NHS England Evidence Review:

Alglucosidase alfa for infantile-onset Pompe disease

NHS England URN: 2107

NHS England Evidence Review

Alglucosidase alfa for infantile-onset Pompe disease

Completed: July 2021

Prepared by NICE on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

People with infantile-onset Pompe disease (IOPD) are currently treated with alglucosidase alfa, which has a marketing authorisation for long-term enzyme replacement therapy in people with a confirmed diagnosis of Pompe disease. The licensed dosage of alglucosidase alfa is 20 mg/kg **once every 2 weeks**. (See the Summary of product characteristics for Myozyme for more information.)

In England, current standard treatment for people with IOPD is alglucosidase alfa 20 mg/kg **once weekly for 3 months** (off label) at diagnosis, followed by 20 mg/kg once every 2 weeks. Some people develop high titres of antibodies against alglucosidase alfa during treatment which is associated with poorer outcomes.

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of alglucosidase alfa 20-40 mg/kg **once weekly** (off label) compared with current standard treatment or the licensed dosage in people with IOPD. In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment more than others, and when patients change dose of alglucosidase alfa.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost-effectiveness of alglucosidase alfa 20-40 mg/kg once weekly compared with current standard treatment (20 mg/kg once weekly for 3 months at diagnosis, followed by 20 mg/kg once every 2 weeks) or the licensed dosage (alglucosidase alfa 20 mg/kg once every 2 weeks) in people with IOPD. In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from treatment more than others, and when patients change dose of alglucosidase alfa.

One paper was identified for inclusion (Poelman et al. 2020). The study (n=18) was a prospective observational before and after study using standardised assessments. It compared outcomes in babies and infants newly diagnosed with IOPD who started treatment with the licensed dosage of alglucosidase alfa between 2003 and 2009 (n=6) with those who started treatment with alglucosidase alfa 40 mg/kg once weekly from 2009 (n=12).

No studies were identified comparing alglucosidase alfa 40 mg/kg once weekly with current standard treatment. Also, no studies were identified comparing alglucosidase alfa 20 mg/kg once weekly with the licensed dosage or current standard treatment.

In terms of clinical effectiveness:

- **Survival:** The before and after study by Poelman et al. (2020) provided very low certainty evidence that a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly (maximum follow up 8.3 years) survived at the end of the study compared with patients using the licensed dosage (maximum follow up 12.6 years). However, the difference between the groups was not statistically significant. Dosages were increased to 40 mg/kg once weekly in 4 surviving patients receiving 20 mg/kg once every 2 weeks because of clinical deterioration. It is possible that this dosage increase caused the difference between the groups to be less than it would have been if they had remained on 20 mg/kg once every 2 weeks.
- **Ventilation-free survival:** Similarly, the study by Poelman et al (2020) found that higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly survived ventilation-free at the end of the study compared with patients using the licensed dosage. The difference between the groups was not statistically significant and the evidence is of very low certainty.
- **Quality of life:** No evidence was identified for this outcome.
- **Gastrostomy/jejunostomy placement:** Few patients had gastrostomy placement in the study by Poelman et al. (2020) and it is unclear whether alglucosidase alfa 40 mg/kg once weekly reduces gastrostomy placement compared with the licensed dosage. No statistical analysis was reported for this outcome and this evidence is of very low certainty.
- **Motor function:** Overall, compared with patients using the licensed dosage, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly achieved walking outcomes, including achieving the ability to walk and maintaining ability to walk at the end of the study by Poelman et al. (2020). However, the difference was reported to be statistically significant only for ability to walk at 3 years of age, with this outcome being the only outcome in the study rated as low certainty (rather than very low certainty). Median Alberta Infant Motor Scale (AIMS) and Bayley Scales of Infant Development II (BSID-II) scores and ranges (measures of motor development) generally appeared

similar in the 40 mg/kg and licensed dosage groups, but statistical analyses were not reported and this evidence is of very low certainty.

- **Disease-related complications:** In the study by Poelman et al. (2020), changes in left ventricular mass index (LVMI) Z-scores (a measure of IOPD-related cardiomyopathy) appeared to be similar between the groups and generally improved, but no statistical analyses were reported and this evidence is of very low certainty.

In terms of safety:

- No evidence was identified for all drug-related adverse events combined.
- In the study by Poelman et al. (2020), a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly had infusion-associated reactions compared with patients using the licensed dosage. Severe infusion-associated reactions were also more frequent in the 40 mg/kg group. However, no statistical analyses were reported and this evidence is of very low certainty.
- No evidence was identified for exacerbation of cardiac dysfunction.
- The study by Poelman et al. (2020) also found that patients using alglucosidase alfa 40 mg/kg once weekly had higher antibody titres than patients using the licensed dosage. Similarly, titres were more often high and sustained in the 40 mg/kg group. However, no statistical analyses were reported and this evidence is of very low certainty.

In terms of cost-effectiveness:

- No evidence was identified for cost-effectiveness.

In terms of subgroups:

- The study by Poelman et al. (2020) suggests that CRIM-negative patients taking alglucosidase alfa 40 mg/kg weekly may live longer and have better motor function than those taking the licensed dosage. However, few CRIM-negative patients were included in the study and this evidence is inconclusive.
- Less information was reported for CRIM-positive patients and the benefits and risks with 40 mg/kg compared with 20 mg/kg are not known for this subgroup**.**

Change in dosage:

- Dosages were increased to 40 mg/kg weekly in all 4 surviving patients taking 20 mg/kg once every 2 weeks when they deteriorated clinically, which occurred at a mean age of 4.1 years.

Please see the results table (section 5) in the review for further details of outcomes and definitions.

Limitations

The study by Poelman et al. (2020) has serious limitations for determining the efficacy and safety of alglucosidase alfa 40 mg/kg once weekly for treating IOPD compared with the licensed dosage (20 mg/kg once every 2 weeks).

It is difficult to conduct high quality studies in rare diseases such as IOPD. Although the study by Poelman et al. (2020) was well designed and reported, considered objective outcomes and followed patients over many years, only 18 patients could be included. In addition, not all patients could be assessed for all outcomes because of death or serious illness. This limited the ability of the investigators to perform statistical analyses.

The study was a before and after observational study, meaning there was no concurrent comparator, and assessments were standardised but probably not blinded. Dosage increases in surviving patients in the licensed dosage group may have influenced some outcomes. This type of study is subject to bias and confounding and cannot prove that an intervention (such as alglucosidase alfa) caused an outcome, only that it is associated with that outcome.

Maximum follow up was shorter in the 40 mg/kg group (8.3 years compared with 12.6 years in the 20 mg/kg group) and median age at the last assessment was younger (4.4 years compared with 9.6 years in the 20 mg/kg group). It is not known if these differences between the groups may have affected comparisons for outcomes which are experienced after a longer period of time; for example, survival.

The AIMS and BDIS-II scales used in the study do not have validated minimal clinically important differences for IOPD, which makes it difficult to determine whether any observed changes are clinically meaningful.

Conclusion

This evidence review found limited low (one outcome) and very low certainty evidence for the efficacy and safety of alglucosidase alfa **40 mg/kg once weekly** for treating IOPD compared with the **licensed dosage** (20 mg/kg once every 2 weeks) for up to 8 years.

At the end of the study, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly survived (overall and ventilation-free) and achieved walking outcomes compared with patients using the licensed dosage. However, the difference between the groups was statistically significant only for one outcome (ability to walk at 3 years of age).

Median AIMS and BSID-II scores, changes in LVMI Z-scores and rates of gastrostomy placement were generally similar in the 40 mg/kg and licensed dosage groups, A higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly had infusion-associated reactions and high antibody titres compared with patients using the licensed dosage. Statistical analyses were not reported for these outcomes.

Many of the results were unclear because of the small number of patients and the possible influence of confounding factors, such as dosage increases and differences between the groups. Any potential benefits of treatment must be balanced against the uncertain adverse effect profile of the 40 mg/kg weekly dosage in this population.

No evidence was identified to determine whether alglucosidase alfa **40 mg/kg weekly** improves outcomes compared with **current standard treatment** (20 mg/kg weekly for 3 months at diagnosis, followed by 20 mg/kg once every 2 weeks).

No evidence was identified to determine whether alglucosidase alfa **20 mg/kg weekly** improves outcomes compared with the **licensed dosage or current standard treatment**.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In IOPD, what is the clinical effectiveness of alglucosidase alfa 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?
2. In IOPD, what is the safety of alglucosidase alfa 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?
3. In IOPD, what is the cost-effectiveness of alglucosidase alfa 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?
4. From the evidence selected, is there any data to suggest that there are particular subgroups of patients that would benefit from treatment with alglucosidase alfa 20-40 mg/kg once weekly more than others?
5. From the evidence selected, when do patients change dose of enzyme replacement therapy?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 21 May 2021.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full texts of potentially relevant studies were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE profiles.

4. Summary of included studies

One paper was identified for inclusion (Poelman et al. 2020). Table 1 provides a summary of this study and full details are given in Appendix E.

The study was a prospective observational before and after study using standardised assessments. It compared outcomes in babies and infants newly diagnosed with IOPD who started treatment with alglucosidase alfa 40 mg/kg once weekly (off label dosage) with outcomes in those who started treatment with 20 mg/kg once every 2 weeks (the licensed dosage).

No studies were identified comparing alglucosidase alfa 40 mg/kg once weekly with current standard treatment (alglucosidase alfa 20 mg/kg once weekly for 3 months at diagnosis, followed by 20 mg/kg once every 2 weeks). Also, no studies were identified comparing alglucosidase alfa 20 mg/kg once weekly with the licensed dosage or current standard treatment.

Table 1: Summary of included study

Study	Population	Intervention and comparison	Outcomes reported

Poelman et al. 2020
 	
Prospective observational study using standardised assessments (before and after study)
 	
The Netherlands
	All Dutch patients newly diagnosed with classic IOPD who were treated with alglucosidase alfa (n=18) between 2003 and 2016
	
	Between 2003 and 2009, infants were given 20 mg/kg once every 2 weeks (n=6, comparator group) then from 2009, newly diagnosed infants were given 40 mg/kg once weekly (n=12, intervention group)
	
	At baseline, median age was lower in the 20 mg/kg comparator group (1.5 months versus 3.6 months)
	
	3/12 (25%) patients in the intervention group and 2/6 (33%) patients in the comparator group were CRIM-negative
		Intervention
		
		Alglucosidase alfa 40 mg/kg IV once weekly (off label dosage)
		
		5/12 patients also received immunomodulation with rituximab, methotrexate and IV immunoglobulin
		
		Maximum follow up 8.3 years
		
		Comparator
		
		Alglucosidase alfa 20 mg/kg IV once every 2 weeks (licensed dosage)
		
		Between 2009 and 2014, dosages were increased to 40 mg/kg once weekly in 4 surviving patients (median age 4.1 years) receiving 20 mg/kg once every 2 weeks because of clinical deterioration
		
		Maximum follow up 12.6 years
			Critical outcome
			• Survival at end of study
			• Ventilation-free survival at end of study
			Important Outcomes
			• Percutaneous endoscopic gastrostomy at end of study
			• Motor function
			  ○ Ability to walk at 3 years of age and at end of study
			  ○ AIMS score at 12 and 18 months of age
			  ○ BSID-II score at 24 and 36 months of age
			• LVMI at the end of the study
			Safety
			• Infusion-associated reactions
			• Antibody formation and detection

Abbreviations

AIMS, Alberta Infant Motor Scale, a 58-item scale to assess motor development in infants aged 18 months or less, with lower scores indicating delayed development; BSID-II, Bayley Scales of Infant Development II, which consists of 3 scales (motor, mental and behaviour) to assess development in infants aged 1 to 42 months, with a score of 100 being average for age, and lower scores indicating delayed development; CRIM, cross-reactive immunological material; IOPD, infantile-onset Pompe Disease; IV, intravenously; LVMI, left ventricular mass index, a measure of disease-related complications in the heart

5. Results

In IOPD, what is the clinical effectiveness and safety of alglucosidase alfa 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Survival **Certainty of evidence:** very low	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that time. Without treatment, life expectancy is less than 2 years and even with current treatment, survival is not guaranteed. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to survival at the end of the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. At the end of the study, the difference between the groups was not statistically significant for this outcome. 11/12 (92%) patients survived in the 40 mg/kg group compared with 4/6 (67%) patients in the 20 mg/kg group (p=0.25). **(VERY LOW)** Dosages were increased to 40 mg/kg once weekly in 4 surviving patients (median age 4.1 years) receiving 20 mg/kg once every 2 weeks because of clinical deterioration. It is possible that this dosage increase caused the difference between the groups to be less than it would have been if they had remained on 20 mg/kg once every 2 weeks. **This study provides very low certainty evidence of no difference in the proportion of people surviving when alglucosidase alfa 40 mg/kg once weekly is compared with the licensed dosage. However, this result might underestimate a survival benefit for the 40 mg/kg once weekly group.**
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome.
Ventilation-free survival **Certainty of evidence:** very low	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** With currently available treatment, more than 50% of patients in the UK with IOPD require ventilatory support. Not requiring ventilation is a very important outcome for patients and their carers. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to ventilation-free survival at the end of the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg

	once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. At the end of the study, the difference between the groups was not statistically significant for this outcome. 11/12 (92%) patients survived ventilation-free in the 40 mg/kg group compared with 3/6 (50%) patients in the 20 mg/kg group (p=0.08). **(VERY LOW)** Dosages were increased to 40 mg/kg once weekly in 4 surviving patients (median age 4.1 years) receiving 20 mg/kg once every 2 weeks because of clinical deterioration. It is possible that this dosage increase caused the difference between the groups to be less than it would have been if they had remained on 20 mg/kg once every 2 weeks. **This study provides very low certainty evidence of no difference in the proportion of people surviving when alglucosidase alfa 40 mg/kg once weekly is compared with the licensed dosage. However, this result might underestimate a survival benefit for the 40 mg/kg once weekly group.**
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome.
Health-related quality of life **Certainty of evidence:** not applicable	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** Quality of life is very important to patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived well-being. No evidence was identified for this outcome.
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
Important outcomes	
Rate of gastrostomy/jejunostomy placement **Certainty of evidence:** very low	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** Patients with IOPD may require gastrostomy or jejunostomy placement because of difficulty swallowing. This impedes the patient's ability to eat and drink normally and requires training for the carers to use. A reduction in gastrostomy/jejunostomy placement would be very important to patients. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to gastrostomy placement at the end of the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg

	once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. Few patients in the study had gastrostomy placement. At the end of the study, 1/12 (8%) patients in the 40 mg/kg group had received percutaneous endoscopic gastrostomy compared with 2/6 (33%) patients in the 20 mg/kg group. No statistical analysis was reported for this outcome. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. **(VERY LOW)** **This study provides very low certainty evidence and it is unclear whether alglucosidase alfa 40 mg/kg once weekly reduces gastrostomy placement compared with the licensed dosage.**
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome.
Motor function **Certainty of evidence:** low to very low	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** The ability for patients to meet motor milestones (including crawling and walking) are important to patients and carers as they are a marker of the development of the brain. This is an important outcome to patients as resolution or reduction of these disease-related complications can reduce the number of times they need to be admitted to hospital or require emergency admissions. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to motor function at various timepoints throughout the study. The study assessed ability to walk and AIMS and BSID-II scores in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). **Ability to walk** Overall, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly achieved walking outcomes compared with patients using the licensed dosage. However, the difference was only reported to be statistically significant for ability to walk at 3 years and results for the other outcomes are unclear. • The ability to walk was achieved by 11/12 (92%) patients in the 40 mg/kg group and 4/6 (67%) patients in the 20 mg/kg group (no statistical analysis reported). **(VERY LOW)** • At the age of 3 years, 11/12 (92%) patients in the 40 mg/kg group maintained the ability to walk compared with 2/6 (33%) patients in the 20 mg/kg group (p=0.02). **(LOW)** • At the end of the study, 10/12 (83%) patients in the 40 mg/kg group maintained the ability to walk compared with 1/6 (17%) patients in the 20 mg/kg group (no statistical analysis reported). **(VERY LOW)** **AIMS scores** AIMS is a 58-item scale on which lower scores indicate delayed development. This scale was used to assess motor development when infants were aged 12 months

	and 18 months. The scale has not been validated for use in Pompe disease and there is no known standard minimal clinically important difference. Median AIMS scores and ranges were similar between the groups, although no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. • At 12 months, the median AIMS score was 39 (range 20-50) in the 40 mg/kg group and 37 (range 20-45) in the 20 mg/kg group (5 patients only because 1 had died). **(VERY LOW)** • At 18 months, the median AIMS score was 57 (range 34-58) in the 40 mg/kg group and 54 (range 25-57) in the 20 mg/kg group (5 patients only because 1 had died). **(VERY LOW)** • Only 6 patients reached the maximum AIMS score of 58 and all were in the in the 40 mg/kg group. **BSID-II scores** BSID-II consists of 3 scales (motor, mental and behaviour) with a score of 100 being average for age, and lower scores indicating delayed development. This scale was used to assess motor development when infants were aged 24 months and 36 months. The scale has not been validated for use in Pompe disease and there is no known standard minimal clinically important difference. Median BSID-II scores and ranges were generally similar between the groups, although no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. • At 24 months, the median BSID-II score was 18 (range 14-25) in the 40 mg/kg group and 17 (range 10.4-21) in the 20 mg/kg group (3 patients only because 1 had died and 2 needed invasive ventilation). **(VERY LOW)** • At 36 months, the median BSID-II score was 30 (range 19-33) in the 40 mg/kg group (11 patients only because 1 had died) and 20 (range 20-32) in the 20 mg/kg group (3 patients only because 1 had died and 2 needed invasive ventilation). **(VERY LOW)** **This study provides low certainty evidence that, compared with patients using the licensed dosage, more patients using alglucosidase alfa 40 mg/kg once weekly are still able to walk at 3 years and very low certainty evidence that more patients achieved the ability to walk and were still able to walk at the end of the study.** **The study provides very low certainty evidence that median AIMS and BSID-II scores and ranges were generally similar in the alglucosidase alfa 40 mg/kg group and the licensed dosage group.**
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome.
Resolution of disease-related complications	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)**

Certainty of evidence: very low	Resolution of disease-related complications (such as clinically significant cardiomyopathy) is an important outcome to patients as resolution or reduction of such complications can reduce the number of times they need to be admitted to hospital or require emergency admissions. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to resolution of disease-related complications. It assessed LVMI at the end of the study, which is a measure of cardiomyopathy, a complication related to Pompe disease. The study compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. The results of the study were presented graphically for this outcome. Changes in LVMI Z-scores appeared to be similar between the groups and generally improved, but no statistical analyses were reported. **(VERY LOW)** The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. LVMI did not normalise in 1 patient in the 20 mg/kg group who died after 3 months of treatment. 2 patients in the 40 mg/kg group had severe cardiomyopathy at baseline, which responded well to treatment, although LVMI was still slightly elevated at the last assessment in 1 patient. **This study provides very low certainty evidence and it is not known whether alglucosidase alfa 40 mg/kg once weekly improves LVMI compared with using the licensed dosage.**
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome**.**
Safety	
Drug-related adverse events **Certainty of evidence:** not applicable	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** Drug-related adverse events (side effects) are important to patients because they will impact on their treatment choices and recovery and can sometimes have long-term consequences. No evidence was identified for this outcome.
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome**.**

Infusion-associated reactions **Certainty of evidence:** very low	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** Infusion-associated reactions are important to patients because they can be very unpleasant and sometimes severe or life threatening. Also, they can occur repeatedly with subsequent infusions. One before and after study (Poelman et al. 2020, n=18) provided evidence relating to infusion-associated reactions during the study. It compared outcomes in infants newly diagnosed with IOPD who were treated with alglucosidase alfa 40 mg/kg once weekly (off label dosage, n=12) with outcomes in those treated with 20 mg/kg once every 2 weeks (the licensed dosage, n=6). Maximum follow up was 8.3 years in the 40 mg/kg group and 12.6 years in the 20 mg/kg group. Overall, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly had infusion-associated reactions compared with patients using the licensed dosage. However, no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. • 8/12 (67%) patients in the 40 mg/kg group experienced infusion-associated reactions compared with 5/6 (83%) patients in the 20 mg/kg group. **(VERY LOW)** • 134 infusion-associated reactions (11 severe) were seen in the 40 mg/kg group compared with 64 reactions (4 severe) in the 20 mg/kg group**. (VERY LOW)** • In all but 2 patients, reactions were treated successfully and had not recurred for at least 12 months. **This study provides very low certainty evidence suggesting that more infusion-related reactions are seen with alglucosidase alfa 40 mg/kg once weekly compared with the licensed dosage of alglucosidase alfa.**
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome**.**
Exacerbation of cardiac dysfunction **Certainty of evidence:** not applicable	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** Exacerbation of cardiac dysfunction is important to patients because it can affect quality of life and have serious consequences. No evidence was identified for this outcome.
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome**.**

Antibody formation and detection **Certainty of evidence:** very low	**Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once every 2 weeks (licensed dosage)** Patients can develop antibodies to alglucosidase alfa. This is important to them because high titres (concentrations) of antibodies are associated with worse outcomes (including adverse events), especially if they are sustained for a long period. Overall, patients using alglucosidase alfa 40 mg/kg once weekly had higher antibody titres than patients using the licensed dosage. However, no statistical analyses were reported. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. • The median peak antibody titre was 1:156,250 (range 1:250 to 1:800,000) in the 40 mg/kg group and 1:6250 (range 1:1250 to 1:31,250) in the 20 mg/kg group. **(VERY LOW)** • 2/6 (33%) patients in the 20 mg/kg group and 7/12 (58%) patients in the 40 mg/kg group developed high sustained titres of 1:31,500 or more. **(VERY LOW)** **This study suggests that higher antibody titres are seen with alglucosidase alfa 40 mg/kg once weekly compared with the licensed dosage of alglucosidase alfa. However, this evidence is of very low certainty.**
	Alglucosidase alfa 40 mg/kg once weekly (off label use) vs 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks (current standard treatment) No evidence was identified for this outcome.
	Alglucosidase alfa 20 mg/kg weekly vs licensed dosage or current standard treatment No evidence was identified for this outcome**.**
Abbreviations AIMS, Alberta Infant Motor Scale; BSID-II, Bayley Scales of Infant Development II; IOPD, infantile-onset Pompe Disease; LVMI, left ventricular mass index	

In IOPD, what is the cost-effectiveness of alglucosidase alfa 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?

Outcome	Evidence statement
Cost-effectiveness	**No evidence was identified regarding the cost-effectiveness of alglucosidase alfa 20-40 mg/kg once weekly for IOPD.**
Abbreviations IOPD, infantile-onset Pompe Disease	

From the evidence selected, is there any data to suggest that there are particular subgroups of patients that would benefit from treatment with alglucosidase alfa 20-40 mg/kg once weekly more than others?

Outcome	Evidence statement
Subgroup: CRIM status	Patients whose bodies do not produce any alfa glucosidase enzyme are known as CRIM-negative. Patients who are CRIM-positive produce a small amount of the enzyme, but it is inactive. CRIM-negative patients produce more antibodies to treatment and have been shown to have worse outcomes. Outcomes in CRIM-positive patients are variable. (Poelman et al. 2020) In the study by Poelman et al. (2020), 5/18 (28%) patients were CRIM-negative, 3/12 (25%) in the 40 mg/kg group and 2/6 (33%) in the 20 mg/kg group. All 3 **CRIM-negative** patients in the 40 mg/kg group survived, whereas the 2 in the 20 mg/kg group died. 2/3 patients in the 40 mg/kg group also received immunomodulation treatment (in another arm of the study), which may have influenced their outcomes, although the study concluded that immunomodulation did not prevent antibody formation in the 40 mg/kg group compared with the 20 mg/kg group. When considering motor scores, 2/3 patients in the 40 mg/kg group who were CRIM-negative reached the maximum AIMS score of 58. No patients in the 20 mg/kg group reached this score, regardless of CRIM status. All 3 CRIM-negative patients in the 40 mg/kg group developed high sustained antibody titres whether they received immunomodulation or not, as did 1 of the 2 CRIM-negative patients in the 20 mg/kg group. One **CRIM-positive** patient died, who was in the 40 mg/kg group. All 3 CRIM-positive patients in the 20 mg/kg group and 4/9 (44%) CRIM-positive patients in the 40 mg/kg group (including 1 also received immunomodulation) developed high sustained antibody titres. CRIM status was not a prespecified subgroup in the study, the number of CRIM-negative patients was very small and no statistical analyses were presented for these outcomes. **The study suggests that CRIM-negative patients taking alglucosidase alfa 40 mg/kg weekly may live longer and have better motor function than those taking the licensed dosage. However, this evidence is inconclusive.** **Less information was reported for CRIM-positive patients and the benefits and risks with 40 mg/kg compared with 20 mg/kg are not known for this subgroup.**
Abbreviations AIMS, Alberta Infant Motor Scale; CRIM, cross-reactive immunological material	

From the evidence selected, when do patients change dose of enzyme replacement therapy?

Outcome	Evidence statement
Change of dosage	In the study by Poelman et al. (2020), 6 patients with IOPD received alglucosidase alfa 20 mg/kg once every 2 weeks between 2003 and 2009. From 2009, all patients received 40 mg/kg once weekly.

	Between 2009 and 2014, dosages were increased to 40 mg/kg once weekly in the 4 surviving patients receiving 20 mg/kg once every 2 weeks because of clinical deterioration. Their median age was 4.1 years (range 1.5 to 9.4 years) at the time of the increase. No further information is reported. **Dosages were increased in patients taking 20 mg/kg once every 2 weeks when they deteriorated clinically at a mean age of 4.1 years.**

Abbreviations

IOPD, infantile-onset Pompe Disease

6. Discussion

The study included in the evidence review (Poelman et al. 2020) has serious limitations for determining the efficacy and safety of alglucosidase alfa **40 mg/kg once weekly** for treating IOPD compared with the **licensed dosage** (20 mg/kg once every 2 weeks). Most of the outcomes were considered to have very low certainty using modified GRADE. One efficacy outcome (retaining the ability to walk at 3 years of age) was considered to have low certainty.

The study provided no evidence to determine whether alglucosidase alfa 40 mg/kg once weekly improves health-related quality of life (a critical outcome) compared with the licensed dosage. Similarly, no evidence was available for exacerbation of cardiac dysfunction (an important outcome).

No evidence was identified to determine whether alglucosidase alfa **40 mg/kg weekly** improves outcomes compared with **current standard treatment** (20 mg/kg weekly for 3 months at diagnosis, followed by 20 mg/kg once every 2 weeks).

No evidence was identified to determine whether alglucosidase alfa **20 mg/kg weekly** improves outcomes compared with the **licensed dosage or current standard treatment**.

It is difficult to conduct high quality studies in rare diseases such as IOPD. Although the study by Poelman et al. (2020) was well designed and reported, considered objective outcomes and followed patients over many years, only 18 patients could be included. In addition, not all patients could be assessed for all outcomes because of death or serious illness. This limited the ability of the investigators to perform statistical analyses.

The study was a before and after observational study, meaning there was no concurrent comparator. Outcomes were compared in 6 infants diagnosed with IOPD and started on alglucosidase alfa 20 mg/kg once every 2 weeks (the licensed dosage) between 2003 and 2009 and 12 infants started on alglucosidase alfa 40 mg/kg once weekly between 2009 and 2016. Assessments were standardised but probably not blinded. This type of study is subject to bias and confounding and cannot prove that an intervention (such as alglucosidase alfa) caused an outcome, only that it is associated with that outcome.

Between 2009 and 2014, dosages were increased to 40 mg/kg once weekly in the 4 surviving patients receiving 20 mg/kg once every 2 weeks (median age 4.1 years, range 1.5 to 9.4 years) because their clinical condition worsened. It is possible that this dosage increase caused the difference between the groups to be less than it would have been if they had remained on 20 mg/kg once every 2 weeks, which may have affected some results. For example, more patients in the 20 mg/kg group may have died if their dosage had not been increased, and fewer of them may have had infusion-associated reactions.

From 2012, the study also assessed the effect of immunomodulation (rituximab, methotrexate and intravenous immunoglobulin) to see whether it improved outcomes in patients using alglucosidase alfa 40 mg/kg weekly by preventing the development of antibodies to treatment. Five of the 12 patients in the 40 mg/kg group received immunomodulation and the other 7 did not. The study authors concluded that immunomodulation may have contributed to the clinical stability of patients, but it did not prevent antibody formation. It is unclear whether immunomodulation affected outcomes in some patients in the 40 mg/kg group and, subsequently, direct comparisons with the 20 mg/kg group.

Maximum follow up was shorter in the 40 mg/kg group (8.3 years compared with 12.6 years in the 20 mg/kg group) and median age at the last assessment was younger (4.4 years compared with 9.6 years in the 20 mg/kg group). It is not known if these differences between the groups

may have affected comparisons for outcomes which are experienced after a longer period of time; for example, survival.

The AIMS and BDIS-II scales used in the study do not have validated minimal clinically important differences for IOPD, which makes it difficult to determine whether any observed changes are clinically meaningful.

The study provided evidence for only 2 potential adverse effects (infusion-associated reactions and antibody formation and detection) and this was of very low certainty. The summary of product characteristics for alglucosidase alfa reports that serious infusion-associated reactions that have been reported in infants with IOPD include urticaria, rales, tachycardia, decreased oxygen saturation, bronchospasm, tachypnoea, periorbital oedema and hypertension. Although infusion-associated reactions were often seen in the study and sometimes severe, the authors noted that they were treated successfully in all but 2 patients and had not recurred for at least 12 months.

No evidence was identified regarding the cost-effectiveness of alglucosidase alfa 20-40 mg/kg once weekly for IOPD.

7. Conclusion

This evidence review found limited low (one outcome) and very low certainty evidence for the efficacy and safety of alglucosidase alfa **40 mg/kg once weekly** for treating IOPD compared with the **licensed dosage** (20 mg/kg once every 2 weeks) for up to 8 years. Many of the results were unclear because of the small number of patients and the possible influence of confounding factors, such as dosage increases and differences between the groups. Any potential benefits of treatment must be balanced against the uncertain adverse effect profile of the 40 mg/kg weekly dosage in this population.

The study by Poelman et al. (2020) provides only very low certainty evidence for the critical outcomes. At the end of the study, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly survived compared with patients using the licensed dosage. However, the difference between the groups did not reach statistical significance for survival or ventilation-free survival. The study did not consider health-related quality of life.

There was also only very low certainty evidence for all but one of the important outcomes (Poelman et al. 2020). Overall, compared with patients using the licensed dosage, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly achieved walking outcomes, including achieving the ability to walk and maintaining ability to walk at the end of the study. However, the difference was reported to be statistically significant only for ability to walk at 3 years of age, with this outcome being the only one rated as low certainty (rather than very low certainty). Median AIMS and BSID-II scores and ranges (measures of motor development) and changes in LVMI Z-scores (a measure of IOPD-related cardiomyopathy) generally appeared similar in the 40 mg/kg and licensed dosage groups, but statistical analyses were not undertaken. Few patients in the study had gastrostomy placement and the difference between the groups was not statistically significant.

Only 2 potential adverse effects (infusion-associated reactions and antibody formation and detection) were reported by Poelman et al. (2020), and this evidence was of very low certainty. Overall, a higher proportion of patients using alglucosidase alfa 40 mg/kg once weekly had infusion-associated reactions compared with patients using the licensed dosage. Also, patients using 40 mg/kg generally had higher antibody titres. However, no statistical analyses were reported for these outcomes. No evidence was identified for exacerbation of cardiac dysfunction.

Regarding subgroups of patients who may benefit from treatment more than others, the study by Poelman et al. (2020) suggests that CRIM-negative patients taking alglucosidase alfa 40 mg/kg weekly may live longer and have better motor function than those taking the licensed dosage. However, few CRIM-negative patients were included in the study and this evidence is inconclusive. Less information was reported for CRIM-positive patients and the benefits and risks with 40 mg/kg compared with 20 mg/kg are not known for this subgroup.

Dosages were increased to 40 mg/kg weekly in all 4 surviving patients taking 20 mg/kg once every 2 weeks when they deteriorated clinically, which occurred at a mean age of 4.1 years.

No evidence was identified to determine whether alglucosidase alfa **40 mg/kg weekly** improves outcomes compared with **current standard treatment** (20 mg/kg weekly for 3 months at diagnosis, followed by 20 mg/kg once every 2 weeks).

No evidence was identified to determine whether alglucosidase alfa **20 mg/kg weekly** improves outcomes compared with the **licensed dosage or current standard treatment**.

No evidence was identified regarding the cost-effectiveness of alglucosidase alfa 20-40 mg/kg once weekly for IOPD.

Appendix A PICO document

The review questions for this evidence review are:

1. In IOPD what is the clinical effectiveness of enzyme replacement therapy given 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?
2. In IOPD what is the safety of enzyme replacement therapy given 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?
3. In IOPD what is the cost-effectiveness of enzyme replacement therapy given 20-40 mg/kg once weekly compared with the licensed dose or current standard treatment?
4. From the evidence selected, is there any data to suggest that there are particular subgroups of patients that would benefit from treatment with enzyme replacement therapy given 20-40 mg/kg once weekly more than others?
5. From the evidence selected, when do patients change dose of enzyme replacement therapy?

P –Population and Indication	Patients with classic IOPD[1] [Pompe disease is also known as acid maltase deficiency] Subgroups: • Treatment naïve patients • Patients already on enzyme replacement who are not invasively ventilated • Patients with discernible clinical decline, despite treatment with 20 mg/kg once weekly • Patients on invasive ventilation with a potentially reversible complication (continuing cardiomyopathy or bladder dysfunction)
I – Intervention	Enzyme replacement therapy with alglucosidase alfa given intravenously at a dose of 20-40 mg/kg once weekly
C – Comparator(s)	Enzyme replacement therapy with alglucosidase alfa given intravenously at a dose of 20 mg/kg once weekly for 3 months followed by 20 mg/kg once every 2 weeks OR Enzyme replacement therapy with alglucosidase alfa given intravenously at a dose of 20 mg/kg once every 2 weeks
O – Outcomes	There are no known standard minimal clinically important differences for any of the outcome measures for patients with IOPD. The clinical effectiveness outcomes may be reported from 3 months onwards apart from survival. **Clinical effectiveness** *Critical to decision-making:* • Survival This outcome is important to patients because it reflects how long people live after treatment, although it does not provide information about patients' health and wellbeing during that

[1] This includes infants with onset of symptoms before 1 year or those over 1 year with cardiomyopathy (as described first in Slonim et al. 2000).

	time. Without treatment, life expectancy is less than 2 years and even with current treatment, survival is not guaranteed. • Ventilation-free survival With currently available treatment, more than 50% of patients in the UK with IOPD require ventilatory support. Not requiring ventilation is a very important outcome for patients and their carers. • Health-related quality of life Quality of life is very important to patients and their carers as it provides a holistic evaluation and indication of the patient's general health and their and their carer's perceived well-being. *Important to decision-making:* • Rate of gastrostomy/jejunostomy placement Patients with IOPD may require gastrostomy or jejunostomy placement because of difficulty swallowing. This impedes the patient's ability to eat and drink normally and requires training for the carers to use. A reduction in gastrostomy/jejunostomy placement would be very important to patients. • Motor function (assessed by scales such as the Alberta Infant Motor Scale, AIMS) and motor milestones (including ambulation and rate of wheelchair utilisation) The ability for patients to meet motor milestones (including crawling and walking) are important to patients and carers as they are a marker of the development of the brain. • Resolution of disease-related complications such as clinically significant cardiomyopathy, urinary retention or spinal curvature. This is an important outcome to patients as resolution or reduction of these disease-related complications can reduce the number of times they need to be admitted to hospital or require emergency admissions. **Safety** • Drug-related adverse events (such as infusion-related reactions, respiratory disorders or others) • Exacerbation of cardiac dysfunction • IgG Antibody formation and detection (anti-rhGAA), to clinically significant titres greater than 12,800. This is an important outcome for patients as the formation of antibodies can affect the efficacy of treatment and may require other medications to be given alongside enzyme replacement therapy. **Cost-effectiveness**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2011-2021

Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, pre-print articles, commentaries, letters, editorials and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, INHHTA and HTA databases were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded. Trial registries were also searched.

Search date: 21 May 2021

Database search strategies
Database: Medline ALL
Platform: Ovid
Version: Ovid MEDLINE(R) ALL <1946 to May 20, 2021>
Search date: 21 May 2021
Number of results retrieved: 90
Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to May 20, 2021>
Search Strategy:
---
1 (alglucosidase or lumizyme* or myozyme* or pompase*).tw. (173)
2 Glycogen Storage Disease Type II/ (1729)
3 (glucosidase or pompe* or iopd*).tw. (17830)
4 ((type 2 or type-ii or generali*) adj5 stor* adj5 glyco*).tw. (434)
5 (acid maltase adj (deficien* or dis*)).tw. (296)
6 (gsd ii or gsd 2 or gsdii or gsd2*).tw. (217)
7 glycogenos*.tw. (1471)
8 (gaa adj (deficien* or dis*)).tw. (98)
9 mckusick 23230.tw. (1)
10 or/2-9 (19449)
11 exp child/ or exp infant/ or pediatrics/ (2565885)
12 (infan* or child* or paediat* or pediat*).tw. (1919241)
13 11 or 12 (3126167)
14 10 and 13 (2169)
15 1 and 14 (95)
16 limit 15 to english language (90)
17 animals/ not humans/ (4798035)
18 16 not 17 (90)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2021 May 20>
Search date: 21 May 2021
Number of results retrieved: 144
Search strategy:

Database: Embase <1974 to 2021 May 20>
Search Strategy:
---
1 alglucosidase alfa/ (67)
2 (alglucosidase or lumizyme* or myozyme* or pompase*).tw. (733)
3 1 or 2 (748)

4 glycogen storage disease type 2/ (4329)
5 (glucosidase or pompe* or iopd*).tw. (22140)
6 ((type 2 or type-ii or generali*) adj5 stor* adj5 glyco*).tw. (584)
7 (acid maltase adj (deficien* or dis*)).tw. (373)
8 (gsd ii or gsd 2 or gsdii or gsd2*).tw. (316)
9 glycogenos*.tw. (1599)
10 (gaa adj (deficien* or dis*)).tw. (186)
11 mckusick 23230.tw. (1)
12 or/4-11 (24465)
13 exp child/ or exp pediatrics/ (2778590)
14 (infan* or child* or paediat* or pediat*).tw. (2387078)
15 13 or 14 (3472027)
16 12 and 15 (3109)
17 3 and 16 (310)
18 limit 17 to english language (301)
19 nonhuman/ not human/ (4792507)
20 18 not 19 (296)
21 limit 20 to (conference abstract or conference paper or "conference review") (152)
22 20 not 21 (144)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue X of 12, Month year
CENTRAL – Issue X of 12, Month year
Search date: 21 May 2021
Number of results retrieved: CDSR –1 ; CENTRAL – 9.

ID	Search	Hits
#1	alglucosidase or lumizyme* or myozyme* or pompase*	53
#2	MeSH descriptor: [Glycogen Storage Disease Type II] this term only	32
#3	glucosidase or pompe* or iopd*	1187
#4	((type 2 or type-ii or generali*) near/5 stor* adj5 glyco*)	3
#5	(acid maltase next (deficien* or dis*))	4
#6	"gsd ii" or gsd 2 or gsdii or gsd2*	105
#7	glycogenos*	16
#8	(gaa next (deficien* or dis*))	3
#9	"mckusick 23230"	0
#10	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9	1297
#11	MeSH descriptor: [Child] explode all trees	57029
#12	MeSH descriptor: [Infant] explode all trees	32600
#13	MeSH descriptor: [Pediatrics] explode all trees	692
#14	infan* or child* or paediat* or pediat*	219870
#15	#11 or #12 or #13 or #14	219880
#16	#10 and #15	157
#17	#1 and #16	28
#18	"conference":pt or (clinicaltrials or trialsearch):so	543843
#19	#17 not #18	11

Database: INAHTA database
Platform: INAHTA
Version: 21 May 2021
Search date: 21 May 2021
Number of results retrieved: 3
Search strategy:
alglucosidase or lumizyme or myozyme or pompase

Database: HTA database
Platform: CRD
Version: Up to 2018
Search date: 21 May 2021
Number of results retrieved: 3
Search strategy:
alglucosidase or lumizyme* or myozyme* or pompase*

Trials registry search strategies

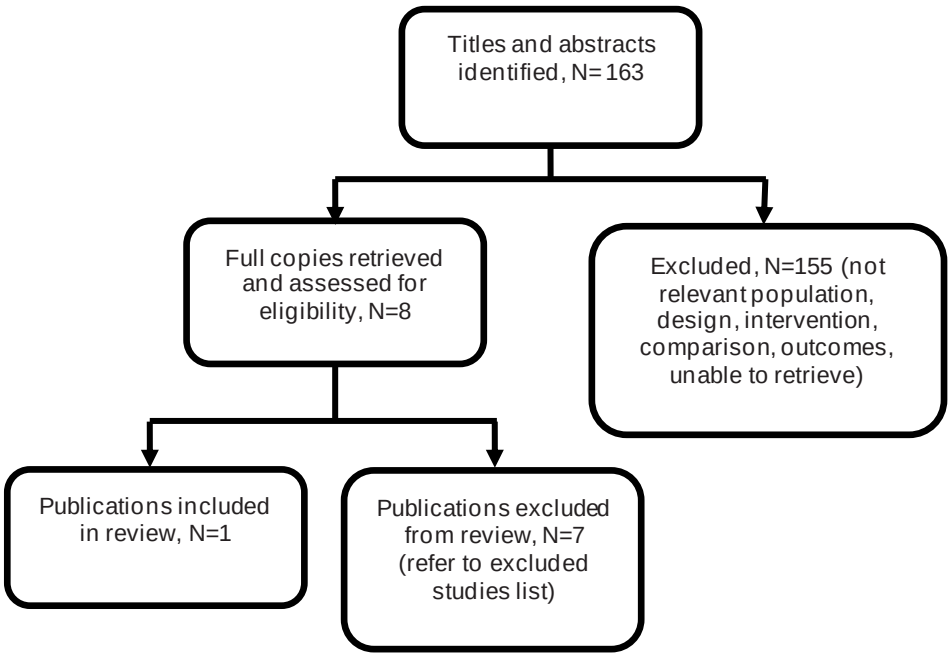
Clinicaltrials.gov
Search date: 21 May 2021
Number of results retrieved: 12
Search strategy:
alglucosidase AND Pompe Disease Infantile-Onset

Clinicaltrialsregister.eu
Search date: 21 May 2021
Number of results retrieved: 0 (relevant results found from clinicaltrials.gov)
Search strategy:
alglucosidase AND Pompe AND Infantile

Appendix C Evidence selection

Example text: The literature searches identified 163 references. These were screened using their titles and abstracts and 8 references were obtained in full text and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 7 references were excluded and are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection - decision and rationale if excluded
Poelman E, van den Dorpel JJA, Hoogeveen-Westerveld M, et al. Effects of higher and more frequent dosing of alglucosidase alfa and immunomodulation on long-term clinical outcome of classic infantile Pompe patients. Journal of Inherited Metabolic Diseases. 2020, 43(6):1243-1253. doi: 10.1002/jimd.12268	Included
Chien Y-H, Tsai W-H, Chang C-L, et al. Earlier and higher dosing of alglucosidase alfa improve outcomes in patients with infantile-onset Pompe disease: evidence from real-world experiences. Molecular Genetics Metabolic Reports. 2020, 23:100591. doi: 10.1016/j.ymgmr.2020.100591	Exclude: no comparator group, heterogeneous dosing
Khan AA, Case LE, Herbert M, et al. Higher dosing of alglucosidase alfa improves outcomes in children with Pompe disease: a clinical study and review of the literature. Genetic Medicine. 2020, 22(5):898-907. doi: 10.1038/s41436-019-0738-0	Exclude: no comparator group, mixed population, results for cases not pooled

Appendix D Excluded studies table

Study reference	Reason for exclusion
Case, Laura E, Bjartmar, Carl, Morgan, Claire et al. (2015) Safety and efficacy of alternative alglucosidase alfa regimens in Pompe disease. Neuromuscular disorders : NMD 25(4): 321-32	Mixed population, no appropriate comparator group
Chen, Min; Zhang, Lingli; Quan, Shuyan (2017) Enzyme replacement therapy for infantile-onset Pompe disease. The Cochrane database of systematic reviews 11: cd011539	The review identified no relevant randomised or quasi-randomised controlled trials at the time of the searches in November 2016
Chien, Yin-Hsiu, Tsai, Wen-Hui, Chang, Chaw-Liang et al. (2020) Earlier and higher dosing of alglucosidase alfa improve outcomes in patients with infantile-onset Pompe disease: Evidence from real-world experiences. Molecular genetics and metabolism reports 23: 100591	No comparator group, heterogeneous dosing
Desai, Ankit K, Walters, Crista K, Cope, Heidi L et al. (2018) Enzyme replacement therapy with alglucosidase alfa in Pompe disease: Clinical experience with rate escalation. Molecular genetics and metabolism 123(2): 92-96	No comparator group, results for cases not pooled
Khan, Aleena A, Case, Laura E, Herbert, Mrudu et al. (2020) Higher dosing of alglucosidase alfa improves outcomes in children with Pompe disease: a clinical study and review of the literature. Genetics in medicine : official journal of the American College of Medical Genetics 22(5): 898	No comparator group, mixed population, results for cases not pooled
Spada, Marco, Pagliardini, Veronica, Ricci, Federica et al. (2018) Early higher dosage of alglucosidase alpha in classic Pompe disease. Journal of pediatric endocrinology & metabolism : JPEM 31(12): 1343-1347	No comparator group, only 1 participant received a weekly dose
van Gelder, C M, Poelman, E, Plug, I et al. (2016) Effects of a higher dose of alglucosidase alfa on ventilator-free survival and motor outcome in classic infantile Pompe disease: an open-label single-center study. Journal of inherited metabolic disease 39(3): 383-390	Duplicate participants, preliminary results for a subgroup of participants in the larger and longer study by Poelman et al. (included)

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Poelman E, van den Dorpel JAA, Hoogeveen-Westerveld M et al. (2020) Effects of higher and more frequent dosing of alglucosidase alfa and immunomodulation on long-term clinical outcome of classic infantile Pompe patients. Journal of inherited metabolic disease 43(6): 1243-1253 **Study location** The Netherlands **Study type** Prospective observational study using standardised assessments (before and after study) **Study aim** 'To compare the long-term outcome of classic infantile Pompe patients treated with 20 mg/kg alglucosidase alfa once every 2 weeks to those treated with 40 mg/kg/week and to study the additional effect of immunomodulation.' **Study dates** 2003 to 31 December 2016	**Inclusion criteria** All Dutch patients newly diagnosed with classic IOPD who were treated with alglucosidase alfa between 2003 and 2016 **Exclusion Criteria** None reported **Total sample size** 18 patients **No. of participants in each treatment group** 6 infants were given alglucosidase alfa 20 mg/kg once every 2 weeks were 2003 and 2009 (comparator group) 12 infants were given alglucosidase alfa 40 mg/kg once weekly from 2009 (intervention group) **Baseline characteristics** At baseline, median age was lower in the 20 mg/kg comparator group (1.5 months versus 3.6 months) 3/12 (25%) patients in the intervention group and 2/6 (33%) patients in the comparator group were CRIM-negative	**Intervention** Alglucosidase alfa 40 mg/kg IV once weekly (off label dosage) Maximum follow up 8.3 years 5/12 patients also received immunomodulation with rituximab, methotrexate and intravenous immunoglobulin. 7/12 did not The study concluded that immunomodulation may have contributed to the clinical stability of patients, but it did not prevent antibody formation **Comparator** Alglucosidase alfa 20 mg/kg IV once every 2 weeks (licensed dosage) 4/6 (67%) patients had their dosage increased to 40 mg/kg weekly at ages ranging from 1.5 to 9.4 years (median 4.1 years) because of clinical deterioration Maximum follow up 12.6 years .	**Critical outcomes** **Survival** At the end of the study,11/12 (92%) patients survived in the 40 mg/kg group compared with 4/6 (67%) patients in the 20 mg/kg group (p=0.25, no statistically significant difference) 3 patients died because of respiratory failure; 1/3 CRIM-positive patients from the 40 mg/kg group and 2/2 CRIM-negative patients from the 20 mg/kg group **Ventilation-free survival** At the end of the study,11/12 (92%) patients survived without requiring ventilation in the 40 mg/kg group compared with 3/6 (50%) patients in the 20 mg/kg group (p=0.08, no statistically significant difference) **Health-related quality of life** No measures of quality of life were reported **Important outcomes** **Rate of gastrostomy/jejunostomy placement** At the end of the study, 1/12 (8%) patients in the 40 mg/kg group had received percutaneous endoscopic gastrostomy compared with 2/6 (33%) patients in the 20 mg/kg group 10/12 (83%) patients in the 40 m/kg group fed orally at the end of the study compared with 3/12 (25%) at baseline, and 1/12 (8%) patients had a nasogastric tube compared with 9/12 (75%) at baseline 3/6 (50%) patients in the 20 mg/kg group fed orally at the end of the study compared with none at baseline, and 1/6 (17%) patients had a nasogastric tube compared with 6/6 (100%) at baseline	This study was appraised using the National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no (concurrent) control group 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. No 7. Yes 8. Not reported, probably not 9. Yes 10. Sometimes 11. Yes 12. Not applicable Quality rating: fair Other comments: The study was a prospective 'before and after' observational study that compared outcomes in infants newly diagnosed with Pompe disease between 2003 and 2009 who were started on the licensed dosage of alglucosidase alfa with outcomes in infants newly diagnosed between 2009 and 2016 who were started on a higher, more frequent dosage of the same treatment. There is no concurrent comparator in the study, the sample size is small, and few statistical analyses could be undertaken. Therefore, the study is rated as poor in the hierarchy of study designs. However, there are few eligible participants for

			No statistical analyses were reported for these outcomes. **Motor function** The ability to walk was achieved by 11/12 (92%) patients in the 40 mg/kg group and 4/6 (67%) patients in the 20 mg/kg group (no statistical analysis reported) At the age of 3 years, 11/12 (92%) patients in the 40 mg/kg group maintained the ability to walk compared with 2/6 (33%) patients in the 20 mg/kg group (p=0.02, statistically significant difference) At the end of the study, 10/12 (83%) patients in the 40 mg/kg group maintained the ability to walk compared with 1/6 (17%) patients in the 20 mg/kg group (no statistical analysis reported). Median AIMS and BSID-II scores and ranges were generally similar in the 2 groups. No statistical analyses were reported for these outcomes. At 12 months, the median AIMS score was 39 (range 20-50) in the 40 mg/kg group and 37 (range 20-45) in the 20 mg/kg group (5 patients only because 1 had died) At 18 months, the median AIMS score was 57 (range 34-58) in the 40 mg/kg group and 54 (range 25-57) in the 20 mg/kg group (5 patients only because 1 had died) Only 6 patients reached the maximum AIMS score of 58. All were in the in the 40 mg/kg group (2 were CRIM-negative) At 24 months, the median BSID-II score was 18 (range 14-25) in the 40 mg/kg group and 17 (range 10.4-21) in the 20 mg/kg group (3 patients only because 1 had died and 2 needed invasive ventilation) At 36 months, the median BSID-II score was 30 (range 19-33) in the 40 mg/kg group (11 patients only because 1 had died) and 20 (range 20-32) in the 20 mg/kg group (3 patients only because 1 had died and 2 needed invasive ventilation)	studies in rare diseases such as Pompe disease, meaning it is difficult to conduct high quality studies. Taking this into account, the study is well designed and reported, most outcomes are relatively objective, and maximum follow up was 12.6 years. Therefore, using this assessment tool, quality of the study is rated as fair. Source of funding: Prinses Beatrix Spierfonds; ZonMw; Erasmus Universitair Medisch Centrum; Sarepta Therapeutics; Amicus Therapeutics; Ministry of Economic Affairs; Sanofi-Genzyme; Conselho Nacional de Desenvolvimento Científico e Tecnológico; Metakids; Tex Net; Sophia Foundation for Medical Research

			Only 3/6 (50%) patients in the 20 mg/kg group compared with 11/12 (92%) patients in the 40 mg/kg group could be adequately tested with the BSID-II at 36 months. **Resolution of disease-related complications** The study assessed change in LVMI and results were presented graphically. Changes in LVMI Z-scores were similar between the groups and generally improved (no statistical analysis) LVMI did not normalise in 1 patient in the 20 mg/kg group who died after 3 months of treatment. 2 patients in the 40 mg/kg group had severe cardiomyopathy at baseline, which responded well to treatment, although LVMI was still slightly elevated at the last assessment in 1 patient **Safety** **Drug-related adverse events** The rate of drug-related adverse events in general was not reported 8/12 (67%) patients in the 40 mg/kg group experienced infusion-associated reactions compared with 5/6 (83%) patients in the 20 mg/kg group (no statistical analysis reported) 134 infusion-associated reactions (11 severe) were seen in the 40 mg/kg group compared with 64 reactions (4 severe) in the 20 mg/kg group In all but 2 patients, reactions were treated successfully and had not recurred for at least 12 months **Exacerbation of cardiac dysfunction** The rate of exacerbation of cardiac dysfunction was not reported **Antibody formation and detection** The median peak antibody titre was 1:156,250 (range 1:250 to 1:800,000) in the 40 mg/kg group and 1:6250 (range 1:1250 to 1:31,250) in the 20 mg/kg group 2/6 (33%) patients in the 20 mg/kg group and 7/12 (58%) patients in the 40 mg/kg group	

			developed high sustained titres of 1:31,500 or more All CRIM-negative patients in the 40 mg/kg group developed high sustained antibody titres whether they received immunomodulation or not	

Abbreviations

AIMS, Alberta Infant Motor Scale, a 58-item scale to assess motor development in infants aged 18 months or less, with lower scores indicating delayed development; BSID-II, Bayley Scales of Infant Development II, which consists of 3 scales (motor, mental and behaviour) to assess development in infants aged 1 to 42 months, with a score of 100 being average for age, and lower scores indicating delayed development; CRIM, cross-reactive immunological material; IOPD, infantile-onset Pompe Disease; IV, intravenously; LVMI, left ventricular mass index, a measure of cardiomyopathy

Appendix F Quality appraisal checklists

The National Institutes of Health (NIH) quality assessment tool for before-after (Pre-Post) study with no (concurrent) control group

Major Components	**Response options** • Yes • No • Other (cannot determine/ not applicable/ not reported)
1. Was the study question or objective clearly stated?	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes
5. Was the sample size sufficiently large to provide confidence in the findings?	No
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	No
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	Not reported, probably not
9. Was the loss to follow up after baseline 20% or less? Were those lost to follow up accounted for in the analysis?	Yes
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Sometimes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	Yes
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	Not applicable
Quality Rating (good/ fair/ poor)	Fair
Additional Comments: The study was a prospective 'before and after' observational study that compared outcomes in infants newly diagnosed with Pompe disease between 2003 and 2009 who were started on the licensed dosage of alglucosidase alfa with outcomes in infants newly diagnosed between 2009 and 2016 who were started on a higher, more frequent dosage of the same treatment. There is no concurrent comparator in the study, the sample size is small, and few statistical analyses could be undertaken. Therefore, the study is rated as poor in the hierarchy of study designs. However, there are few eligible participants for studies in rare diseases such as Pompe disease, meaning it is difficult to conduct high quality studies. Taking this into account, the study is well designed and reported, most outcomes are relatively objective, and maximum follow up was 12.6 years. Therefore, using this assessment tool, quality of the study is rated as fair.	

Appendix G GRADE profiles

Table 2: Question: In IOPD, what is the clinical effectiveness and safety of alglucosidase alfa 40 mg/kg once weekly compared with the licensed dose, 20 mg/kg once every 2 weeks?[1]

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	40 mg/kg once weekly	20 mg/kg once every 2 weeks	Result (95%CI)		
Survival (prospective observational before and after study using standardised assessments)									
Number of patients surviving at the end of the study (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	11/12 (92%) patients survived	4/6 (67%) patients survived	p=0.25, no statistically significant difference	Critical	Very low
Ventilation-free survival (prospective observational before and after study using standardised assessments)									
Number of patients surviving at the end of the study (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	11/12 (92%) patients survived ventilation-free	3/6 (50%) patients survived ventilation-free	p=0.08, no statistically significant difference	Critical	Very low
Rate of gastrostomy/jejunostomy placement (prospective observational before and after study using standardised assessments)									
Number of patients receiving percutaneous endoscopic gastrostomy at the end of the study (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	1/12 (8%) patients underwent gastrostomy	2/6 (33%) patients underwent gastrostomy	No statistical analysis reported	Important	Very low
Motor function (prospective observational before and after study using standardised assessments)									
Number of patients becoming able to walk									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	11/12 (92%) patients	4/6 (67%) patients	No statistical analysis reported	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**40 mg/kg once weekly**	**20 mg/kg once every 2 weeks**	**Result (95%CI)**		
Number of patients still able to walk at 3 years of age									
1 before and after study Poelman et al. 2020	No serious limitations	No serious indirectness	Not applicable	Not calculable	11/12 (92%) patients	2/6 (33%) patients	p=0.02, statistically significant difference	Important	Low
Number of patients still able to walk at the end of the study (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	10/12 (83%) patients	1/6 (17%) patients	No statistical analysis reported	Important	Very low
Median AIMS score at 12 months of age (a 58-item scale, with lower scores indicating delayed development)									
1 before and after study Poelman et al. 2020	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	39 (range 20-50)	37 (range 20-45)	No statistical analysis reported	Important	Very low
Median AIMS score at 18 months of age (a 58-item scale, with lower scores indicating delayed development)									
1 before and after study Poelman et al. 2020	Serious limitations[4]	No serious indirectness	Not applicable	Not calculable	57 (range 34-58)	54 (range 25-57)	No statistical analysis reported	Important	Very low
Median BSID-II score at 24 months of age (a score of 100 is average for age, with lower scores indicating delayed development)									
1 before and after study Poelman et al. 2020	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	18 (range 14-25)	17 (range 10.4-21)	No statistical analysis reported	Important	Very low
Median BSID-II score at 36 months of age (a score of 100 is average for age, with lower scores indicating delayed development)									
1 before and after study Poelman et al. 2020	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	30 (range 19-33)	20 (range 20-32)	No statistical analysis reported	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	40 mg/kg once weekly	20 mg/kg once every 2 weeks	Result (95%CI)		
Resolution of disease-related complications (prospective observational before and after study using standardised assessments)									
Changes in LVMI Z-scores over the course of the study (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	Results presented graphically. Scores improved	Results presented graphically. Scores improved	No statistical analysis reported	Important	Very low
Infusion-associated reactions (prospective observational before and after study using standardised assessments)									
Number of patients who had infusion-associated reactions (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	8/12 (67%) patients	5/6 (83%) patients	No statistical analysis reported	Safety	Very low
Number of infusion-associated reactions (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	134 reactions	64 reactions	No statistical analysis reported	Safety	Very low
Number of severe infusion-associated reactions (maximum follow up 8.3 years in the intervention group and 12.6 years in the comparator group)									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	11 reactions	4 reactions	No statistical analysis reported	Safety	Very low
Antibody formation and detection (prospective observational before and after study using standardised assessments)									
Median peak antibody titre									
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	1:156,250 (range 1:250 to 1:800,000)	1:6250 (range 1:1250 to 1:31,250	No statistical analysis reported	Safety	Very low
Number of patients who developed high sustained antibody titres of 1:31,500 or more									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	40 mg/kg once weekly	20 mg/kg once every 2 weeks	Result (95%CI)		
1 before and after study Poelman et al. 2020	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	7/12 (58%) patients	2/6 (33%) patients	No statistical analysis reported	Safety	Very low

Abbreviations

AIMS, Alberta Infant Motor Scale; BSID-II, Bayley Scales of Infant Development II; IOPD, infantile-onset Pompe disease; LVMI, left ventricular mass index

1 No studies were identified comparing alglucosidase alfa 40 mg/kg once weekly with current standard treatment (alglucosidase alfa 20 mg/kg once weekly for 3 months at diagnosis, followed by 20 mg/kg once every 2 weeks). Also, no studies were identified comparing alglucosidase alfa 20 mg/kg once weekly with the licensed dosage or current standard treatment.
2 Downgraded. Dosages were increased to 40 mg/kg once weekly in 4 surviving patients (median age 4.1 years) receiving 20 mg/kg once every 2 weeks because of clinical deterioration. It is possible that this dosage increase caused the difference between the groups to be less than it would have been if they had remained on 20 mg/kg once every 2 weeks.
3 Downgraded. No statistical analysis was reported for this outcome. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes.
4 Downgraded. No statistical analysis was reported for this outcome. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. 1 patient in the comparator group could not be assessed because they had died. This scale has not been validated in Pompe disease.
5 Downgraded. No statistical analysis was reported for this outcome. The study authors reported that statistical analyses could only be applied for a limited number of outcome measures because of the small sample sizes. 3 patients in the comparator group could not be assessed because 1 had died and 2 needed invasive ventilation. This scale has not been validated in Pompe disease.

Glossary

Alberta Infant Motor Scale (AIMS)	A 58-item scale to assess motor development in infants aged 18 months or less, with lower scores indicating delayed development
Bayley Scales of Infant Development II; BSID-II	Consists of 3 scales (motor, mental and behaviour) to assess development in infants aged 1 to 42 months, with a score of 100 being average for age, and lower scores indicating delayed development

References

Included studies

- Poelman E, van den Dorpel JAA, Hoogeveen-Westerveld M et al. (2020) Effects of higher and more frequent dosing of alglucosidase alfa and immunomodulation on long-term clinical outcome of classic infantile Pompe patients. Journal of inherited metabolic disease 43(6): 1243-1253

Other references

- Sanofi Genzyme (2021) Summary of product characteristics for Myozyme

NHS England and NHS Improvement
Skipton House
80 London Road
London
SE1 6LH