

Model 2: ERT, single time dependent covariant
The second model uses ERT as the only time dependent covariant.

Two analyses were carried out for each model:

- a primary analysis (a) on an "intention to treat" (ITT) basis, in which patients who discontinued their treatment remained in the treatment group until the end of the follow-up period (models 1a and 2a).

- a secondary analysis (b) on a "censor of time after treatment discontinuation" was also carried out to take into account the actual treatment duration with MYOZYME. In this second approach, all patients who stopped treatment were "censored" from the time they stopped treatment (models 1b and 2b).

Results:
The population included in this cohort comprised of 283 adults, including 79 (28%) who were not treated and 204 (72%) who were treated with MYOZYME.

Table 1: characteristics of the population included

Total number of patients included: 283	**Treated with ERT (n=204)**	**Not treated (n=79)**
	At the start of ERT	**At inclusion in the study**
Women, n (%)	104 (51)	46 (58)
Median age at diagnosis, years (min; max)	38 (1-68)	42 (2-67)
Median age at inclusion in the trial, years (min; max)	47 (19-73)	51 (20-81)
Median age at start of ERT, years (min; max)	51 (24-76)	-
Median disease duration, years (min; max)	11 (0.2-33)	12 (0-32)
Median follow-up period, years (min; max)	7 (1-9)	4 (0.04-9)
Median ERT duration, years (min; max)	4 (0.2-8)	-
Country of residence, n (%)		
The Netherlands	86 (42)	23 (29)
The United Kingdom	18 (9)	5 (6)
The United States	44 (22)	27 (34)
Germany	37 (18)	11 (14)
Other	19 (9)	13 (17)
Severity of the disease at inclusion in trial/at start of ERT, n (%)		
No use of wheelchair or respiratory assistance*	70 (34)	35 (44)
Use of a wheelchair	37 (18)	12 (14)
Respiratory assistance	29 (14)	11 (14)
Use of a wheelchair and respiratory assistance	68 (33)	22 (28)
Deceased patients, n (%)	18 (9)	28 (35)

The median age on inclusion of non-treated patients was 51 years (20 to 81 years), comparable to the median age of treated patients, which was 51 years (24 to 76 years).
The percentage of patients not requiring respiratory assistance or the use of a wheelchair was 34% in the MYOZYME group and 44% in the non treatment group.
In this cohort, the majority of non-treated patients were put on MYOZYME during the follow-up period. However the criteria for starting treatment were not recorded in the applicant's dossier.

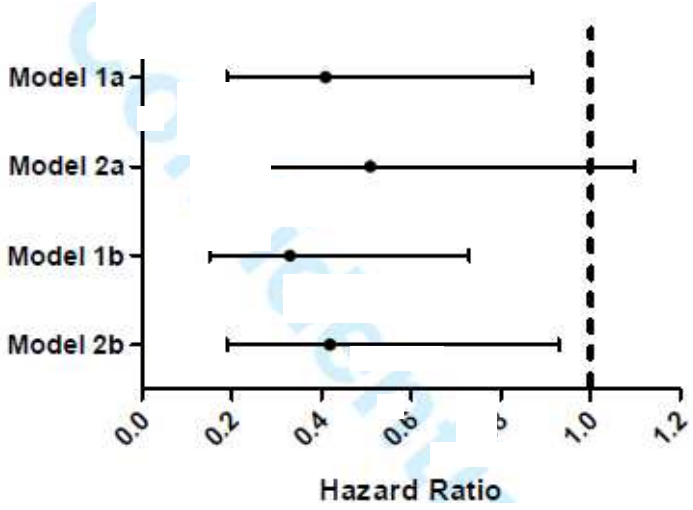
Number of deaths:
During the follow-up period, with a median duration of 6 years (0.04 to 9 years), one death occurred in 18 of the 204 patients treated (9%) and 28 of the 79 non-treated patients (35%).

The median age at death was 59 years (23 to 86 years).
Regarding the reason for the 46 deaths (e.g. acute respiratory distress), the cause:
- was linked to Pompe disease (16 cases),
- may have been linked to Pompe disease (4 cases),
- was not related to the disease (22 cases),
- was not documented (4 cases).

Statistical approach (a) on an "ITT" basis for survival:
The model using treatment with MYOZYME as the only time dependant variant gives an HR of 0.51 95% CI [0.24 - 1.10] (model 2a).
After adjustment for age, sex, severity of the disease and country of residence, the hazard ratio HR will be 0.41 95% CI [0.19 - 0.87] (model 1a).

Statistical approach (b) on a "censor of time after treatment discontinuation" basis:
During follow-up, 19 patients treated with MYOZYME discontinued treatment.
The analyses in which patients who suspended treatment were "censored" from the discontinuation date resulted in an HR of 0.33 95% CI [0.15 - 0.73] and 0.42 95% IC [0.19 - 0.93] respectively for the 1b and 2b models.

Figure 1: hazard ratio (HR) and 95% confidence intervals (CI) for all models



Treatment discontinuation:
Nineteen of the 204 patients (9.3%) treated with ERT stopped treatment during follow-up. The median treatment duration for these patients was 1.4 years (from 0.2 to 4.7 years) and the median follow-up after treatment discontinuation was 1.2 years (from 0.05 to 4.0 years).
The causes for discontinuation were linked to allergic-type infusion reactions or other adverse events (n = 10), the absence of treatment effect (n = 4), pregnancy (n = 2) and for unknown reasons (n = 3). Four patients who stopped treatment died, including three who were treated for less than 1.5 years. One on these four patients died 6 weeks after stopping treatment and the other three died from 1 to 2.5 years after stopping treatment.

However, the following points should be noted:

- the numerical disparity between the two groups in terms of severity of the disease, especially the number of patients not requiring respiratory assistance or the use of a wheelchair varied between the two groups (34% versus 44% in the non-treatment group)
- the absence of information on the reasons for starting or not starting ERT.

Finally, given the observational nature of this study and the bias linked to this type of approach, the level of evidence of results for this trial remains modest. Therefore, these results can only be considered on an exploratory basis in particular all do not enable reliable and precise quantification of the effect of treatment.

8.1.2 Other observational studies

The other observational studies presented were carried out on cohorts with a small number of participants on patients treated with MYOZYME at a dose of 20 mg/kg every two weeks after laboratory confirmation of the diagnosis and determination of the basal intensity of the signs of muscular and/or respiratory weakness.

Among in the numerous criteria used to evaluate motor and respiratory function of patients with late-onset Pompe disease, only the following are systematically detailed:

- the distance covered in the 6-minute walk test (6MWT*)*
- forced vital capacity (FVC).

These criteria, which are reliable and reproducible, were used as the most relevant parameters to assess the efficacy of therapeutic intervention in the late-onset form of Pompe disease[5]

8.1.2.1 Vries et al study (published in 2012)[7]

This was an observational, open-label, single-centre study, carried out between 2004 and 2009 on 71 Dutch adult patients.

The assessment criteria included:
-motor function: manual muscular testing (MRC scale)[12]
-respiratory function: FVC in a seated and recumbent position.
It should be noted that the assessment criteria do not meet Pompe disease assessment and treatment committee (CETP)[2] guidelines, especially in terms of motor function, as the 6-minute walk test was not carried out.

Results:
The data for 69 of the 71 patients included in the study were used for the analysis (there were insufficient data for 2 patients). At inclusion, the median age of patients was 52.1 years. A wheelchair was not needed by 61% (42/69) of patients and no respiratory assistance was required for 64% (44/69) of patients.
The median follow-up period on ERT was 23 months.
The available results for motor skills and respiratory function are only in the form of a mean difference between the state before and after treatment.

- Motor function:

The muscular strength increased between the start and end of treatment, with a mean increase of 1.4% per year ($p<0.001$).

- Respiratory function:

FVC while seated remained stable. FVC in a recumbent position decreased by 1.1% per year ($p=0.03$).

[12] Manual muscle testing enables muscular strength to be assessed using a rating from 5 (normal strength) to 0 (absence of contraction).

8.1.2.2 Bembi et al Study (published in 2010)[8]

This was an observational, open-label, single-centre study carried out over 3 years, which included 24 Italian patients.

The assessment criteria included:
-motor function: 6-minute walk test
-respiratory function: FVC in a seated position.

Results:
The age when the first symptoms appeared was under 16 years (mean age 2.5 years) for 7 patients and over 16 years (mean age 27 years) for 17 patients. According to the Walton Score[13] (WS), 38% (9/24) of patients had a significant change in motor function. Respiratory assistance was required by 38% (9/24) of patients.

- Motor function:

Analysis involved two sub-groups, defined based on Walton Score on entry into the study. However, given the restricted number of participants in each of the sub-groups (11 and 13 patients), this data does not enable reliable conclusions to be drawn on the effect of treatment for this parameter.

- Respiratory function:

No difference was observed in changes to FVC in a seated position between the state before and after treatment: 54% at entry into the study and 59.5% after 3 years' treatment.

8.1.2.3 Angelini et al study (published in 2011)[9]

This was an observational, open-label, multi-centred study, carried out over 12 to 54 months which included 74 Italian patients who had previously been treated with MYOZYME for at least 12 months.

The assessment criteria included:
- motor function: 6-minute walk test
- respiratory function: FVC in a seated position.

Results:
At inclusion, the mean age of patients was 43 years (from 7 to 72 years). A wheelchair was needed by 10% (7/74) of patients and respiratory assistance was required for 36% (27/74) of patients.

- Motor function:

The 6-minute walk test was performed by 58 of the 74 patients included. An increase of 20% in the distance covered corresponding to an absolute increase of 63 m ($p<0.0001$) was observed.

- Respiratory function:

FVC was measured for 69 of the 74 patients included. No difference was observed in seated FVC.

8.1.2.4 Regnery et al study (published in 2012)[10]

This was an observational, open-label, multi-centred study, which included 38 German patients who were monitored for 3 years.

The assessment criteria included:
- motor function: 6-minute walk test
- respiratory function: FVC in a seated position.

[13] The Walton score enables functional activity to be assessed using a scale (Gardner-Medwin and Walton scale) which ranges from 0 (normal activity) to 10 (patient bedridden).

- quality of life: SF-36 questionnaire[14]

Results:
At inclusion, the mean age of patients was 53 years (from 27 to 73 years). A wheelchair was needed by 29% (11/38) of patients and respiratory assistance was required for 34% (13/38) of patients.

- Motor function:

The 6-minute walk test was performed by 21 of the 38 patients included.
The mean distance covered increased over the first year with an absolute gain of 32 m and then was stabilised during the second and third years of follow-up.

- Respiratory function:

FVC was measured for 28 of the 38 patients included. No difference was observed for this criterion.

- Quality of life:

The mean overall score between the state before and after treatment did not change during the 36 months of the study.

8.1.2.5 Studies from a bibliographical review

Furthermore, the applicant has reported on a literature analysis,[15] combining 24 observational studies, including some of which that have been analysed in this document. In view of the heterogeneity of the aims and the patient characteristics, the pooled results of this analysis do not enable any conclusions to be drawn and will not be presented.

08.2 National and international registries

8.2.1 French Pompe disease register

The French Pompe disease register was set up in 2004 to enable prospective monitoring of patients with Pompe disease in France. It is an observational, multi-centred programme, coordinated by the Institute of Myology at the Pitié-Salpêtrière Hospital.

Aims:
- to record all patients with Pompe disease in France
- to gather clinical and paraclinical information, in order to better understand the natural course of untreated patients, to assess the influence of therapies and to provide information on the cause of death of patients
- to enable scientific research to be developed through networks of neuromuscular disease and metabolic disorders reference centres.

Inclusion criteria:
- diagnosis of Pompe disease confirmed through evidence of low GAA enzyme activity and/or the two mutations of the GAA gene
- there were no exclusion criteria.

Treatment:
MYOZYME was administered every two weeks via IV infusion at a dose of 20 mg/kg. Patients were monitored every 6 months based on CETP guidelines[2]

Assessment criteria:

[14]Questionnaire that enables the physical and mental health of an individual aged 14 years or under to be assessed, using 36 questions relating to 8 areas of health (physical activities, social activities, mental, physical and emotional ability to accomplish everyday tasks, physical pain, general mental health, vitality and perception of general state of health). The scores range from 0 to 100 in each category. An algorithm that enables the overall score to be calculated, from 0 to 100, determined for both physical and mental health.
[15]Toscano A, Schoser B. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. J Neurol. 2012 Aug 28. Published on line.

Data collected were based on clinical and laboratory follow-up criteria recommended by CETP.
The follow-up of patients was recorded *retrospectively,* by defining the "initial" appointment as the nearest visit to the start of treatment for treated patients or as the first visit recorded for non-treated patients.

Results:
On 7 July 2011, 104 adult patients were registered, however 94/104 patients were assessable: 81 patients were treated with MYOZYME and 13 patients did not receive treatment. At inclusion, the median duration of the disease was 16 years in the treated patients group and 10 years in the group of non-treated patients. The primary reasons for not starting treatment were the non-serious nature of muscle weakness and the absence of a significant impact on respiratory signs.
For each evaluation criteria, the slope was calculated via linear regression by stratifying the calculation by the treatment group.

- Motor function:

After 66 months of follow-up, a decrease in the distance covered (6-minute walk test) was observed in patients treated, although no difference was observed for non-treated patients during the whole follow-up period. The decrease in distances measured for treated patients may have been due to a threshold effect. Indeed, patients who received treatment for the longest time were more severely affected when treatment was started. Thus, no negative impact was observed after modelling the changes in distance covered for an observation window that did not exceed 48 months.

Table 2: overall analysis of changes for 6-minute walk test

Group	Visit	Slope	Standard deviation	p
Treated	Initial - month 66	-1.53	0.52	<0.01
	Initial - month 18	2.19	1.69	NS
	Month 18 - month 66	-4.45	3.06	NS
Not treated	Initial - month 66	1.05	1.69	NS
	Initial - month 18	-4.29	5.92	NS
	Month 18 - month 66	6.53	4.36	NS

- Respiratory function:

An improvement in forced vital capacity in a seated position was observed for the first 18 months of treatment. However, no difference was seen between the initial state and that at 66 months for this criterion.

Table 3: overall analysis of changes in FVC

Group	Visit	Slope	Standard deviation	p
Treated	Initial - month 66	-0.1	0.07	NS
	Initial - month 18	0.57	0.25	0.02
	Month 18 - month 66	-0.04	0.36	NS
Not treated	Initial - month 66	0.09	0.17	NS
	Initial - month 18	-0.49	0.64	NS
	Month 18 - month 66	-0.17	0.32	NS

8.2.2 The International Pompe disease registry

The international Pompe disease registry is an observational programme with inclusion by doctors and patients being on a voluntary basis. It was established in 2004 to monitor patients with Pompe disease over at least a 15 year period. GENZYME is the sponsor for this registry.

Aims:
- to enhance the understanding of the variability, progression, and natural history of the key manifestations of Pompe disease
- to assist with the development of guidelines for monitoring patients and reports on patient outcomes to help optimize patient care
- to characterize and describe the Pompe disease population as a whole
- to evaluate the long-term effectiveness and safety of available treatment options

Inclusion criteria:
- diagnosis of Pompe disease confirmed through evidence of low GAA enzyme activity and/or the two mutations of the GAA gene.
-there were no exclusion criteria.

Treatment:
MYOZYME was administered every two weeks via IV infusion at a dose of 20 mg/kg.

The assessment criteria included:
- motor function: 6-minute walk test
- respiratory function: FVC in a seated position
- quality of life: SF-36 questionnaire

Results:
On 3 October 2011, 430 patients with late-onset Pompe disease had been recorded in the registry, including 371 (86%) patients treated with MYOZYME. The median treatment duration was 2.95 years, with a maximum period of 5.8 years.
Due to the absence of statistical analysis, the results are presented for descriptive purposes only and do not enable any conclusions to be drawn.

- Motor function:

Table 4: performance in the 6-minute walk test for treated patients >18 years

Parameter	Statistic	Baseline	12 months	24 months	36 months	48 months
Total distance covered (m)	n		60	42	33	19
	Mean (SD)	300.2	330.2 (136.47)	340.7 (120.98)	353.7 (125.38)	352.4 (120.19)
	Median		360.0	351.5	360.0	360.0
	Min, Max		30; 620	75; 620	75; 620	159; 620

SD: Standard deviation

- Respiratory function:

Table 5: FVC for treated patients >18 years

Parameter	Statistic	Baseline	12 months	24 months	36 months	48 months
FVC	n	157	152	116	73	46
	Mean (SD)	2.4 (1.0)	2.3 (1.0)	2.4 (1.1)	2.1 (0.97)	2.0 (0.92)
	Median	2.4	2.2	2.2	1.9	1.8
	Min, Max	0; 6	0; 6	0; 6	1; 5	0; 5

SD: Standard deviation

- Quality of life:

The mean overall score was not calculated; however the individual variations in the eight sub-scores were minimal (between 0 and 31 on a scale from 0 to 100).

08.3 Treatment suspension or discontinuation criteria

At the present time, data from clinical trials, the pathophysiological rationale and the absence of identified predictive factors still do not enable agreed enzyme replacement therapy discontinuation criteria to be established for late-onset forms of the disease.
According to the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) guidelines published in October 2011[3], ERT should be started on the appearance of the first signs of musculoskeletal or respiratory impairment. Treatment should be re-assessed annually and may be continued until the annual clinical assessment shows an improvement or stabilisation of the disease (improvement or stabilisation in motor function or respiratory function).

08.4 Adverse Effects

8.4.1 SPC data

Since the Committee's previous opinion, the following amendments have been made to the SPC:

- "adverse effects" section:
  - identification of the potential occurrence of severe cutaneous reactions, possibly immune mediated, have been reported including ulcerative and necrotizing skin lesions;
  - addition of clinical signs reported within the context of infusion reactions: conjunctivitis, abdominal pain, arthralgia, apnoea and respiratory arrest.
- "Special warnings and precautions for use" section: addition of a warning regarding monitoring of patients for signs and symptoms of systemic immune-mediated reactions involving skin and other organs, as well as the actions to take if necessary.

8.4.2 Risk management plan

The RMP combines all the data collected on an international level, regardless of the distribution method of MYOZYME (clinical trial, compassionate use programme and post-marketing experience). On 1st August 2011, the plan enabled the accumulated number of patient-years to be estimated at between 4,038 and 4,519.

New data collected confirms the established safety profile. The adverse effects are mainly infusion associated reactions, including hypersensitivity and anaphylactic reactions.
Some infusion associated reaction risk factors have been identified:

- a history of infusion reactions
- a high MYOZYME infusion rate
- a high dose (40 mg/kg) of MYOZYME
- an acute underlying condition
- IgE antibodies in the treated patient
- high IgG antibody titres for patients treated for the infantile form

In conclusion, the adverse events linked to treatment are primarily infusion associated reactions, including severe hypersensitivity/anaphylactic reactions in approximately 3% of patients treated. This risk of infusion associated reactions is estimated at 28% of the treated population. In the majority of cases, progress is favourable following appropriate treatment. The majority of patients (approximately 90% of patients), however, develop anti-rhGAA antibodies, the levels of which tend to decrease during treatment. At the present time, no correlation could be seen between the appearance of these antibodies and clinical progress or the tolerance observed.

08.5 Usage data

In France, approximately 95 patients, aged between 11 and 78 years with a median age of 50 years, were treated for late-onset Pompe disease (value calculated in June 2012).

08.6 Summary & discussion

The applicant presented new clinical data in response to the request by the Committee and sought a re-assessment of the actual benefit and the level of improvement in actual benefit for late-onset Pompe disease.
This new data concerns:

- an observational study (Güngör study), the aim of which was to compare the overall mortality of patients who were either treated or not treated with alglucosidase alfa,
- four observational studies with the specific aim of assessing motor and respiratory function in patients treated with alglucosidase alfa.

In the Güngör study, which included 283 adults, including 79 (28%) who were not treated and 204 (72%) who were treated with alglucosidase alfa, the analysis of overall mortality, carried out on an ITT basis, showed:

- HR of 0.51 95% CI [0.24 - 1.10] for treatment with alglucosidase alfa as the single time-dependent variant.
- HR of 0.41 95% CI [0.19 - 0.87] for treatment with alglucosidase alfa after adjustment for age, sex, severity of the disease and the country of residence.

Analysis on a “censor of time after treatment discontinuation” basis showed:

- HR of 0.42 95% CI [0.19 - 0.93] for treatment with alglucosidase alfa as the single time dependent variant
- HR of 0.33 95% CI [0.15 - 0.73] for treatment with alglucosidase alfa after adjustment for age, sex, severity of the disease and the country of residence

However, it should be noted that:

- the absence of information on the reasons for starting or not starting enzyme replacement therapy
- the numerical disparity between the two groups in terms of severity of the disease, especially the higher percentage of patients needing respiratory assistance or the use of a wheelchair in patients treated with alglucosidase alfa than in those not treated (66% versus 56%).

Given the bias associated with the observational nature of this study, the level of evidence for these results remains modest. Therefore, these results can only be considered on an exploratory basis, and in particular do not enable reliable and precise quantification of the effect of treatment.

For the other four observational studies on cohorts with a small number of participants of patients treated with alglucosidase alfa, described in this document, they mainly focus on motor and respiratory function.
The 6-minute walk test performed in two of the studies showed an absolute increase of 32 and 63 metres for 70% (79/112) of the patients evaluated.
The seated forced vital capacity evaluated in three studies, i.e. 92% (190/207) of patients, did not show any difference in the state before and after treatment.
Quality of life was only evaluated in one study, and no improvement was seen.

In conclusion, new observational clinical data presented did not enable the effect of treatment with alglucosidase alfa to be demonstrated on overall survival and motor and respiratory function in late-onset Pompe disease.

Since the last assessment by the Transparency Committee in 2010, additions to the SPC have mainly concerned severe skin reactions (possibly immune mediated) including ulcerative and necrotizing skin lesions.

The risk of a previously identified infusion-associated reaction is currently estimated at 28% in the treated population. These reactions include severe hypersensitivity and anaphylactic type reactions that are encountered by approximately 3% of patients treated.

09 THERAPEUTIC USE

Treatment of the late-onset form of Pompe disease combines enzyme replacement therapy with alglucosidase alfa and the management of symptoms.
MYOZYME is the only ERT for acid alfa glucosidase deficiency currently available. According to guidelines[2,3], treatment should be started from the first signs of musculoskeletal or respiratory impairment in patients who have had their diagnosis confirmed through laboratory tests. Follow-up is based on a biannual assessment of motor (6MWT, MSM etc.) and respiratory (FVC, FIF max, PEF max) function. Treatment can be continued until the annual clinical assessment shows an improvement or stabilisation in musculoskeletal or diaphragm deficiencies. This is combined with symptomatic treatment which changes based on the degree of motor or respiratory impairment: walking aids (sticks, frames) then a wheelchair, non invasive then invasive respiratory assistance.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above data and information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

- Late-onset Pompe disease is a serious and life-threatening condition.
- MYOZYME is intended as a replacement therapy.
- The efficacy/adverse effects ratio is modest.
- There are no treatment alternatives.
- This medicinal product is a first-line treatment.

- Public health benefit:
  Pompe disease, also in its late-onset forms, is a serious condition which can lead to functional disability and loss of independence, but it is a minor public health burden regarding the orphan character of this disease.

  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).

  On the basis of available data (from observational studies), it is considered that MYOZYME does not have an impact on morbidity and the quality of life of patients treated. The medicinal product MYOZYME is therefore unlikely to meet any identified public health need.

  Consequently, it is not anticipated that MYOZYME will benefit public health in this indication (late-onset form of Pompe disease).

On this basis, the Committee considers that the actual benefit of MYOZYME remains low in the treatment of late-onset Pompe disease.

010.2 Improvement in actual benefit

In light of available data, the Committee considers that the improvement in actual benefit provided by MYOZYME remains minor (level IV) for the late-onset form of Pompe disease.

010.3 Target population

According to the French Pompe disease register, 132 patients (whose age on inclusion on the register was ≥ 14. 7 years) were reported in France on 11 January 2013. Paediatric patients (those whose first symptoms appeared from the age of 1 year) and those under 14.7 years on inclusion do not appear on the register.

The target population of MYOZYME for late-onset Pompe disease may be estimated at 150 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Specific requests inherent to the treatment

The Transparency Committee recommends an annual assessment of all patients treated with MYOZYME for the late-onset form of Pompe disease in order to complete a periodic reassessment of efficacy and confirm continuation of treatment.

Request for data

The Committee would like to receive the results of the evaluations that may be carried out within the scope of the French register, in particular regarding the reason for continuing with or discontinuing treatment with MYOZYME for late-onset Pompe disease.

Other requests

The packaging is still not appropriate for the administration of MYOZYME in adults.