Common Drug Review
Clinical Review Report

January 2018

Drug	taliglucerase alfa (Elelyso) (30 to 60 U/kg intravenous infusion)
Indication	Long-term enzyme replacement therapy for adults and children (2 to 17 years old) with a confirmed diagnosis of type 1 Gaucher disease and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 Gaucher disease.
Listing request	As per indication
Manufacturer	Pfizer Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in pediatric inherited metabolic diseases who provided input on the conduct of the review and the interpretation of findings.

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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ABBREVIATIONS

AE	adverse event
Ab	antibody
BMD	bone mineral density
BW	biweekly
CCL18	Chemokine (C-C motif) ligand 18
CDR	CADTH Common Drug Review
CHQ-PF28	Child Health Questionnaire–Parent Form 28
CP	completer population
DB	double-blind
DEXA	dual-energy X-ray absorptiometry
ERT	enzyme replacement therapy
GD	Gaucher disease
Hb	hemoglobin
HRQoL	health-related quality of life
ICGG	International Collaborative Gaucher Group
IgG	immunoglobulin G
IV	intravenous
LOCF	last observation carried forward
MCID	minimal clinically important difference
MD	mean difference
mITT	modified intention-to-treat population
MN	multiples of normal
MRI	magnetic resonance imaging
NGFC	National Gaucher Foundation of Canada
OL	open-label
plt	platelet
QCSI	quantitative chemical shift imaging
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SDS	standard deviation score
SGDG	Spanish Gaucher Disease Group
SRT	substrate reduction therapy
TALI	taliglucerase alfa
WDAE	withdrawal due to adverse events

EXECUTIVE SUMMARY

Introduction

Gaucher disease (GD) is an autosomal, recessively inherited disease that results from deficiency of the lysosomal enzyme glucocerebrosidase, which causes the enzyme's substrate, glucocerebroside, to accumulate in macrophages in the spleen, liver, bone marrow, and lung(s). This leads to multiple manifestations, including anemia, thrombocytopenia, hepatosplenomegaly, growth retardation, skeletal disease, and increased rates of malignancies. GD is classified into three subtypes based on the presence and nature of central nervous system involvement.[1,2]

The most prevalent form (95%) is the non-neuronopathic type 1 variant. Type 2 GD is the acute neuronopathic form characterized by early onset, within one year after birth, and premature death by ages two to four.[3] Type 3 GD is the subacute, neuronopathic form with a later onset than type 2 GD and a slower progression of similar manifestations. The prevalence of GD is approximately one in 50,000 to 100,000 globally,[4] reaching frequencies of one in 400 to one in 600 among Ashkenazi Jewish people.[5]

The Ontario guidelines for treatment of GD[6] recommend two pharmacotherapeutic modalities to prevent the accumulation of glucocerebroside in patients with GD with moderate to severe clinical symptoms of the disease.[7] Enzyme replacement therapy (ERT), which replaces the missing or defective lysosomal enzyme, has been used as a first-line treatment for type 1 GD for more than two decades.[8] ERT is administered by intravenous (IV) infusion. The indicated initial treatment regimen varies from 2.5 U/kg three times a week to 60 U/kg biweekly.[9,10] According to the clinical expert involved in this review, biweekly treatments are favoured for their convenience, and the typical dose is 30 U/kg. However, dosing may be individualized to each patient.[6] In addition to taliglucerase alfa (TALI), other ERTs available in Canada are imiglucerase (Cerezyme)[9] and velaglucerase alfa (VPRIV).[10] Substrate reduction therapy (SRT) aims to decrease the production of glucocerebroside rather than accelerating its elimination. Only one medication used for SRT is available in Canada. Miglustat (Zavesca) is an oral drug indicated for the treatment of adults with mild to moderate type 1 GD for whom ERT is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access).[11] Evidence suggests that miglustat 100 mg three times a day is less efficacious than ERT and is associated with increased adverse events (AEs), but its oral formulation is more convenient than IV infusions.[6]

TALI is a recombinant form of human glucocerebrosidase expressed in carrot cells in culture. It replaces the defective enzyme in GD, principally in macrophages. As with other ERTs, TALI cannot cross the blood-brain barrier and does not have benefits with regard to the neurological symptoms of GD. TALI is available as a lyophilized, sterile powder in a single-use vial designed to deliver 200 U of TALI for IV infusion upon reconstitution and dilution. TALI is administered intravenously over one to two hours every two weeks. Initial doses range from 30 U/kg to 60 U/kg, but this dose can be adjusted thereafter.

Indication under review
Long-term enzyme replacement therapy for adults and children (2 to 17 years old) with a confirmed diagnosis of type 1 GD and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 GD.
Listing criteria requested by sponsor
As per indication

The objective of this systematic review is to assess the beneficial and harmful effects of TALI for the treatment of adults and children (two to 17 years old) with a confirmed diagnosis of type 1 GD, and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 GD.

Results and Interpretation

Included Studies

The evidence included in this review was derived from four phase 3, multi-centre trials that evaluated the efficacy and safety of TALI IV infusions biweekly in adults (N = 120) and pediatric patients (N = 16, of which two were confirmed type 3 GD patients) with GD. Previously untreated patients enrolled in studies PB-06-001 (Study 001) and PB-06-005 (Study 005) were randomized between two groups that received either 30 U/kg or 60 U/kg of TALI biweekly. Patients and investigators in these two trials were blinded to dosing. Study 001 (N = 33) enrolled only adults and had a nine-month duration. The primary objective of Study 001 was to compare two doses of TALI for the percentage change from baseline of spleen volume in untreated patients. Study 001 was the only one to conduct statistical analyses. Study 005 (N = 11) enrolled only pediatric patients and lasted for 12 months. The primary objective of Study 005 was to compare two doses of TALI on the median percentage change in hemoglobin levels from baseline. Patients in studies PB-06-002 (Study 002) and PB-06-004 (Study 004) were previously on imiglucerase and were switched to TALI administered at a dose of enzyme equivalent to their previous imiglucerase dose, or the dose received before imiglucerase shortage. Study 002 (N = 33) enrolled stable adult and pediatric patients on imiglucerase and lasted nine months. The primary objective of Study 002 was to evaluate the clinical stability of patients, as assessed by platelet counts, hemoglobin levels, and spleen and liver volumes. [redacted]

Other efficacy outcomes included growth in children, biomarkers (chitotriosidase and Chemokine [C-C motif] ligand 18 [CCL18] levels), and bone density (with dual-energy X-ray absorptiometry [DEXA] and quantitative chemical shift imaging [QCSI]). Quality of life (QoL) was assessed in a few pediatric patients with the Child Health Questionnaire Parent Form 28 (CHQ-PF28). End points were measured at nine months and 12 months. In all trials, efficacy was based on surrogate outcomes, which are routinely used in clinical practice. Health-related quality of life (HRQoL) was not assessed in the majority of patients, even though overall health was reported as an important treatment target by the clinical expert consulted for this review. As reported by a patient group and by the clinical expert involved in this review, bone crises were among the most important concerns for patients with GD. Bone pain was recorded as an AE and occurred in 3.8% of patients, but given the small sample sizes and the lack of comparison groups, no conclusions on the efficacy of TALI for this outcome could be drawn.

The four trials were limited by the lack of a control group, preventing a comparison of TALI to the standard of care (i.e., other ERTs available in Canada). All patients and investigators were aware they were receiving or giving TALI during the studies, and therefore there is a high probability that subjective outcomes like HRQoL could be influenced. In Studies 002, 004, and 005, the sample sizes were not based on power calculations, statistical inferences were not reported, and missing data were not imputed. This is likely to be in favour of the efficacy of the study drug. The small sample size of all studies made it unlikely that uncommon AEs would be detected and impaired the generalizability to the general GD population. Data on pediatric patients (N = 16) and on patients with type 3 GD (N = 2) were limited. Low discontinuation rates and good compliance were reported over nine and 12 months for studies 001, 002, and 005, but higher discontinuation rates were reported for Study 004, in which the population was more likely to be responders to and able to tolerate TALI because they were ERT-experienced patients.

The baseline characteristics of the patients enrolled in the trials appeared to be representative of patients with GD seen in Canadian clinical practice, but due to imiglucerase shortage, there is a possibility that patients in studies 002 and 004 were not optimally treated with ERT at baseline.

In addition to the studies that met the inclusion criteria for the review, evidence from a manufacturer-submitted extension study (Study 003) and three systematic reviews of ERTs for GD are summarized and critically appraised as supplemental issues. Study 003 was an extension study that enrolled 45 patients from studies 001 and 002 and reported end points after 36 months and 39 months of ERT.

Efficacy

Hemoglobin levels were improved from baseline (statistically significant for both dose groups in Study 001) when treatment-naive patients were treated with TALI at 30 U/kg and 60 U/kg doses for nine, 12, or 39 months. At end point, previously untreated patients met normal hemoglobin values suggested as therapeutic target,[6,12] but many patients in studies 001 and 005 were only very mildly anemic at baseline. When patients were switched from imiglucerase to TALI, hemoglobin levels remained stable after nine (studies 002 [redacted]) and 39 months (Study 003).

The platelet counts improved from baseline in treatment-naive patients treated with TALI for nine to 12 months, with numerically better improvements after 39 months. Increases were numerically higher in pediatric patients (increases from 30.9% to 73.7%) than in adults (increases from 15.2% to 63.8%). In Study 001, the only study with statistical inferences, the increase from baseline to nine months was only statistically significant in patients who received 60 U/kg TALI, and a statistically significant difference was observed between the two dosing groups. Adult patients with lower platelet counts at baseline had an increase of 50% after nine months, as targeted by clinical practice guidelines,[6,12] but remained thrombocytopenic on average. Pediatric patients had higher values at baseline and reached normal values after 12 months. Most of the patients in studies 002 [redacted] who were switched from imiglucerase to TALI had maintenance or numerical increase in platelet counts in the range of normal values.

Patients who were previously untreated had decreases in spleen volume from baseline (statistically significant in Study 001) ranging from 26.9% to 41.1% after nine and 12 months, and from 47% to 62% after 36 months. These values are consistent with the expected decreases as per guidelines[6,12] for treatment of patients with GD. In patients who were previously treated with imiglucerase and then switched to TALI, spleen volume was maintained over nine months and numerically decreased over 36 months.

Previously untreated patients who received TALI had liver volume decreases from baseline ranging from 6.3% to 14.0% across trials after nine and 12 months, and by approximately 25% after 36 months. The increase was statistically significant for both dose groups in Study 001. These results were below the therapeutic target suggested by clinical practice guidelines.[6,12] Patients switched from imiglucerase to TALI had their liver volume maintained after nine and 36 months.

Child growth and HRQoL were measured in Study 005, which had a very small sample size, including two patients with type 3 GD. Although patients had numerical increases in height and weight from baseline after 12 months, changes from baseline in height and weight based on chronological age and bone age were not significant. As acknowledged by the clinical expert involved in the review, the few patients in that study were heterogeneous for age at baseline. Thus, it was difficult to draw conclusions for these growth-related end points. The score for general health of CHQ-PF28 numerically increased from

baseline at 12 months, but the validity of this instrument for patients with GD has not been demonstrated in the literature. This type of outcome is also sensitive to ascertainment bias, of which there was a high risk in Study 005.

Chitotriosidase and CCL18 were measured as biomarkers for GD. Treatment-naive patients had improvements from baseline in both biomarkers after nine and 12 months, and this response was numerically greater after 39 months. No specific therapeutic targets were identified for biomarkers. In patients who switched from imiglucerase to TALI, numerical improvements from baseline were observed in chitotriosidase activities but CCL18 levels were stable after nine months, while both biomarkers appeared improved from baseline after 39 months. These results indicate that TALI had a biological effect per its mechanism of action, as expected.

Bone disease was evaluated with z score, t score, and bone mineral density (BMD) and QCSI scores at nine, 12, and 36 months. According to the clinical expert involved in the review, the differences observed were too small to be clinically relevant. Also, results from Study 005 were too heterogeneous to be interpreted. The clinical expert questioned the value of DEXA and QCSI scores for short duration clinical trials in GD, especially in children.

In Study 001, the comparison of the 30 U/kg dose with the 60 U/kg dose for TALI did not show a statistically significant difference except for platelet counts. Hence, a higher dose of TALI did not appear to add additional clinical benefits for patients with GD.

The individual results of two type 3 GD patients showed no or very few benefits for hemoglobin, platelet counts, spleen volume, and liver volume. Therefore, the efficacy data to support the use of TALI for type 3 GD patients is very limited.

Notwithstanding all the limitations mentioned for the trials, based on a naive side-by-side comparison with the results of three systematic reviews on ERTs for GD, the efficacy results observed for TALI do not appear to be different from efficacy results reported for other ERTs. However, there are numerous limitations with naive or informal indirect comparisons, meaning there is a high degree of uncertainty with respect to this type of comparison between ERTs.

Harms

The small population under review and the lack of power to detect changes in AEs rendered the chance of detecting infrequently occurring AEs improbable. Overall rates for AEs ranged from 68.8% to 100%. Incidence rates of AEs did not appear to be associated with a specific dose of TALI. The most common AEs were headache (total occurrence of 19.7%), arthralgia (16.7%), upper respiratory tract infection (14.4%), and nasopharyngitis (12.9%), which are often reported as AEs in clinical trials. Serious adverse events (SAEs) occurred in 4.5% of patients. Neither a trend in the nature of SAEs, nor an association with a dosing regimen, was observed. Withdrawal due to adverse events (WDAEs) occurred in 3% of all patients, all related to hypersensitivity or infusion-related reactions. No deaths occurred during the trials.

Notable harms were determined a priori and included hypersensitivity reactions, particularly anaphylaxis, infusion-related reactions, and positive detection of anti-TALI antibodies. No cases of anaphylaxis were reported. Hypersensitivity and infusion-related reactions each occurred in approximately 5% of patients. A positive anti-TALI antibody test was observed in approximately 23% of all patients. It was also observed that patients who received imiglucerase for a prolonged period (i.e.,

more than two years), could develop antibodies for TALI when they switched to this drug. Although the clinical consequence of immunogenicity is unclear, the proportion of patients who developed anti-TALI antibodies appeared numerically higher than rates reported for imiglucerase (15%) or velaglucerase alfa (2%).[13] According to the clinical expert involved in the review, the high immunogenicity of TALI is a concern and should be further monitored during post-marketing studies.

As for efficacy, safety data could not be directly or indirectly compared with placebo or another ERT due to the single-arm design of the TALI studies. A naive side-by-side comparison with the limited safety data from two systematic reviews did not show obvious differences for safety data between ERTs. However, as mentioned previously, this type of comparison had numerous limitations that increased uncertainty about the comparative safety of TALI versus other ERTs. Safety was monitored for 39 months in extension Study 003, and no additional safety signals or obvious increases in the frequency of AEs were observed compared with the pivotal trials.

Conclusions

Results from four phase 3, multi-centre trials suggest that TALI biweekly IV infusions improved hemoglobin levels, platelet counts, and spleen and liver volumes from baseline; however, only one study conducted a statistical analysis showing a statistically significant improvement in outcomes from baseline. Efficacy results for these outcomes generally met clinical targets defined in clinical practice guidelines for GD, with the exception of liver volume. It is uncertain whether the 60 U/kg TALI dose added clinical benefits to the 30 U/kg TALI dose, except for platelet counts. The evidence for the use of TALI in type 3 GD patients is extremely limited and is based on changes in hematological factors in only two patients. Safety data revealed no important AEs other than hypersensitivity and infusion-related reactions, and a somewhat high rate of immunogenicity to TALI. An extension study provided longer-term safety and efficacy data for TALI after three years, which were in line with results observed at nine and 12 months. HRQoL and bone crises were identified as key end points by the clinical expert involved in the review and a patient group, respectively, but HRQoL was not assessed in most of the trials and the bone crises could not be interpreted given the limitations of the data. A key limitation of the reviewed data is the lack of a head-to-head comparison with another ERT or a formal indirect comparison between ERTs. Neither patients nor investigators were blinded to the administration of TALI, rendering studies prone to related bias, such as the Hawthorne effect. For these reasons, the superiority or non-inferiority of TALI compared with other ERTs could not be assessed and the comparative results reported by the pivotal trials are associated with a high degree of uncertainty.

TABLE 1: SUMMARY OF RESULTS

	Study 001 (9 Months)		Study 002 (9 Months)		Study 004 (9 Months)	Study 005 (12 Months)	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Efficacy Set [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Hemoglobin Levels (g/dl)							
n (%)	14 (93.3)	15 (93.8)	25 (96.2)	5 (100)	[redacted]	6 (100)	5 (100)
Baseline, mean (SD)	12.2 (1.7)	11.4 (2.6)	13.5 (1.6)	13.5 (0.5)	[redacted]	11.3 (1.7)	10.6 (1.4)
Mean at end point[a] (SD)	14.0 (1.4)	13.6 (2.0)	13.3 (1.6)	13.9 (1.3)	[redacted]	12.7 (1.2)	12.2 (1.1)
Change from baseline, mean (SD)	1.6 (1.4)	2.2 (1.4)	–0.2 (0.7)	0.4 (1.4)	[redacted]	1.4 (1.3)	1.6 (0.7)
P value	0.0010	< 0.0001	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.719		NR		NR	NR	
Percentage change from baseline: mean (SD), median (interquartile range)	NR NR	NR NR	–1.8 (4.9) –2.5 (NR)	3.3 (10.7) 0.7 (NR)	NR NR	13.8 (14.5) 12.2 (20.6)	15.8 (8.3) 14.2 (10.4)
Platelet Counts (/mm^3)							
n (%)	15 (100)	16 (100)	25 (96.2)	5 (100)	[redacted]	6 (100)	5 (100)
Baseline, mean (SD)	75,320 (NR)	65,038 (NR)	160,447 (79,086)	164,587 (38,731)	[redacted]	162,667 (71,838)	99,600 (42,899)
Mean at end point[a] (SD)	86,747 (50,989)	106,531 (53,212)	157,920 (87,130)	177,400 (37,554)	[redacted]	208,167 (90,747)	172,200 (89,290)
Change from baseline, mean (SD)	11,427 (20,214)	41,494 (47,063)	–2,527 (29,871)	12,813 (43,756)	[redacted]	45,500 (52,884)	72,600 (59,197)
P value	0.0460[b]	0.0031	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.042		NR		NR	NR	
Percentage change from baseline, mean (SD)	NR	NR	–1.5 (21.6)	11.7 (34.9)	NR	30.9 (35.1)	73.7 (61.9)
Spleen Volume (mL)							
n (%)	15 (100)	16 (100)	20 (76.9)	5 (100)	NR	6 (100)	5 (100)
Baseline, mean (SD)	2,130.94 (1,154.72)	2,117.38 (1,356.17)	822.4 (603.7)	313.0 (156.0)	NR	1,218 (638.4)	1,023 (753.4)
Mean at end point[a] (SD)	1,566.08 (900.17)	1,376.89 (1,055.81)	749.3 (559.7)	276.3 (107.9)	NR	811.6 (409.6)	524.0 (281.1)
Change from baseline, mean (SD)	NR	NR	–73.1 (146.9)	–36.7 (52.5)	NR	–407 (372.7)	–499 (493.3)
Percentage change from baseline, mean (SD)	–26.91 (7.79)	–38.01 (9.38)	–7.6 (13.3)	–6.6 (15.6)	NR	–28.6 (21.5)	–41.1 (13.8)
P value	< 0.0001	< 0.0001	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.060		NR		NR	NR	

	Study 001 (9 Months)		Study 002 (9 Months)		Study 004 (9 Months)	Study 005 (12 Months)	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Efficacy Set [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Liver Size (mL)							
n (%)	14 (93.3)	15 (93.8)	23 (88.5)	5 (100)	NR	6 (100)	5 (100)
Baseline, mean (SD)	2,880.60 (736.12)	2,481.31 (452.74)	1,857 (440.0)	1,346 (431.7)	NR	1,214 (424.7)	991.7 (301.3)
Mean at end point[a] (SD)	2,564.07 (559.57)	2,190.99 (376.70)	1,786 (423.7)	1,393 (506.0)	NR	1,116 (366.9)	849.1 (271.9)
Change from baseline, mean (SD)	NR	NR	–71.6 (166.3)	47.7 (97.5)	NR	–98.7 (75.0)	–143 (102.9)
Percentage change from baseline, mean (SD)	–10.48 (11.27)	–11.11 (6.68)	–3.5 (8.1)	2.4 (6.8)	NR	–6.3 (8.5)	–14.0 (9.0)
P value	0.0041	< 0.0001	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.349		NR		NR	NR	
Height (cm)							
n (%)	NR	NR	NR	NR	NR	6 (100)	5 (100)
Baseline, mean (SD)	NR	NR	NR	NR	NR	129.3 (21.7)	107.8 (14.3)
Mean at end point[a] (SD)	NR	NR	NR	NR	NR	134.4 (20.8)	115.7 (13.9)
Percentage change from baseline, mean (SD)	NR	NR	NR	NR	NR	4.2 (2.2)	7.6 (2.1)
Height velocity (cm/year)	NR	NR	NR	NR	NR	5.1 (2.2)	8.0 (1.3)
Weight (kg)							
n (%)	NR	NR	NR	NR	NR	6 (100)	5 (100)
Baseline, mean (SD)	NR	NR	NR	NR	NR	27.9 (10.5)	17.7 (4.8)
Mean at end point[a] (SD)	NR	NR	NR	NR	NR	30.3 (10.5)	20.4 (6.0)
Percentage change from baseline, mean (SD)	NR	NR	NR	NR	NR	9.6 (7.0)	14.7 (5.7)
Withdrawals							
Total, n/N (%)	2/16 (12.5)	2/17 (11.8)	3/28 (10.7)	0	[redacted]	0	0
Harms							
SAEs, n/N (%)	0	0	3/26 (11.5)	0	[redacted]	0	1/5 (20.0)
WDAEs, n/N (%)	1/16 (6.3)	1/16 (6.3)	0[c]	0	[redacted]	0	0
Notable Harms, n/N (%)							
Anaphylaxis	NR	NR	NR	NR	NR	NR	NR
Infusion-related reactions	NR	NR	4/26 (15.4)	0	[redacted]	NR	NR

	Study 001 (9 Months)		Study 002 (9 Months)		Study 004 (9 Months)	Study 005 (12 Months)	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Efficacy Set [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Hypersensitivity	1/16 (6.3)	1/16 (6.3)	1/26 (3.8)	0	[redacted]	0	2/5 (40.0)
Anti-human TALI Ab results							
IgG positive to human TALI	1/16 (6.3)	1/16 (6.3)	5/26 (19.2)	2/5 (40.0)	[redacted]	1/6 (16.7)	2/5 (40.0)
Treatment-induced Ab, n (%)	NR	NR	NR	NR	[redacted]	NR	NR
Positive for neutralizing Ab	0	0	1/26 (3.8)[c]	0	NR	NA	NA

Ab = antibody; IgG = immunoglobulin G; NA = reported as not available; NR = not reported; SAEs = serious adverse events; SD = standard deviation; TALI = taliglucerase alfa; U = unit; WDAEs = withdrawals due to adverse event.
[a] The time of end point was 9 months for studies 001, 002, and 004, and 12 months for Study 005.
[b] The pre-specified alpha level was 0.025; thus, the difference was not statistically significant.
[c] One patient withdrew consent after experiencing hypersensitivity reaction during the first infusion.
[d] One patient was positive for *in vitro* neutralizing activity, but negative for the *in vivo* neutralizing activity test.
Source: Clinical Study Reports for studies 001,[14] 002,[15] 004,[16] and 005.[17]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Gaucher disease (GD) is an autosomal, recessively inherited lysosomal storage disease that results from deficiency of the lysosomal enzyme glucocerebrosidase (glucosidase beta acid [GBA]). Consequently, the enzyme's substrate, glucocerebroside, accumulates in macrophages of the reticuloendothelial system, particularly those in the spleen, liver, bone marrow, and lung(s). This leads to multiple manifestations, including anemia, thrombocytopenia, hepatosplenomegaly, growth retardation in children, skeletal disease, and increased rate of malignancies. GD is classified into three subtypes based on the presence and nature of central nervous system involvement.[1,2]

The most prevalent form, accounting for 95% of cases, is the non-neuronopathic (type 1) variant, which lacks primary involvement of the central nervous system characteristic of the type 2 and type 3 variants.[1,2] However, type 1 GD patients may present with peripheral neuropathy. Half of patients with type 1 GD are diagnosed before 20 years of age. A symptomatic disease in childhood is associated with more severe disease manifestations and a greater burden of disease as a patient ages.[18] Clinical manifestations and time of onset are very heterogeneous among patients, as some patients may be asymptomatic or show very mild symptoms.[2] Skeletal manifestations of GD have a greater impact on quality of life (QoL) than hematological and visceral abnormalities. Accumulation of glucocerebroside in bone marrow is associated with delayed growth in childhood and adolescence, osteopenia, lytic lesions, pathological fractures, chronic bone pain, acute episodes of bone crisis (i.e., severe bone pain), bone infarcts, osteonecrosis, and skeletal deformities.[19,20]

Type 2 GD is the acute neuronopathic form characterized by early onset, typically within a few months after birth. Extensive and severe visceral involvements are usually accompanied by pulmonary disease, ichthyosis, and central nervous system symptoms such as oculomotor dysfunction, developmental delay, severe hypertonia, rigidity, arching, swallowing impairment, and seizures leading to premature death by ages two to four.[3]

Type 3 GD is the subacute, neuronopathic form. Typically, it has a later onset than type 2 GD, with a slower progression of similar manifestations. The distinction between type 1 and early stage type 3 is often difficult to make. Type 3 GD may also feature severe visceral complications and bone disease before the development of neurological complications. Lifespan of type 3 GD patients is typically 30 to 40 years of age.[3]

The prevalence of GD is approximately one in 50,000 to 100,000 people globally.[4] Of the 3,337 patients entered in the International Collaborative Gaucher Group (ICGG) Registry by the end of 2003, 4% were Canadian.[21] The frequency of type 1 GD ranges from one in 20,000 to one in 200,000 in the general population, reaching one in 400 to one in 600 among Ashkenazi Jewish people.[5]

Although more than 50 mutations of the *GBA* gene have been identified, four of these (N370S, L444P, 84G > GG, and IVS2 (+1) G > A) account for more than 90% of the mutations seen in Ashkenazi Jewish individuals affected with GD and for approximately 60% of disease-causing alleles seen in the non-Jewish population. Importantly, the concordance between the genotype and phenotype in GD is only partial, which limits the prognostic value of genotyping.[3]

GD is diagnosed with reduced glucocerebrosidase activity in peripheral leukocytes and targeted genetic analysis. The variables providing the best indication of the severity of disease are the age of onset, platelet count, hemoglobin concentration, the size of the spleen and/or liver relative to total body mass,

and the amount of bone marrow replacement by storage cells.[6] According to the clinical expert involved in the review, bone crises are also an indicator of severe disease.

1.2 Standards of Therapy

The general treatment goal in GD patients with moderate to severe clinical symptoms of the disease is to achieve a state of equilibrium such that degradatory activity within the endosomal and lysosomal systems can maintain homeostasis and prevent the accumulation of glucocerebroside.[7] Two pharmacotherapeutic modalities have been used to achieve this target in GD: enzyme replacement therapy (ERT), which replaces the missing or defective lysosomal enzyme, and substrate reduction therapy (SRT), which aims to decrease the production of glucocerebroside rather than accelerating its elimination. Because the systemic manifestations of type 1 GD respond well to ERT with human beta-glucocerebrosidase, this type of therapy has been used as a first-line treatment for more than two decades.[8] In addition to taliglucerase alfa (TALI), other ERTs available in Canada are imiglucerase (Cerezyme), derived from recombinant deoxyribonucleic acid (DNA) production methods in mammalian cells,[9] and velaglucerase alfa (VPRIV), produced by gene-activation technology in a human cell line.[10]

ERT is administered by intravenous (IV) infusion. The indicated initial treatment regimen with ERT varies from 2.5 U/kg three times a week to 60 U/kg biweekly,[9,10] which is aligned with the Ontario guidelines.[6] Dosing may be individualized to each patient based on the severity of the disease.[6] According to the clinical expert involved in this review, biweekly treatments, of a dose between 30 U and 60 U/kg, but closer to 30 U/kg, are favoured for their convenience. The clinical expert also stated that the majority of patients receive 30 U/kg biweekly.

Because of the wide clinical variability in the severity of symptoms and the course of the disease, the magnitude and time course of responses to ERT are variable.[22,23] Hemoglobin levels respond most rapidly (50% improvement in four to six months), followed by platelet count (five to 18 months), decrease in spleen size (27 to 54 months), and decrease in liver size (24 to 90 months).[24] Patients with GD identified bone crises as their major concern. While the severity, frequency, and duration of painful bone crises may be reduced within the first year of ERT,[25,26] long-term treatment over three to four years is required to improve marrow composition and bone mass.[20,27] In children, in addition to the effect on hematological parameters and organ size reduction, long-term continuous ERT was shown to decrease bone crises (after two years of ERT), normalize growth parameters, and restore bone mineral density (BMD) (within six to seven years of treatment).[28]

Only one medication used for SRT is available in Canada. Miglustat (Zavesca) is an oral competitive reversible inhibitor of glucosylceramide synthase. It is indicated for the treatment of adults with mild to moderate type 1 GD for whom ERT is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access).[11] Evidence suggests miglustat 100 mg three times a day is less efficacious than ERT and is associated with increased adverse events (AEs), but is more convenient than IV infusions. For these reasons, miglustat is used as a second-line therapy for GD.[6]

ERT or SRT may be supplemented by treatment with analgesics, anti-inflammatory drugs, bisphosphonates, or other medications for specific complications of the disease.[6]

Hematopoietic stem cells transplantation has also been used successfully in some cases to treat GD, although the risks are currently felt to outweigh the benefits.[3]

1.3 Drug

TALI is a recombinant form of human glucocerebrosidase expressed in carrot cells in culture, which catalyzes the degradation of the glycolipid glucocerebrosides and reduces its accumulation in organs and tissues. TALI replaces the defective enzyme in GD, principally in macrophages. As with other ERTs, TALI cannot cross the blood-brain barrier and does not have benefits with regard to the neurological symptoms of GD.

In Canada, TALI is indicated for long-term ERT for adults and children (two to 17 years old) with a confirmed diagnosis of type 1 GD and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 GD.

TALI is administered as an IV infusion over one to two hours every two weeks, supervised by a physician experienced in the management of patients with GD. Dose adjustments should be made based on an individual basis, but initial doses range from 30 U/kg to 60 U/kg. TALI is available as a lyophilized, sterile powder in a single-use vial designed to deliver 200 U of TALI for IV infusion upon reconstitution with 5.1 mL sterile water for injection and further dilution with sterile saline solution (100 mL to 200 mL).

Indication under review
Long-term enzyme replacement therapy for adults and children (two to 17 years old) with a confirmed diagnosis of type 1 GD, and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 GD.
Listing criteria requested by sponsor
As per indication

TABLE 2: KEY CHARACTERISTICS OF TALIGLUCERASE ALFA, IMIGLUCERASE, AND VELAGLUCERASE ALFA

	TALI	Imiglucerase	Velaglucerase alfa
Mechanism of Action	Replacement of beta-glucocerebrosidase in monocyte/macrophage-derived cells		
Indication[a]	Long-term ERT for adults and children (2 to 17 years old) with a confirmed diagnosis of type 1 GD, and for hematological manifestations in pediatric patients with a confirmed diagnosis of type 3 GD	Long-term ERT in patients with a confirmed diagnosis of non-neuropathic (type 1) or chronic neuropathic (type 3) GD who exhibit non-neurological manifestations of the disease	Long-term ERT for pediatric and adult patients with type 1 GD
Route of Administration	IV infusion		
Recommended Dose	From 30 U/kg to 60 U/kg every 2 weeks as an initial dose	From 2.5 U/kg three times a week up to 60 U/kg every 2 weeks as initial dosage	60 U/kg administered every other week; dosage adjustments can be made
Serious Side Effects/ Safety Issues	Infusion-related reactions, hypersensitivity (including anaphylaxis), development of anti-drug Ab	Infusion-related reactions, hypersensitivity (including anaphylaxis), development of anti-drug Ab	Infusion-related reactions, hypersensitivity (including anaphylaxis), development of anti-drug Ab

Ab = antibodies; ERT = enzyme replacement therapy; GD = Gaucher disease; IV = intravenous; TALI = taliglucerase alfa; U = unit.
[a] Health Canada indication.
Source: Product monographs for TALI,[29] imiglucerase,[9] and velaglucerase alfa.[10]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of TALI (30 U/kg to 60 U/kg IV infusion every two weeks) for long-term ERT in adults and children with a confirmed diagnosis of type 1 GD, and for hematological manifestations in pediatric patients with type 3 GD.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	• Adult and pediatric patients (2 to 17 years old) with a confirmed diagnosis of type 1 GD. • Pediatric patients with type 3 GD who suffer from hematological manifestations. Sub-groups of interest: adult versus pediatric patients; patients with type 1 versus type 3 GD; patients with mild versus moderate or severe disease.
Intervention	TALI 30 U/kg to 60 U/kg IV infusion every two weeks (with or without supportive care)
Comparators	• Imiglucerase • Velaglucerase alfa With or without supportive care
Outcomes	**Key efficacy outcomes:** • Days of work (or school) missed • Number of hospitalizations • Need for surgical intervention • Improvement of hematological parameters (Hb concentration, platelet count) • Reduction in liver and spleen size • Growth in children • Incidence of bone crises **Other efficacy outcomes:** • Changes in GD-specific biomarkers (chitotriosidase, CCL18) • Decreased use of analgesics • QoL **Harms outcomes:** • AEs • SAEs • WDAEs • Mortality • Notable harms: hypersensitivity reactions (particularly anaphylaxis), infusion-related reactions, anti-drug Ab
Study Design	Published and unpublished phase 3 RCTs

Ab = antibodies; AEs = adverse events; CCL18 = Chemokine (C-C motif) ligand 18; GD = Gaucher disease; Hb = hemoglobin; IV = intravenous; QoL = quality of life; RCT = randomized controlled trial; SAEs = serious adverse events; TALI = taliglucerase alfa; U = unit; WDAEs = withdrawals due to adverse events

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concept was Elelyso (taliglucerase alfa).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on March 25, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on July 15, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessments, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases, and an Internet search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers, and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4. No studies were excluded.

3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

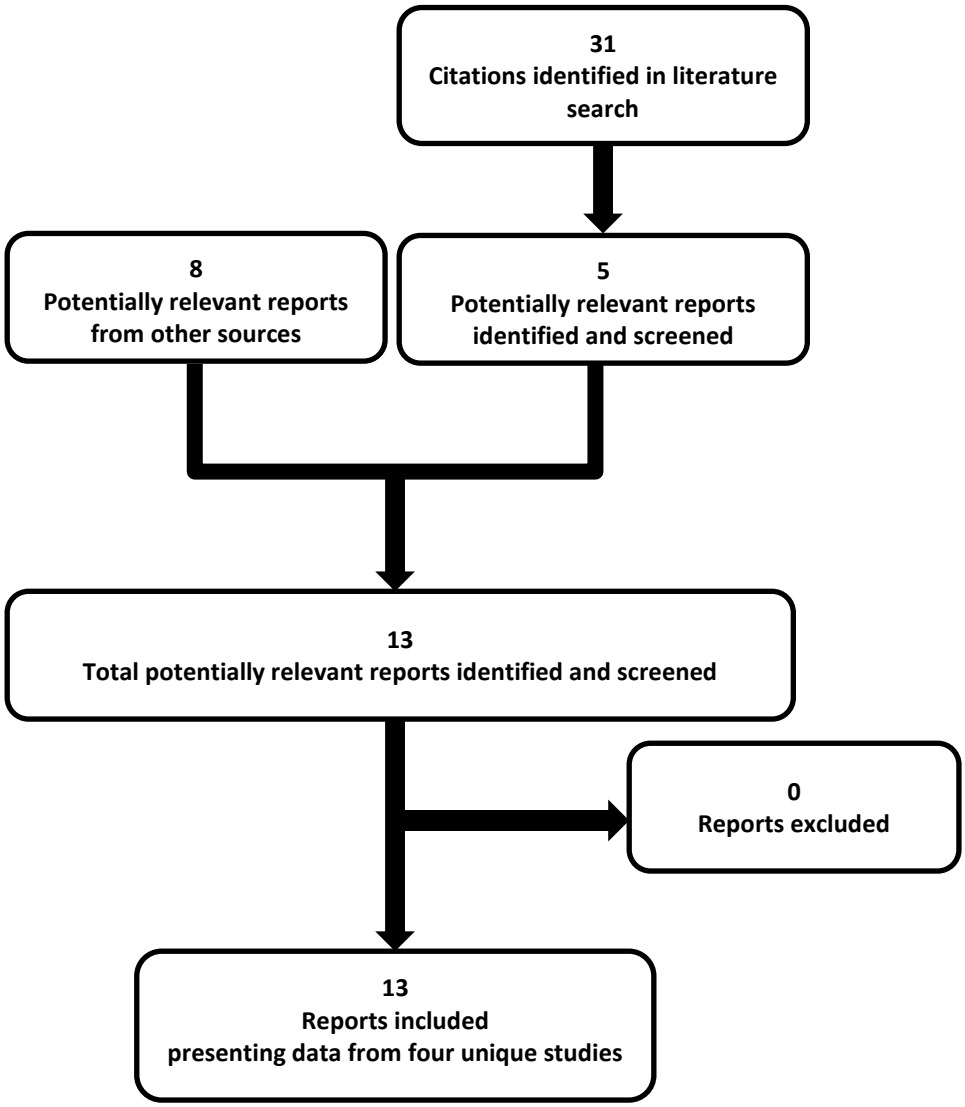


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 001	Study 002	Study 004	Study 005
DESIGNS & POPULATIONS	**Study Design**	Multi-centre, randomized, dose-blind, uncontrolled trial	Multi-centre, single-arm, OL, switchover trial	Multi-centre, OL, expanded access, switchover trial	Multi-centre, randomized, dose-blind, uncontrolled pediatric trial
	Locations	11 centres in Israel, South Africa, the United Kingdom, Spain, Italy, Canada, Serbia, Mexico, and Chile	11 centres in Israel, Germany, the United Kingdom, Spain, the United States, Canada, Serbia, Australia, and Singapore	18 centres in the United States and Israel	3 centres in Israel, South Africa, and Paraguay
	Randomized (N)	33	33	[redacted]	11
	Inclusion Criteria	18 years or older; GD diagnosis with leukocyte glucocerebrosidase activity level ≤ 30% of the mean activity of the reference range (≤ 3 nmol/mg/h); splenomegaly determined by MRI (> 8 times the expected volume); thrombocytopenia (< 120,000/mm^3); have not received ERT or SRT in the last 12 months and have negative anti-glucocerebrosidase antibody test	2 years or older; GD diagnosis with leukocyte glucocerebrosidase activity level ≤ 30% of the mean activity of the reference range (≤ 3 nmol/mg/h); stable GD (stable hemoglobin and platelet count, no major surgery, blood transfusion, major bleeding, acute avascular necrosis, or spleen or liver enlargement over the last year); receiving imiglucerase therapy for ≥ 2 years with stable regimen for ≥ 6 months	18 years or older; diagnosis of GD treated historically with imiglucerase	2 years to < 18 years of age; GD diagnosis with leukocyte glucocerebrosidase activity level ≤ 30% of the mean activity of the reference range; clinical condition requiring treatment with ERT; have not received ERT or SRT in the last 12 months; and have negative anti-glucocerebrosidase Ab test
	Exclusion Criteria	Severe neurological signs and symptoms (ocular paralysis, overt myoclonus, seizures); previous anaphylactoid reaction to imiglucerase; allergy to carrots	Previous infusion-related allergic reaction to imiglucerase or alglucerase, or receiving premedication to prevent infusion reactions; allergy to carrots or beta lactam antibiotics;	Previous infusion-related allergic reaction to imiglucerase or alglucerase, or receiving premedication to prevent infusion reactions; allergy to carrots or beta lactam antibiotics	Presence of neurological signs and symptoms characteristic of GD with complex neuronopathic features other than longstanding oculomotor gaze palsy; previous hypersensitivity

		Study 001	Study 002	Study 004	Study 005
			unresolved anemia		reaction to imiglucerase or alglucerase; allergy to carrots or beta lactam antibiotics; unresolved anemia
DRUGS	**Intervention**	TALI 30 U/kg TALI 60 U/kg Every 2 weeks by IV infusion	TALI at a dose equivalent to the stable imiglucerase dose received in the past 6 months, or to the dose prior to the shortage of imiglucerase	TALI at a dose equal to each patient's previous imiglucerase dose before its shortage	TALI 30 U/kg TALI 60 U/kg Every 2 weeks by IV infusion
	Comparator(s)	None			
DURATION	**Phase**				
	Run-in	None	12 weeks	None	None
	Study	38 weeks (9 months)	38 weeks (9 months)	[redacted]	52 weeks (12 months)
OUTCOMES	**Primary End Point**	Percentage change from baseline of spleen volume	Clinical stability measured with platelet counts, Hb spleen volume, and liver volume	Safety of TALI as measured by AEs, anti-TALI Ab, and clinical laboratory parameters	Median percentage change in hemoglobin levels from baseline
	Other End Points	**Major secondary outcomes:** Change from baseline of: • Hb • Percentage change of liver volume • Platelet counts **Other secondary outcomes:** • Chitotriosidase and CCL18 levels • Proportion of patients with > 10% reduction in spleen volume at 9 months **Tertiary outcomes:** • QCSI • Change in bone mineral density measured with DEXA	None	**Secondary outcomes:** • Change from baseline in Hb levels • Change from baseline in platelet counts	**Secondary efficacy outcomes:** Percentage change from baseline in: • Chitotriosidase and CCL18 • Spleen and liver volume • Platelet count **Exploratory outcomes:** • Change in height and weight • Change in Tanner stage • Change in bone age by X-ray • Change in bone density by DEXA • Occurrence of bone crises • QoL using the CHQ-PF28

		Study 001	Study 002	Study 004	Study 005
NOTES	**Publications**	Zimran et al. (2011)[30]	Pastores et al. (2014)[31]	None	Zimran et al. (2015)[32]

Ab = antibodies; AEs = adverse events; CCL18 = Chemokine (C-C motif) ligand 18; CHQ-PF28 = Child Health Questionnaire Parent Form 28; CSR = Clinical Study Report; DEXA = Dual-energy X-ray absorptiometry; ERT = enzyme replacement therapy; GD = Gaucher disease; Hb = hemoglobin; IV = intravenous; MRI = magnetic resonance imaging; OL = open-label; QCSI = quantitative chemical shift imaging; QoL = quality of life; SRT = substrate reduction therapy; TALI = taliglucerase alfa; U = unit.
Source: CSRs for studies 001,[14] 002,[15] 004,[16] and 005.[17]Note: Eight additional reports were included: the manufacturer's submission[33] and CSRs for studies 001,[14] 002,[15] 004,[16] and 005,[17] and the Health Canada reviewer's report,[34] and two Food and Drug Administration reports (medical and statistical reviews).[13,35]

3.2 Included Studies

3.2.1 Description of Studies

All four included studies were manufacturer-funded trials: Study PB -06-001 (hereafter called Study 001), Study PB-06-002 (Study 002), Study PB-06-004 (Study 004), and Study PB-06-005 (Study 005).

Studies 001 and 005 were phase 3, multi-centre, randomized, dose-blind, uncontrolled trials comparing two doses of TALI (30 U/kg and 60 U/kg). The primary objective of Study 001 was to evaluate the efficacy of TALI as reflected by the percentage in reduction from baseline of spleen volume after nine months in previously untreated patients with important signs and symptoms of GD. The primary objective of Study 005 was to evaluate the efficacy of TALI as measured by the median percentage change in hemoglobin levels from baseline in pediatric patients with GD. Studies 001 and 005 had durations of nine months and 12 months, respectively. Patients in Study 001 (N = 33) and in Study 005 (N = 11, of which two had type 3 GD) were randomized to the two dosing treatment groups at a ratio of 1:1 using a computer-generated randomization. All patients and study personnel were blinded to the dose received. Patients received IV infusions of TALI every two weeks and AEs were recorded at each visit. Efficacy parameters were collected at screening (Study 001 only), at baseline (studies 001 and 005), at month 6 (studies 001 and 005), at month 9 (studies 001 and 005), and at month 12 (Study 005 only).

Studies 002 and 004 were conducted in the context of an imiglucerase shortage, when TALI was the only ERT available.

Study 002 was a phase 3, multi-centre, single-arm, open-label (OL), switchover trial. The primary objective of Study 002 was to assess the clinical stability as measured with platelet counts, hemoglobin levels, and spleen and liver volumes after nine months in stable adult and pediatric patients with GD switching from imiglucerase to TALI. After a 12-week stability evaluation period, in which the stability of patients was confirmed, 33 patients were enrolled in Study 002, which was of a nine-month duration. The study included 28 adults and five patients aged between two and 18 years. Patients received IV infusions of TALI every two weeks at a dose equivalent to the stable imiglucerase dose received in the past six months, or to the dose prior to the shortage of imiglucerase. Neither patients nor study personnel were blinded to treatment. Efficacy parameters were collected at baseline, at month 6, and at month 9.

At the end of the treatment period for studies 001, 002, and 005, eligible patients were offered enrolment in an extension study.

Study 004 was a phase 3, multi-centre, single-arm, OL, expanded access, switchover trial that allowed access to TALI for patients with GD in need of ERT. The primary objective of Study 004 was to evaluate the safety of switching from imiglucerase to TALI in adult patients diagnosed with GD, as measured by AEs, anti-TALI antibodies, and clinical laboratory parameters. The study enrolled [redacted] adult patients. [redacted] These patients received IV infusions of TALI every two weeks at a dose equal to each patient's previous imiglucerase dose before its shortage. AEs were recorded at each visit. Neither patients nor study personnel were blinded to treatment. [redacted]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Studies 001, 002, and 005 included patients with a GD diagnosis with leukocyte glucocerebrosidase activity level ≤ 30% of the mean activity of the reference range. Patients with severe neurological symptoms were excluded. The expanded access Study 004 included adult patients (aged 18 years and older) with a diagnosis of GD requiring ERT with imiglucerase.

Studies 001 and 005 excluded patients who had previous treatment with ERT or SRT in the last 12 months and patients with positive anti-glucocerebrosidase antibody test. More specifically, Study 001 included adult patients with splenomegaly (> 8 times the expected volume) and thrombocytopenia (< 120,000/mm^3). Study 005 included patients between two and 18 years of age with a clinical condition requiring treatment with ERT, in the opinion of the investigator.

The switchover Study 002 included patients who were two years or older with GD defined as stable based on hemoglobin level, platelet counts, and the absence of major surgery, blood transfusion, major bleeding, acute avascular necrosis, or spleen or liver enlargement over the last year. Patients included in this trial had been receiving imiglucerase therapy for more than two years with a stable regimen for more than six months.

b) Baseline Characteristics

Baseline characteristics of patients in studies 001, 002, 004, and 005 are summarized in Table 5. In Study 001, patients who were randomized to the 30 U/kg TALI group were similar to patients in the 60 U/kg group for age, gender, ethnicity, weight, and spleen volume. Differences between these two groups were noted for liver volume, hemoglobin level, platelet count, and chitotriosidase activity, where higher numbers were observed in the 30 U/kg group. Patients in Study 002 were not randomized and the subdivision into adult and pediatric patients exposed differences at baseline that were expected in this context. Patients in Study 004 were neither randomized nor sub-grouped. Due to the small number of patients included in Study 005, baseline characteristics were not balanced for age, weight, spleen and liver volumes, platelet counts, chitotriosidase activity, and CCL18 levels.

The mean age of participants across groups in the included trials ranged between 36.0 years and 47.1 years for adults, and 6.6 years and 13.0 years of age for pediatric patients. The male to female ratio was balanced in the adult population, but the proportion of males was 68.8% in the pediatric population. Caucasian patients represented 96.2% of all patients. Mean weight ranged from 67.3 kg to 68.8 kg in adults in Study 001. Pediatric patients included in the trials weighed between 17.7 kg and 44.1 kg on average. Mean baseline disease characteristics, when available, included the following: spleen volume varied between 4.1 and 29.4 multiples of normal, liver volume varied between 1.0 and 2.2 multiples of

normal, hemoglobin levels varied between 10.6 g/dL and 13.5 g/dL, platelet counts varied between 65,038/mm^3 and 168,821/mm^3, chitotriosidase activity varied between 34,961 nmol/mm/h and 6,934 nmol/mm/h, and CCL18 levels varied between 306.4 ng/mL and 1,339.4 ng/mL.

It is important to note that baseline disease characteristics of patients in studies 002 and 004 represented values for a treated disease.

TABLE 5: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

	Study 001		Study 002		Study 004	Study 005	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Safety Set [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Age (years)							
Mean (SD)	36.3 (12.2)	36.0 (12.2)	47.1 (12.9)	13.0 (4.1)	[redacted]	9.5 (4.0)	6.6 (3.1)
Range	19 to 74	19 to 58	18 to 66	6 to 16	[redacted]	3 to 14	2 to 10
Gender							
Male, n (%)	7 (46.7)	8 (50.0)	14 (53.8)	3 (60.0)	[redacted]	4 (66.7)	4 (80.0)
Female, n (%)	8 (53.3)	8 (50.0)	12 (46.2)	2 (40.0)	[redacted]	2 (33.3)	1 (20.0)
Religion							
n (%)	15 (100)	16 (100)	26 (100)	3 (60.0)	[redacted]	6 (100)	5 (100)
Jewish — Ashkenazi	6 (40.0)	4 (25.0)	14 (53.8)	0	[redacted]	0	2 (40.0)
Jewish — non-Ashkenazi	0	0	0	0	[redacted]	0	0
Non-Jewish	9 (60.0)	12 (75.0)	12 (46.2)	3 (100.0)	[redacted]	6 (100.0)	3 (60.0)
Weight (kg)							
Mean (SD)	68.8 (11.8)	67.3 (8.9)	NR	44.1 (15.3)	NR	27.9 (10.5)	17.7 (4.8)
Range	52 to 93	50 to 81	NR	20 to 62	NR	13.4 to 40.0	12.5 to 23.0
Spleen volume							
n (%)	15 (100)	16 (100)	20 (76.9)	5 (100)	NR	6 (100)	5 (100)
Mean volume, mL (SD)	2,130.94 (1,154.72)	2,117.38 (1,356.17)	822.4 (603.7)	313.0 (156.0)	NR	1,218 (638.4)	1,023 (753.4)
Range	886.41 to 4,901.13	913.65 to 5,417.82	14 to 2,151	152 to 534	NR	240 to 2,062	325 to 1,996
Mean multiples of normal (SD)	15 (NR)	17 (NR)	5.5 (4.8)	4.1 (2.7)	NR	22.2 (12.1)	29.4 (24.3)
Range	8 to 35	8 to 54	0.1 to 20.5	1.7 to 7.9	NR	9.0 to 41.2	10.0 to 69.3
Liver volume							
n (%)	15 (100)	16 (100)	23 (88.5)	5 (100)	NR	6 (100)	5 (100)
Mean volume, mL (SD)	2,880.60 (736.12)	2,481.31 (452.74)	1,857 (440.0)	1,346 (431.7)	NR	1,214 (424.7)	991.7 (301.3)
Range	2,282.47 to	1,758.30 to	1,167 to 2,659	827 to 1,911	NR	475 to 1,750	612 to 1,295

	Study 001		Study 002		Study 004	Study 005	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Safety Set [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
	5,095.80	3,297.33					
Mean multiples of normal (SD)	1.7 (NR)	1.6 (NR)	1.0 (0.2)	1.3 (0.3)	NR	1.8 (0.5)	2.2 (0.5)
Range	1.4 to 2.9	0.9 to 2.6	0.7 to 1.7	1.0 to 1.6	NR	1.1 to 2.7	1.8 to 3.0
Hb (g/dL)							
n (%)	14 (93.3)	16 (100)	25 (96.1)	5 (100)	[redacted]	6 (100)	5 (100)
Mean (SD)	12.2 (1.7)	11.4 (2.6)	13.5 (1.6)	13.5 (0.5)	[redacted]	11.3 (1.7)	10.6 (1.4)
Median	12.3	11.2	13.6	13.4	[redacted]	11.5	11.1
Range	7.9 to 14.6	5.5 to 16.0	11 to 16	13 to 14	[redacted]	8 to 13	9 to 12
Platelet count (/mm^3)							
n (%)	15 (100)	16 (100)	25 (96.1)	5 (100)	[redacted]	6 (100)	5 (100)
Mean (SD)	75,320 (NR)	65,038 (NR)	160,447 (79,086)	164,587 (38,731)	[redacted]	162,667 (71,838)	99,600 (42,899)
Range	27,000 to 163,000	28,000 to 134,000	37,833 to 309,833	119,667 to 206,000	[redacted]	66,000 to 273,000	76,000 to 176,000
Chitotriosidase activity (nmol/mL/h)							
n	15 (100)	15 (93.8)	23 (88.5)	5 (100)	NR	6 (100)	4 (80.0)
Mean (SD)	28,158 (11,686)	24,702 (17,428)	6,934 (9,651)	7,947 (9,790)	NR	24,820 (17,902)	34,961 (22,080)
Range	7,791 to 50,254	4,639 to 66,628	136 to 41,528	111 to 20,005	NR	3,598 to 49,733	15,420 to 63,179
CCL18 (ng/mL)							
n	NR	NR	23 (88.5)	5 (100)	NR	6 (100)	5 (100)
Mean (SD)	NR	NR	316.3 (284.3)	306.4 (316.7)	NR	1,139.3 (781.3)	1,339.4 (617.9)
Range	NR	NR	34.0 to 1,046	30.0 to 701.0	NR	283 to 2,336	611 to 2,230

CCL18 = Chemokine (C-C motif) ligand 18; Hb = hemoglobin; NR = not reported; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Reports for Study 001,[14] Study 002,[15] Study 004,[16] and Study 005.[17]

Across the trials, the medications most often used at baseline included drugs acting on the renin-angiotensin system, analgesics, antianemic preparations, beta-blocking drugs, vitamins, mineral supplements, sex hormones, and modulators of the genital system (see Table 6). Baseline medications for Study 002 were not described. Baseline doses of TALI in Study 002 are given in Table 7. The mean dose of TALI was 28.8 U/kg for adults and 42.0 U/kg for pediatric patients, which reflected the average dose of ERT administered to patients with GD, around 30 U/kg, according to the clinical expert consulted for this review. The history of treatment of patients in Study 004 is detailed in Table 8. Approximately [redacted]% and [redacted]% of the patients had a history of receiving ERT or SRT, respectively.

TABLE 6: BASELINE MEDICATIONS (SAFETY SET)

	Study 001		Study 004	Study 005	
	TALI 30 U/kg N = 16	TALI 60 U/kg N = 16	Safety Set [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Drug utilization,[a] n (%)					
Drugs acting on the RAS	1 (6.3)	3 (18.8)	[redacted]	NR	NR
Analgesics	2 (12.5)	2 (12.5)	[redacted]	NR	NR
Antianemic preparations	3 (18.8)	1 (6.3)	[redacted]	3 (50.0)	3 (60.0)
Beta-blocking drugs	0	2 (12.5)	[redacted]	NR	NR
Sex hormones and modulators of the genital system	2 (12.5)	2 (12.5)	[redacted]	NR	NR
Vitamins	1 (6.3)	1 (6.3)	[redacted]	1 (16.7)	1 (20.0)
Mineral supplements	1 (6.3)	0	[redacted]	1 (16.7)	0

NR = not reported; RAS = renin-angiotensin system; TALI = taliglucerase alfa; U = unit.
[a] Used by at least two patients.
Source: Clinical Study Reports for Study 001,[14] Study 004,[16] and Study 005.[17]

TABLE 7: BASELINE TALIGLUCERASE ALFA DOSING IN STUDY 002 (UNITS PER KILOGRAM)

	Study 002	
	Adults N = 26	Pediatric Patients N = 5
Mean (SD)	28.8 (16.8)	42.0 (16.4)
Range	9 to 60	26 to 60

SD = standard deviation.
Source: Clinical Study Report, Study 002.[15]

TABLE 8: HISTORY OF TREATMENT IN STUDY 004

	Study 004
	All Patients [redacted]
Number of patients who had previous treatment, n (%)	
ERT	[redacted]
SRT	[redacted]
Other	[redacted]
Untreated	[redacted]

ERT = enzyme replacement therapy; SRT = substrate reduction therapy.
Source: Clinical Study Report, Study 004.[16]

3.2.3 Interventions

The general procedure for IV infusion of TALI in studies 001, 002, and 004 was the following: the individual dose for each patient was prepared according to patient's weight and treatment group. The dose, in terms of total units, was rounded up to avoid use of partial vials. Each dose was prepared by a non-blinded pharmacist at each site. Dose was adjusted if a patient's weight changed by more than 5% from the previous weight measurement. Patients in studies 004 and 005 were eligible for home therapy after three months, based on approval of the investigator and the medical director. In studies 001 and 005, investigators and patients were blinded to the assigned dose, except the site pharmacist and staff responsible for product accountability, who did not have access to clinical data. Study 002 and 004 were both open-label studies. Across all studies, patients received IV infusion of TALI every two weeks as of day 1. Treatment duration was nine months for studies 001 and 002, 12 months for Study 005, and up to 33 months for Study 004.

In studies 001 and 005, patients received the assigned dosage as per randomization; i.e., 30 U/kg or 60 U/kg. For studies 002 and 004, TALI dosage was equivalent to the patient's imiglucerase dose for the past six months (or before imiglucerase shortage). During these latter studies, the dosage could be increased to a maximum dose of 60 U/kg if the patient experienced deterioration according to the defined criteria for platelet count and hemoglobin, upon approval from the investigator and the sponsor. The number of patients who had their dose increased during the trials was not reported.

3.2.4 Outcomes

The key efficacy outcomes were based on organ volumes, hematological parameters, and growth in pediatric patients. Other efficacy outcomes included biomarkers, health-related quality of life (HRQoL) (in pediatric patients in Study 005 only) and bone disease, as assessed by dual-energy X-ray absorptiometry (DEXA) and quantitative chemical shift imaging (QCSI). The validity of outcomes is discussed in more detail in APPENDIX 4: THERAPEUTIC GOALS FOR ENZYME REPLACEMENT THERAPY IN GAUCHER DISEASE AND VALIDITY OF OUTCOME MEASURES. No clear minimal clinically important differences (MCIDs) were identified for any of the end points.

a) Spleen and Liver Volumes

In studies 001, 002, and 005, organ volumes were measured by magnetic resonance imaging (MRI) using a standardized protocol for capturing images. Two independent radiologists read images at a central reading centre. In Study 004, organ volumes were measured by MRI, computed tomography, or ultrasound at local sites, but were not analyzed due to lack of standardization and validation. Organ volumes were expressed as mL or multiples of normal. Normal spleen and liver volumes were estimated as 2 mL/kg and 25 mL/kg of body weight, respectively.

For splenomegaly, therapeutic goals include a reduction in volume and alleviation of splenomegaly-related discomfort, such as abdominal distension, early satiety, and new splenic infarction. Patients with severe baseline splenomegaly (> 15 times normal) are not expected to achieve normalized volume.[12,32] Data have demonstrated significant decreases in spleen volume with ERT, with a 30% to 50% decrease by one year and a 50% to 60% decrease over two to five years.[12]

For hepatomegaly, the therapeutic goal is to decrease and maintain liver volume to 1.0 to 1.5 times normal.[6,12] In the IGCC Registry,[12] patients with moderate (>1.25 times normal) or severe (>2.5 times normal) hepatomegaly demonstrated a decrease of 20% to 30% within 12 months and of 30% to 40% over two to five years. Normalization of liver volume was more likely among patients with moderate hepatomegaly compared with severe hepatomegaly (50% to 58% versus 6% to 9% by two years).[12]

b) Hematological Parameters

Hematological parameters were measured by laboratory analysis. Hemoglobin was analyzed at a central laboratory and platelet counts were measured locally due to platelet instability.

Anemia is defined as a hemoglobin concentration < 12.0 g/dL in males 12 years of age and older, and < 11.0 g/dL in females and children aged between two and 12 years. Therapeutic goals included improving hemoglobin concentration to normal levels, eliminating dependency on blood transfusions, and alleviating symptoms associated with anemia.[6,12]

Thrombocytopenia is defined as platelet counts < 150,000/mm^3 with moderate thrombocytopenia being between 120,000/mm^3 and 60,000/mm^3 and severe thrombocytopenia less than 60,000/mm^3. The immediate therapeutic goal of thrombocytopenia treatment is to prevent bleeding. Other goals include avoiding splenectomy for the purpose of improving thrombocytopenia, and normalizing platelet counts (for patients with splenectomy) or increasing counts by 1.5 to 2-fold (for patients with intact spleen) during the first year of treatment.[6,12]

c) Biomarkers

Chitotriosidase activity and CCL18 levels were measured in studies 001, 002, and 005. In Study 004, blood samples for biomarkers were collected but the samples were not analyzed.

Circulating biomarkers, such as chitotriosidase and CCL18, have been used in clinical trials for patients with GD.[36,37] It was reported that there was a similarly strong correlation of chitotriosidase with disease severity.[36] No validity and MCID information on these biomarkers was found for ERT treatment in GD.

d) Bone Disease

Bone disease was assessed with DEXA and QCSI. A DEXA test measures BMD and compares it to that of an established norm or standard. T score is calculated by comparing DEXA test results to the ideal or peak BMD of a healthy 30-year-old adult.[38] A t score of 0 means that BMD is equal to the norm for a healthy young adult. Differences between a value and that of the healthy young adult norm are measured in standard deviations (SDs). A t score between +1 and –1 is considered normal or healthy. A t score between –1 and –2.5 indicates low bone mass, although not low enough to be diagnosed with osteoporosis. A t score of –2.5 or lower indicates osteoporosis. However, t scores are not applicable to children and adolescents who have not yet reached peak bone mass.[39] Z score is calculated by comparing the DEXA results with age- and sex-matched groups.[38,40] No MCID was specified for t score or z score.

QCSI is used to quantify bone marrow response (fat fraction content) to ERT in GD.[41] The mean fat fraction value in a healthy population is 0.37 (normalization value) and a fat fraction of ≤ 0.23 is an indication of bone complications and bone at risk.[41] No validity information was identified and no MCID in GD is specified.

Episodes of bone pain and bone crises were captured as AEs of special interest in each trial.

e) Efficacy Outcomes Specific for Pediatric Patients

Growth evaluation

Height and weight were measured for growth evaluation. Children with GD often have growth retardation and delayed onset of puberty.[42] Goals of treatment include normalizing height within three years and achieving normal onset of puberty.[6,12] Studies have shown growth normalization with ERT.[43,44]

Child Health Questionnaire Parent Form 28

CHQ-PF28 is a survey questionnaire used to assess quality of life (QoL) for children based on the last four weeks recall on dimensions such as family cohesion, global health, physical functioning, and self-esteem. Items are scored and summed to produce scales (standardized scores) that range from 0 to 100; 0 is the worst possible and 100 the best possible health state.[45] In the included studies, only question 1.1 addressed the general health of the child; no index or overall standardized scores were available. CHQ-PF28 was considered valid for patients aged five to 18 years.[17] It was reported that the questionnaire was acceptable for parents and school nurses,[42,45] and children with asthma or allergy.[46,47] However, neither evidence for validity information nor a MCID was found in children with GD.

f) Safety

Safety was monitored through collection of AEs, withdrawals due to adverse events (WDAEs), mortality, serious adverse events (SAEs), concomitant medications, clinical laboratory evaluation (biochemistry, urinalysis, and hematology), electrocardiogram, echocardiogram, pulmonary function test, physical examination, and anti-human TALI antibodies.

3.2.5 Statistical Analysis

In Study 001, the primary analysis was the percentage change from baseline of spleen volume after nine months. The power calculation assumed an SD for the percentage change in spleen volume of 12%. Based on previous research, the patients in this protocol are expected to have spleen volumes eight times (approximately 0.96 L) the normal size of 0.12 L. Thus, a 20% reduction in spleen volume is anticipated to be equal to a 0.192 L change in the mean spleen volume. By enrolling 12 patients in each treatment group (30 U/kg and 60 U/kg), there was greater than 95% power to detect a change of 20% or more using a one-sample t test (alpha error = 0.025; two-sided test) to evaluate the primary outcome of percentage change in spleen volume after nine months. Should the actual SD be as large as 19%, there would still be 83% power to detect a difference of 20% or larger in this study. The alpha level for the primary and major secondary end points was adjusted to 0.025, because each analysis was conducted for each dose level. The analyses were conducted in a hierarchical step-down manner. With 12 patients per group, the power to detect a difference in the secondary analyses was of 84% for a 16% difference in hemoglobin, 86% for an 11% change in liver volume, and 81% for a 47% change in platelet counts. Missing data for the primary efficacy analysis were handled using a multiple imputation approach to determine patients' final efficacy. A sensitivity analysis was done by using the following approach: a "no-change from baseline" imputation was used for patients with an SAE and missing efficacy data, and a last observation carried forward (LOCF) approach was used for patients with no SAE and missing efficacy data.

For Study 002, the primary efficacy analysis was the evaluation of clinical deterioration. Only descriptive statistics were presented. Clinical deterioration was determined by evaluating the following parameters. Platelet counts: a decrease of > 20% from the mean of six stability evaluation period values of ≤ 120,000, or a decrease of > 40% from the mean of six stability evaluation period values of > 120,000 was considered a clinically relevant deterioration. Hemoglobin: a decrease of > 20% from the mean of six stability evaluation period values was considered a clinically relevant deterioration. Spleen volume: a 20% increase in spleen volume by MRI from baseline to month 9 was considered a clinically relevant deterioration. Liver volume: a 10% increase in liver volume by MRI from baseline to month 9 was considered a clinically relevant deterioration. The sample size of Study 002 was not based on power calculation. No imputation for dropouts or missing data was used in any efficacy analysis.

For Study 004, the primary objective was the assessment of safety. No formal hypothesis testing for efficacy was planned or done. Study end points were not analyzed by inferential statistics. Only descriptive statistics were provided. The sample size was not based on a power calculation. Missing data were not imputed.

In Study 005, the primary analysis was the median percentage change from baseline in hemoglobin. The study end point was not analyzed by inferential statistics. Descriptive statistical analyses were performed by age and by dose. The sample size was not based on power calculation. Missing data were not imputed. Some other secondary analyses were post-hoc analyses.

a) Analysis Populations

In Study 001, three analysis populations were defined:

- Modified intention-to-treat (mITT): patients who received at least one dose of medication and had at least the screening or baseline evaluation.
- Per-protocol (PP) population: all mITT patients who completed nine months and had no major protocol violations.
- Safety population: patients who received at least one dose of study medication.

In studies 002 and 005, the study population included all patients who received at least one dose of study medication.

In Study 004, two analysis populations were defined as follows:

- The safety population: all patients who received any dose of study medication.
- The efficacy population: all patients who received at least one complete dose of study medication and completed the month 9 visit.

3.3 Patient Disposition

Patient disposition in studies 001, 002, 004, and 005 is summarized in Table 9. Across studies, discontinuation rates ranged from 0% in Study 005 to [redacted]% in Study 004. Study 004 had the greatest discontinuation rate ([redacted]%), but was by far the longest trial with a [redacted]. Even when comparing across studies for the same duration (i.e., nine months), [redacted]% (calculated from the efficacy set) of patients in Study 004 who received the drug discontinued before the nine-month end point ([redacted]% of all discontinuations). Across the trials, the two most common reasons for discontinuation were AEs (13.8%)and withdrawal of consent (65.5%) for all discontinuations. Of note: three patients (10.3% of all discontinuations) withdrew consent because of AEs. No apparent imbalance in discontinuation rates was observed between treatment groups for a different dosing regimen.

TABLE 9: PATIENT DISPOSITION

	Study 001		Study 002		Study 004	Study 005	
	TALI 30 U/kg	TALI 60 U/kg	Adults	Pediatric Patients	All Patients	TALI 30 U/kg	TALI 60 U/kg
Screened, N	44		46		[redacted]	11[a]	
Randomized or eligible, N (%)	16	17	28	5	[redacted]	6	5
Discontinued study, N (%)	2 (12.5)	2 (11.8)	3 (10.7)	0	[redacted]	0	0
• AE	1 (6.3)	1 (5.9)	0	0	[redacted]	NR	NR
• Major protocol deviation	1 (6.3)	0	0	0	[redacted]	NR	NR
• Withdrew consent/voluntary withdrawal	0	1 (5.9)[b]	3 (10.7)[c]	0	[redacted][d]	NR	NR
• Investigator recommendation	NR	NR	NR	NR	[redacted]	NR	NR
• Lost to follow-up	NR	NR	NR	NR	[redacted]	NR	NR
mITT, N (%)	15 (93.8)[e]	16 (94.1)	NR	NR	NR	NR	NR
PP, N (%)	15 (93.8)	15 (88.2)	NR	NR	NR	NR	NR
Safety set, N (%)	16 (100)	16 (94.1)	26 (92.9)	5 (100)	58 (98.3)[f]	NR	NR
Efficacy set, N (%)	NR	NR	NR	NR	[redacted]	NR	NR

AE = adverse event; mITT = modified intention-to-treat; NR = not reported; PP = per-protocol population; TALI = taliglucerase alfa; U = unit.

[a] All screened patients were eligible and randomized. No patients were excluded from the study analyses.

[b] One patient withdrew consent after randomization but before having received the drug.

[c] Two patients withdrew from the study prior to the treatment. One patient discontinued the study after he experienced an allergic reaction during the first infusion and refused to continue infusions with premedication.

[redacted]

[e] One patient experienced an AE and received only a partial dose of study medication (3.3% of the dose) during the first infusion, and was excluded from the intention-to-treat population..

[f] One patient with very mild disease did not meet inclusion criteria and was discontinued prior to treatment.

Source: Clinical Study Reports for Study 001,[14] Study 002,[15] Study 004,[16] and Study 005.[17]

3.4 Exposure to Study Treatments

Exposure to the study drug is presented in Table 10. Across trials, pediatric patients were generally more compliant to treatment than adults. However, the number of missed doses was more related to discontinuations rather than a lack of compliance. [redacted]

TABLE 10: EXTENTOF EXPOSURE TO STUDY DRUG

	Study 001		Study 002		Study 004	Study 005	
	TALI 30 U/kg N = 16	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Safety Set N = [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Number of patients who did not receive complete dosing, n (%)	2 (12.5)	1 (6.3)	5 (19.2)	0	NR	1 (16.7)	1 (20.0)
Total number of incomplete or missed doses, n	30	9	20	0	NR	1	1
Mean dose of all infusions in U/kg (SD)	NR	NR	28.8 (16.8)	42.0 (16.4)	[redacted]	34.7 (5.4)	63.7 (3.5)
Mean duration of treatment, in months (SD)	NR	NR	NR	NR	[redacted]	NR	NR

NR = not reported; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Note: Patients who withdrew from study before receiving treatment were not included in the analysis.
Source: Clinical Study Reports for Study 001,[14] Study 002,[15] Study 004,[16] and Study 005.[17]

In studies 001, 002, 004, and 005, concomitant therapy to treat hypersensitivity reactions (e.g., epinephrine, norepinephrine, glucagon, albuterol), anemia (e.g., iron, folic acid, vitamin B12), bone disease (bisphosphonates), and pain (e.g., nonsteroidal anti-inflammatory drugs) were allowed. Concomitant medications are reported in Table 14. The extent of concomitant medication use was not detailed for Study 002.

3.5 Critical Appraisal

3.5.1 Internal Validity

All of the included studies had major limitations. The four trials were limited by a lack of a control group, preventing comparison of TALI to the standard of care (i.e., other ERTs available in Canada). In the trials, all patients and investigators were aware they were receiving or giving TALI during the studies, with the anticipated expectation of improvement. The absence of blinded treatment and blinded outcome assessment rendered the studies susceptible to expectation bias (or Hawthorne effect). Although most of the efficacy outcomes were objective by nature (i.e., change from baseline in hemoglobin level, platelet count, organ size), the absence of a comparator group and potential expectation bias may have influenced more subjective outcomes such as HRQoL. None of the trials used a true intention-to-treat (ITT) approach to perform analyses, which could bias results.

Statistical inferences were not reported in studies 002, 004, and 005; only descriptive statistics were provided. Thus, no inference to the broader GD population can be ascertained from these study samples. Also, these three studies did not account for missing data. Missing data is an issue in all studies due to the small sample sizes; however, this was particularly an issue for Study 004, in which [redacted]% of patients who received the study drug discontinued the study before the nine-month end point. By not taking into account patients who discontinued the study in the analysis and not making any formal comparison with appropriate comparators (namely, other ERTs) it is likely that the efficacy results were

biased in favour of TALI. Low discontinuations rates and good compliance were reported over nine months for studies 001, 002, and 005. The consulting clinical expert deemed the study duration of nine to 12 months adequate for efficacy assessment. The small sample size of all the included studies made it very unlikely that uncommon AEs could be detected.

In studies 001 and 005, patients were randomized according to dose of TALI. The parameters used for randomization, if any, were not disclosed, and a large number of patients were enrolled in a single study site in Study 001. As randomization was likely ineffective because of the small sample sizes, the baseline characteristics were not equally distributed between groups, making it difficult to draw conclusions on differences between treatment groups. Because there was no control group in those studies, randomization or allocation concealment (in regard to dosing) issues were not deemed to be priority concerns. However, it decreases the validity of comparing between the two dosing groups.

Specific internal validity points for each trial are:

- In Study 001, four patients whose laboratory values did not meet the protocol inclusion criteria (i.e., two patients with glucocerebrosidase activities greater than 3 nmol/mg/h and two patients with platelet counts that were > 120,000/mm^3) were approved for randomization. Although it was a protocol deviation, a slightly higher glucocerebrosidase activity was deemed unimportant by the clinical expert involved in the review. Efficacy analyses were performed on an mITT population excluding patients who withdrew from study after randomization and those who discontinued study before having received a complete first dose of study drug, which may overestimate treatment effects and underestimate safety end points. In addition, the statistical analysis did not account for multiple testing after six months and after nine months, but did adjust for testing of two dosing groups. In a study with a small sample size, missing data could have biased the results irrespective of the method used to handle the data. However, sensitivity analyses were performed using a different missing data technique (LOCF) or a different population (PP population), and their results were similar to the primary analyses.
- In Study 002, many protocol amendments were made after the initiation of the study that may have affected study results. The sample size was not based on power calculation.
- In Study 004, [redacted]% of patients were diagnosed with a diagnostic test other than the glucocerebrosidase activity test, DNA sequencing, or bone marrow testing, raising doubts about their diagnosis. The sample size was not based on power calculation.
- In Study 005, amendments to the protocol, including supplemental analyses, were made after the initiation of the study and after unblinding and may have affected study results. Many parameters measured at baseline were not equally distributed between the treatment groups, owing to the small sample size. The sample size was not based on power calculation and was extremely small. The lack of blinding impaired the internal validity of the QoL results. Patients with type 3 GD were analyzed along with patients with type 1 GD, even though the former did not respond to the treatment and therefore may underestimate effects for the group overall.

3.5.2 External Validity

The lack of a head-to-head comparison with any of the other ERTs approved for GD in Canada limited the extrapolation of the results to the GD population. In addition, given that GD shows heterogeneous phenotypes and that studies had small sample sizes, the generalizability of the efficacy and safety results to the general GD population is uncertain. Presumably, the caveat is that this may not be easily avoided in the context of a rare disease. Nonetheless, only one of the four studies reported inferential statistics, making generalizability even more difficult.

In terms of inclusion and exclusion criteria, although the threshold for glucocerebrosidase activity was more stringent than expected by the clinical expert (i.e., a decrease of 10% would have been expected), the clinical expert deemed the criteria were appropriate in general. In terms of baseline characteristics, the clinical expert would have expected higher hemoglobin levels at baseline for patients in studies 002 and 004. The clinical expert also acknowledged that the overall portrait of baseline characteristics of treatment-naive patients was representative of a population with GD.

The treatment regimens used in the trials were aligned with Health Canada's product monograph, but according to the clinical expert involved in the review, doses in clinical practice are closer to 30 U/kg biweekly rather than 60 U/kg biweekly. Patients with type 3 GD were underrepresented in the trials, with only two patients enrolled. Furthermore, these two patients did not show response to the treatment, which was 30 U/kg TALI for both. Of note: the clinical expert involved in the review mentioned that these two patients may have benefited from a dose increase. Nevertheless, based on the efficacy results included, the evidence for the use of TALI for patients with type 3 GD is very limited. As highlighted in the product monograph,[29] the data on pediatric patients (N = 16 patients) are also very limited.

In terms of baseline characteristics, the clinical expert consulted for this review mentioned that the characteristics of the enrolled patients appeared to be representative of patients with GD seen in Canadian clinical practice. Approximately 75% of patients screened were included in Study 001 and 002, and 100% of screened patients were included in Study 005. Inclusion and exclusion criteria were in line with what was expected by the clinical expert. Due to its expanded access purpose, inclusion criteria for Study 004 were very liberal and approximately [redacted] % of the screened patients were enrolled.

Low discontinuation rates may suggest that the study drug was well tolerated in studies 001, 002, and 005. Indeed, the 12-week stability evaluation run-in phase in Study 002 was likely to remove patients with poor compliance or poor tolerance to ERT prior to the study. By contrast, in Study 004, where the population was more likely to be responders to and able to tolerate TALI, [redacted]% of patients who received the drug discontinued before the nine-month end point. This percentage is quite high in comparison to study discontinuations for studies 001 (12.1%), 002 (9.1%), and 005 (0%). The clinical expert involved in the review mentioned that tolerance and adherence with ERT is usually very high.

Studies 002 and 004 switched patients from imiglucerase to TALI, but were conducted in the context of an imiglucerase production shortage. Because of the shortage, patients continuing on imiglucerase prior to switching to TALI may have had their imiglucerase dose lowered (to conserve their remaining supply) or discontinued. Therefore, there is a possibility that some of these patients were not optimally treated at baseline (i.e., they were treated with a reduced dose of ERT because of imiglucerase shortage). This hypothesis may explain why some patients in studies 002 and 004 showed improvements from baseline after switching to TALI at a dose equivalent to the pre-shortage imiglucerase dose.

The input from a patient group mentioned that bone crises were among the most important concerns for GD. This outcome was captured as an AE of special interest and, given the small sample sizes and lack of comparison groups, it could not be interpreted for efficacy assessment. Only Study 005 intended to address improvement for bone crises as an efficacy outcome, but with the very small sample size of 11 patients, no patients had such crises at baseline. Across all trials, efficacy end points relied on surrogate outcomes. According to the clinical expert consulted for the review, taken individually, these outcomes do not equate to improved general health status or improved HRQoL. Rather, in clinical practice, improvements in GD-related bone manifestations (often assessed by reduced use of analgesics

to relieve bone pain), hematological factors, and organ size are assessed together when evaluating treatment effects. Notably, HRQoL was not assessed in studies 001, 002, and 004.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (see Section 2.2, Table 3) are reported below in Table 11 and Table 12. See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Improvement in Hemoglobin Concentration

The two dosing groups in Study 001 showed a statistically significant increase from baseline in hemoglobin level after nine months (1.6 g/dL, $P = 0.001$ for the 30 U/kg group and 2.2 g/dL, $P < 0.0001$ for the 60 U/kg group). No statistical difference was observed between the two groups.

Patients in Study 005 had mean increases from baseline of 1.4 g/dL (relative increase of 13.8%) and 1.6 g/dL (relative increase of 15.8%) after 12 months for the 30 U/kg and 60 U/kg groups, respectively. Individual percentage changes in hemoglobin levels after 12 months are shown in Figure 2. The median percentage changes from baseline at 12 months, which were used as primary efficacy outcomes for this study, were of 12.2% and 14.2% for the 30 U/kg and 60 U/kg groups, respectively. A post-hoc analysis showed similar absolute changes in hemoglobin levels among patients who were anemic at baseline (see Table 18). At nine months, mean changes in hemoglobin levels were numerically lower than at the 12-month end point; i.e., 1.0 g/dL and 1.3 g/dL for the same groups, respectively (see Table 15).

After nine or 12 months, patients in studies 001 and 005 reached normal hemoglobin values that were expected after ERT (i.e., > 11 g/dL for women and children and > 12 g/dL),[6,12] but their baseline values indicated that many patients were very mildly anemic at baseline. No MCID was reported for this outcome in patients with GD.

Patients in Study 002 had small mean changes in hemoglobin from baseline after nine months (e.g., –0.2 g/dL, –1.8% for adults; and 0.4 g/dL, 3.3% for pediatric patients). None of these stable patients had a clinically relevant deterioration; i.e., a decrease of > 20% from the stability evaluation period values. In Study 004, mean changes in hemoglobin after nine months ([redacted]g/dL) and at last visit ([redacted]g/dL; see Table 16) [redacted].

3.6.2 Improvement in Platelet Counts

Patients in Study 001 appeared to have dose-dependent mean changes from baseline in platelet counts at nine months of 11,427/mm^3 ($P = 0.046$, not statistically significant at pre-specified alpha level of 0.025) and 41,494/mm^3 ($P = 0.0031$) for the 30 U/kg and 60 U/kg groups, respectively. The difference observed between the two dosing groups was statistically significant ($P = 0.042$).

In Study 005, mean changes from baseline in platelet counts after 12 months were 45,500/mm^3 (30.9%) and 72,600/mm^3 (73.7%) for the 30 U/kg and 60 U/kg groups, respectively. Individual changes in platelet counts after 12 months are shown in Figure 3. A post-hoc analysis showed increases in platelet counts from baseline after 12 months of 56,500/mm^3 (53.3%) and 57,750/mm^3 (73.4%) among patients who were thrombocytopenic at baseline (see Table 19).

Treatment goals for platelet counts[6,12] depend on baseline values. Previously untreated adult patients in Study 001 who had low platelet counts at baseline reached the expected 50% improvement after nine months when they were treated with a 60 U/kg TALI dose, but still remained under normal values. In comparison, adult patients treated at the 30 U/kg dose had improvement from baseline of

approximately 15%. Previously untreated pediatric patients in Study 005 had higher values at baseline and reached mean normal values after 12 months. No MCID was reported for this outcome in patients with GD.

Patients in Study 002 had mean changes in platelet counts after nine months of –2,527/mm^3 (–1.5%) for adults and 12,813/mm^3 (11.7%) for pediatric patients. Two adult patients (8%) showed a clinically relevant deterioration: i.e., a decrease of >20% from the stability evaluation period values of ≤ 120,000, and of > 40% from the stability evaluation period values of > 120,000 (see Table 15).

In Study 004, mean changes in platelet counts from baseline after nine months and at last visit were of [redacted]/mm^3 and [redacted]/mm^3.

3.6.3 Improvement in Spleen Volume

For the primary outcome in Study 001, patients had statistically significant (P < 0.0001) changes in spleen volume from baseline after nine months of –26.9% and –38.0% for the 30 U/kg and 60 U/kg groups, respectively. No statistically significant difference was observed between these two groups (P = 0.06). All patients in Study 001 reached a 10% reduction in spleen volume (see Table 20).

In Study 005, changes in spleen volume from baseline at 12 months were of –28.6% (–8.2 multiples of normal) and –41.1% (–16.5 multiples of normal) for the 30 U/kg and 60 U/kg groups, respectively. Individual changes in spleen volume after 12 months are shown in Figure 4.

Patients in studies 001 and 005 met the expected decreases of 30% to 50% in spleen volume after one year, as per guidelines[6,12] for treatment of patients with GD. No MCID was reported for this outcome in patients with GD.

In Study 002, after nine months, adult patients had a mean change of spleen volume from baseline of –7.6% (a change of –0.4 multiples of normal). For pediatric patients, this change was of –6.6% (a change of –0.8 multiples of normal). One (5%) adult patient had a clinically relevant deterioration; i.e., a 20% increase in spleen volume at month 9 (see Table 15).

Changes in spleen volume from baseline were not reported in Study 004.

3.6.4 Improvement in Liver Volume

In Study 001, statistically significant changes in liver volume from baseline of –10.48% (P = 0.0041) and –11.11% (P < 0.0001) were observed for the 30 U/kg and 60 U/kg groups, respectively. No statistically significant difference was observed between these two groups (P = 0.349).

For patients in Study 005, changes in liver volume from baseline were of –6.3% (–0.3 multiples of normal) and –14.0% (–0.6 multiples of normal) for the 30 U/kg and 60 U/kg groups, respectively. Individual changes in liver volume after 12 months are shown in Figure 5.

Although no clear MCID was identified for this outcome, the decreases observed in studies 001 and 005 did not meet the therapeutic target of normal volume (1.0 to 1.5 multiples of normal) or a decrease of 20% to 30% after 12 months.[6,12]

In Study 002, patients had changes in liver volume from baseline of –3.5% and 2.4% for adult and pediatric patients, respectively, after nine months. One adult patient (4.3%) and one pediatric patient

(20.0%) had clinically relevant deterioration for liver volume; i.e., a 10% increase in liver volume after nine months (see Table 15).

Changes in liver volume from baseline were not reported in Study 004.

3.6.5 Growth in Pediatric Patients

Growth, assessed by height and weight, was evaluated in Study 005 only (see Table 12). Changes in height from baseline after 12 months were of 4.2 cm and 7.6 cm for the 30 U/kg and 60 U/kg groups, respectively. Height velocities were of 5.1 cm and 8.0 cm per year for the same groups, respectively. Changes from baseline in height SD scores based on chronological age and bone age reported by a post-hoc analysis were of less than 1 cm. Changes in weight from baseline after 12 months were of 9.6 kg and 14.7 kg for the 30 U/kg and 60 U/kg groups, respectively. Changes from baseline in weight SD scores based on chronological age and bone age (post-hoc analysis) were of less than 0.3 kg. Changes in bone age from baseline assessed by X-ray were of 1.9 years and 1.4 years for the 30 U/kg and 60 U/kg groups, respectively, after 12 months.

The therapeutic target for growth is normalization,[6,12] but based on results from Study 005, it is too difficult to state whether patients had improvements. Also, no MCID was reported for this outcome in patients with GD.

3.6.6 Other Efficacy Outcomes

In Study 001, statistically significant changes from baseline in chitotriosidase activity of –13,264 ($P <$ 0.0001) and –12,165 nmol/mL/h ($P = 0.0016$) were observed for the 30 U/kg and 60 U/kg groups, respectively, after nine months (see Table 21). Patients in Study 005 had changes in chitotriosidase activity of –13,210 (–58.5%) and –20,528 (–66.1%) nmol/mL/h for the 30 U/kg and 60 U/kg groups, respectively, after 12 months. In comparison, after nine months, the changes in chitotriosidase activity were numerically lower with decreases of 57.2% and 58.9% for the same groups, respectively. In Study 002, changes from baseline after nine months were of –1,206 (–21.3 %) and –1,877 (–29.7%) nmol/mL/h for adult and pediatric patients, respectively. No MCID was reported for this outcome in patients with GD.

CCL18 levels were reported in studies 002 and 005. In study 002, mean changes in CCL18 levels from baseline at nine months were of –18.8 ng/mL (–6.6%) for adults and of –88.8 ng/mL (–4.4%) for pediatric patients (see Table 21). In Study 005, mean changes from baseline at 12 months were of –498.2 ng/mL (–50.6%) and –637.0 ng/mL (–52.6%) for the 30 U/kg and 60 U/kg groups, respectively. In comparison, after nine months, patients in Study 005 had mean changes of CCL18 levels from baseline of –508.5 ng/mL (–49.9%) and –555.0 ng/mL (–46.5%), for the same groups, respectively. No MCID was reported for this outcome in patients with GD.

The CHQ-PF28 was used to collect data on HRQoL in Study 005 (see Table 22). Standardized scores for general health (question 1.1) numerically increased from baseline at 12 months. Changes were of 10.8 points for the 30 U /kg group and 10.0 points for the 60 U/kg group. No MCID was reported for this outcome in patients with GD.

Bone disease was evaluated with DEXA scores (z score, t score, and BMD; see Table 23 to Table 27) and QCSI scores (see Table 28). DEXA scores for lumbar spine, femoral neck, and total hip were reported in Study 001. In that study, z scores and t scores had small numerical increases (from 0.1 to 0.7 points) for lumbar spine and femoral neck, but small numerical decreases (from 0.1 to 0.5 points) for total hip.

BMD was more or less stable for all bone sites. In Study 005, changes from baseline in z and t scores after 12 months ranged from −0.30 to 0.50 for lumbar spine and femoral neck. BMD at 12 months remained stable in Study 005 compared with baseline. No MCID was reported for this outcome in patients with GD.

QCSI score was assessed in Study 001. After nine months, patients had changes from baseline of 0.0700 and 0.1225 for the 30 U/kg and 60 U/kg groups, respectively. No MCID was reported for this outcome in patients with GD.

TABLE 11: KEY EFFICACY OUTCOMES — HEMATOLOGICAL PARAMETERS, AND SPLEEN AND LIVER VOLUMES

	Study 001 (9 Months)		Study 002 (9 Months)		Study 004 (9 Months)	Study 005 (12 Months)	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Efficacy Set N = [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Hb Levels (g/dL)							
n (%)	14 (93.3)	15 (93.8)	25 (96.2)	5 (100)	[redacted]	6 (100)	5 (100)
Baseline, mean (SD)	12.2 (1.7)	11.4 (2.6)	13.5 (1.6)	13.5 (0.5)	[redacted]	11.3 (1.7)	10.6 (1.4)
Mean at end point[a] (SD)	14.0 (1.4)	13.6 (2.0)	13.3 (1.6)	13.9 (1.3)	[redacted]	12.7 (1.2)	12.2 (1.1)
Change from baseline, mean (SD)	1.6 (1.4)	2.2 (1.4)	–0.2 (0.7)	0.4 (1.4)	[redacted]	1.4 (1.3)	1.6 (0.7)
P value	0.0010	< 0.0001	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.719		NR		NR	NR	
Percentage change from baseline: mean (SD), median (interquartile range)	NR NR	NR NR	–1.8 (4.9) –2.5 (NR)	3.3 (10.7) 0.7 (NR)	NR NR	13.8 (14.5) 12.2 (20.6)	15.8 (8.3) 14.2 (10.4)
Platelet Counts (/mm^3)							
n (%)	15 (100)	16 (100)	25 (96.2)	5 (100)	[redacted]	6 (100)	5 (100)
Baseline, mean (SD)	75,320 (NR)	65,038 (NR)	160,447 (79,086)	164,587 (38,731)	[redacted]	162,667 (71,838)	99,600 (42,899)
Mean at end point[a] (SD)	86,747 (50,989)	106,531 (53,212)	157,920 (87,130)	177,400 (37,554)	[redacted]	208,167 (90,747)	172,200 (89,290)
Change from baseline, mean (SD)	11,427 (20,214)	41,494 (47,063)	–2,527 (29,871)	12,813 (43,756)	[redacted]	45,500 (52,884)	72,600 (59,197)
P value	0.0460[b]	0.0031	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.042		NR		NR	NR	
Percentage change from baseline, mean (SD)	NR	NR	–1.5 (21.6)	11.7 (34.9)	NR	30.9 (35.1)	73.7 (61.9)

	Study 001 (9 Months)		Study 002 (9 Months)		Study 004 (9 Months)	Study 005 (12 Months)	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Efficacy Set N = [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Spleen Volume							
In mL							
n (%)	15 (100)	16 (100)	20 (76.9)	5 (100)	NR	6 (100)	5 (100)
Baseline, mean (SD)	2,130.94 (1,154.72)	2,117.38 (1,356.17)	822.4 (603.7)	313.0 (156.0)	NR	1,218 (638.4)	1,023 (753.4)
Mean at end point[a] (SD)	1,566.08 (900.17)	1,376.89 (1,055.81)	749.3 (559.7)	276.3 (107.9)	NR	811.6 (409.6)	524.0 (281.1)
Change from baseline, mean (SD)	NR	NR	–73.1 (146.9)	–36.7 (52.5)	NR	–407 (372.7)	–499 (493.3)
Percentage change from baseline, mean (SD)	–26.91 (7.79)	–38.01 (9.38)	–7.6 (13.3)	–6.6 (15.6)	NR	–28.6 (21.5)	–41.1 (13.8)
P value	< 0.0001	< 0.0001	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.060		NR		NR	NR	
In MN							
n (%)	NR	NR	20 (76.9)	5 (100)	NR	6 (100)	5 (100)
Baseline, mean (SD)	NR	NR	5.5 (4.8)	4.1 (2.7)	NR	22.2 (12.1)	29.4 (24.3)
Mean at end point[a] (SD)	NR	NR	5.1 (5.1)	3.3 (1.8)	NR	14.0 (8.6)	12.9 (7.2)
Change from baseline, mean (SD)	NR	NR	–0.4 (1.1)	–0.8 (0.9)	NR	–8.2 (6.4)	–16.5 (17.1)
Percentage change from baseline, mean (SD)	NR	NR	–7.9 (13.0)	–12.4 (14.4)	NR	–34.1 (22.7)	–48.5 (12.3)
Liver Volume							
In mL							
n (%)	14 (93.3)	15 (93.8)	23 (88.5)	5 (100)	NR	6 (100)	5 (100)
Baseline, mean (SD)	2,880.60 (736.12)	2,481.31 (452.74)	1,857 (440.0)	1,346 (431.7)	NR	1,214 (424.7)	991.7 (301.3)
Mean at end point[a] (SD)	2,564.07 (559.57)	2,190.99 (376.70)	1,786 (423.7)	1,393 (506.0)	NR	1,116 (366.9)	849.1 (271.9)
Change from baseline, mean (SD)	NR	NR	–71.6 (166.3)	47.7 (97.5)	NR	–98.7 (75.0)	–143 (102.9)

	Study 001 (9 Months)		Study 002 (9 Months)		Study 004 (9 Months)	Study 005 (12 Months)	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Efficacy Set N = [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Percentage change from baseline, mean (SD)	–10.48 (11.27)	–11.11 (6.68)	–3.5 (8.1)	2.4 (6.8)	NR	–6.3 (8.5)	–14.0 (9.0)
P value	0.0041	< 0.0001	NR	NR	NR	NR	NR
Difference between groups, *P* value	0.349		NR		NR	NR	
In MN							
n (%)	NR	NR	23 (88.5)	5 (100)	NR	6 (100)	5 (100)
Baseline, mean (SD)	NR	NR	1.0 (0.2)	1.3 (0.3)	NR	1.8 (0.5)	2.2 (0.5)
Mean at end point[a] (SD)	NR	NR	0.9 (0.2)	1.2 (0.3)	NR	1.5 (0.4)	1.7 (0.3)
Change from baseline, mean (SD)	NR	NR	–0.0 (0.1)	–0.1 (0.1)	NR	–0.3 (0.2)	–0.6 (0.3)
Percentage change from baseline, mean (SD)	NR	NR	–3.7 (6.6)	–4.0 (4.2)	NR	–14.5 (6.5)	–25.0 (6.6)

Hb = hemoglobin; MN = multiples of normal; NR = not reported; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
[a] The time of end point was 9 months for studies 001, 002, and 004, and 12 months for Study 005.
[b] The pre-specified alpha level was 0.025; thus, the difference was not statistically significant.
Source: Clinical Study Reports for Study 001,[14] Study 002,[15] Study 004,[16] and Study 005.[17]

TABLE 12: KEY EFFICACY OUTCOME — CHANGE IN HEIGHT AND WEIGHT IN PEDIATRIC PATIENTS AT 12 MONTHS IN STUDY 005 (POST-HOC ANALYSIS FOR STANDARD DEVIATION SCORE DATA)

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Height (cm)		
n (%)	6 (100)	5 (100)
Baseline, mean (SD)	129.3 (21.7)	107.8 (14.3)
Mean at 12 months (SD)	134.4 (20.8)	115.7 (13.9)
Percentage change from baseline, mean (SD)	4.2 (2.2)	7.6 (2.1)
Height velocity (cm/year)	5.1 (2.2)	8.0 (1.3)
Height SDS by Chronologic Age		
n (%)	6 (100)	5 (100)
Baseline, mean (SD)	–1.3 (1.3)	–2.5 (1.2)
Mean at 12 months (SD)	–1.3 (1.5)	–2.0 (1.0)

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Change from baseline, mean (SD)	0.0 (0.3)	0.5 (0.2)
Height SDS by Bone Age		
n (%)	4 (66.7)	4 (80.0)
Baseline, mean (SD)	0.1 (1.8)	0.9 (1.7)
Mean at 12 months (SD)	–0.6 (2.0)	0.5 (1.5)
Change from baseline, mean (SD)	–0.8 (1.2)	–0.3 (0.5)
Weight (kg)		
n (%)	6 (100)	5 (100)
Baseline, mean (SD)	27.9 (10.5)	17.7 (4.8)
Mean at 12 months (SD)	30.3 (10.5)	20.4 (6.0)
Percentage change from baseline, mean (SD)	9.6 (7.0)	14.7 (5.7)
Weight SDS by Chronologic Age		
n	3 (50.0)	4 (80.0)
Baseline, mean (SD)	–0.8 (1.5)	–2.0 (1.8)
Mean at 12 months (SD)	–0.8 (1.8)	–1.8 (1.8)
Change from baseline, mean (SD)	0.0 (0.3)	0.2 (0.3)
Weight SDS by Bone Age		
n	2 (33.3)	5 (100)
Baseline, mean (SD)	0.3 (2.2)	0.3 (0.8)
Mean at 12 months (SD)	0.0 (2.2)	0.0 (0.7)
Change from baseline, mean (SD)	–0.3 (0.0)	–0.3 (0.3)
Bone Age by X-ray (years)		
n	4 (66.7)	5 (100)
Baseline, mean (SD)	9.0 (2.8)	4.5 (2.6)
Mean at 12 months (SD)	10.9 (3.1)	5.9 (2.8)
Change from baseline, mean (SD)	1.9 (1.4)	1.4 (0.3)

N = number of patients; n = number of patients with event; SD = standard deviation; SDS = standard deviation scores; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 005.[17]

3.7 Harms

Only those harms identified in the review protocol (see 2.2.1, Protocol) are reported in Table 13. AEs, SAEs, mortality WDAEs, and notable AEs identified in consultation with the clinical expert are reported. The long-term safety of TALI was reported in Study 003 (see APPENDIX 5: SUMMARY OF THE EXTENSION STUDY).

3.7.1 Adverse Events

Across trials, incidence rates of AEs for each group varied between 68.8% and 100%. No apparent association of AE rates with dosing regimen was observed.

The most common AEs were headache (total occurrence of 19.7%), arthralgia (16.7%), upper respiratory tract infection (14.4%), and nasopharyngitis (12.9%). Due to small differences in the number of events, no increased occurrence could be associated with a specific dosing regimen.

Bone pain and bone crises were captured as AEs of special interest in the included trials. One event of bone pain occurred in one adult in Study 002, [redacted] events occurred during Study 004, and one event occurred in the 30 U/kg group of Study 005 for a total occurrence of 3.8%.

3.7.2 Serious Adverse Events

Across trials, SAEs occurred in 4.5% of all patients. The occurrence of SAEs did not seem to be related to the dosing regimen of TALI. No trend in the nature of SAEs was observed.

3.7.3 Withdrawals due to Adverse Events

Overall, WDAEs occurred in 3.0% of all patients. Four cases were reported and all were due to hypersensitivity or infusion-related reactions. Of note: one patient in Study 002 withdrew consent after experiencing hypersensitivity reaction and [redacted] patients in Study 004 withdrew consent mainly because of AEs, but these [redacted] patients were not imputed as WDAEs by the investigators.

3.7.4 Mortality

No deaths occurred during the trials.

3.7.5 Notable Harms

Notable harms identified in consultation with the clinical expert were anaphylaxis, infusion-related reactions, hypersensitivity reactions, and positive detection of anti-TALI antibodies. No cases of anaphylaxis were reported. Infusion-related and hypersensitivity reactions occurred in 5.3% and 4.5% of all patients, respectively. A positive anti-TALI antibody test was observed in 22.7% of all patients. In Study 004, [redacted]% of patients were positive for anti-TALI antibodies, of which [redacted]% had treatment-induced antibodies (defined as a patient who is negative at baseline but has one positive sample thereafter, or who is positive at baseline and has one titer that is ≥ 6-fold the initial titer thereafter). A single patient with a positive in vivo test for neutralizing antibodies was observed, but a small proportion of the patients with anti-TALI antibodies were tested for neutralizing antibodies. No association of notable AEs with dosing regimen was observed.

TABLE 13: HARMS

	Study 001		Study 002		Study 004	Study 005	
	TALI 30 U/kg N = 16	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Safety Set N = [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
AEs							
Patients with > 0 AEs, n (%)	12 (75.0)	11 (68.8)	25 (96.2)	4 (80.0)	[redacted]	5 (83.3)	5 (100.0)
Most common AEs[a], n (%)							
Headache	1 (6.3)	5 (31.3)	3 (11.5)	1 (20.0)	[redacted]	1 (16.7)	1 (20.0)
Upper respiratory tract infection	3 (18.8)	2 (12.5)	2 (7.7)	1 (20.0)	[redacted]	1 (16.7)	0
Arthralgia	1 (6.3)	3 (18.8)	3 (11.5)	1 (20.0)	[redacted]	NR	NR
Nasopharyngitis	0	2 (12.5)	4 (15.4)	0	[redacted]	0	2 (40.0)
Vomiting	2 (12.5)	0	0	1 (20.0)	[redacted]	2 (33.3)	2 (40.0)
Pharyngitis	3 (18.8)	2 (12.5)	1 (3.8)	0	[redacted]	NR	NR
Influenza	1 (6.3)	3 (18.8)	1 (3.8)	0	[redacted]	0	1 (20.0)
Urinary tract infection	0	2 (12.5)	3 (11.5)	0	[redacted]	NR	NR
Cough	1 (6.3)	0	2 (7.7)	1 (20.0)	[redacted]	0	1 (20.0)
Dizziness	2 (12.5)	1 (6.3)	NR	NR	[redacted]	NR	NR
Nausea	1 (6.3)	2 (12.5)	NR	NR	[redacted]	NR	NR
Fatigue	1 (6.3)	2 (12.5)	NR	NR	[redacted]	NR	NR
Back pain	0	1 (6.3)	1 (3.8)	0	[redacted]	NR	NR
Pain in extremity	NR	NR	3 (11.5)	0	[redacted]	1 (16.7)	1 (20.0)
Nasal congestion	NR	NR	NR	NR	[redacted]	NR	NR
Oropharyngeal pain	NR	NR	NR	NR	[redacted]	NR	NR
Peripheral oedema	NR	NR	NR	NR	[redacted]	NR	NR
SAEs							
Patients with > 0 SAEs, n (%)	0	0	3 (11.5)	0	[redacted]	0	1 (20.0)
WDAEs							
WDAEs, n (%)	1 (6.3)	1 (6.3)	0[b]	0	[redacted]	0	0
Most common reason for WDAEs							
Hypersensitivity or infusion-related reaction	1 (6.3)	1 (6.3)	NR	NR	[redacted]	NR	NR
Deaths							
Number of deaths, n (%)	0	0	0	0	[redacted]	0	0
Notable harms							
Anaphylaxis	NR	NR	NR	NR	NR	NR	NR
Infusion-related reactions	NR	NR	4 (15.4)	0	[redacted]	NR	NR
Hypersensitivity	1 (6.3)	1 (6.3)	1 (3.8)	0	[redacted]	0	2 (40.0)

	Study 001		Study 002		Study 004	Study 005	
	TALI 30 U/kg N = 16	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	Safety Set N = [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Anti-human TALI Ab results							
IgG positive to human TALI, n (%)	1 (6.3)	1 (6.3)	5 (19.2)	2 (40.0)	[redacted]	1 (16.7)	2 (40.0)
Treatment-induced Ab, n (%)	NR	NR	NR	NR	[redacted]	NR	NR
Positive for neutralizing Ab, n (%)	0	0	1 (3.8)[c]	0	NR	NA	NA

Ab = antibodies; AEs = adverse events; IgG = immunoglobulin G; n = number of patients with event; N = number of patients; NA = reported as not available; NR = not reported; SAEs = serious adverse events; TALI = taliglucerase alfa; U = unit; WDAE = withdrawal due to adverse event.

[a] Experiences by ≥ 12% of patients.

[b] One patient withdrew consent after experiencing hypersensitivity reaction during the first infusion.

[c] One patient was positive for in vitro neutralizing activity, but negative for the in vivo neutralizing activity test.

Source: Clinical Study Reports for Study 001,[14] Study 002,[15] Study 004,[16] and Study 005.[17]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence included in this review was derived from four phase 3, multi-centre trials that evaluated the efficacy and safety of TALI IV infusions biweekly in adults (N = 120) and pediatric patients (N = 16, of which two were confirmed type 3 GD patients) with GD. Untreated patients in studies 001 and 005 were randomized 1:1 between two groups who received 30 U/kg and 60 U/kg of TALI biweekly, respectively. Study 001 enrolled only adults and had a nine-month duration. The primary objective of Study 001 was to compare two doses of TALI for the percentage change from baseline of spleen volume in untreated patients. Study 005 enrolled only pediatric patients and lasted for 12 months. The primary objective of Study 005 was to compare two doses of TALI on the median percentage change in hemoglobin levels from baseline. Patients in studies 002 and 004 were previously on ERT and were switched to TALI administered at a dose equivalent to their previous imiglucerase dose, or to the dose prior to the imiglucerase shortage. Study 002 lasted nine months and Study 004 had duration of up to 33 months. The primary objective of Study 002 was to show the clinical stability of patients as assessed by platelet counts, hemoglobin levels, and spleen and liver volumes. The primary objective of Study 004 was to assess the safety of TALI as measured by AEs, anti-TALI antibodies, and clinical laboratory parameters, but was not more specifically described. Other efficacy outcomes assessed in the trials included growth in children, biomarkers (chitotriosidase and CCL18) levels, and bone density (with DEXA and QCSI). Quality of life was assessed in pediatric patients with the CHQ-PF28. End points were measured at nine months and 12 months.

The four trials were limited by the lack of a control group, preventing comparison of TALI to the standard of care (i.e., other ERTs available in Canada). All patients and investigators were aware that they were receiving or giving TALI during the studies, and there is therefore a high probability that knowledge of treatment status could influence assessment of certain outcomes; namely, those of a subjective nature such as HRQoL. However, three of the four studies used fairly objective outcome measures (i.e., hemoglobin levels, platelet counts, and organ size); hence, any potential bias introduced by patients and/or investigator knowledge of the treatment received or administered may be lessened. In studies 002, 004, and 005, the sample sizes were not based on power calculations, statistical inferences were not reported, and missing data were not imputed. This is likely to be in favour of the efficacy of the study drug. The small sample size of all studies made it very improbable that uncommon AEs would be detected and also impaired generalizability to the general GD population. Data on pediatric patients (N = 16) and on patients with types 3 GD (N = 2) are limited. Low discontinuation rates and good compliance were reported over nine months for studies 001, 002, and 005, but higher discontinuations were reported for Study 004, in which the population was likely be more used to ERT. The study population from the trials appeared to be representative of patients with GD seen in Canadian clinical practice, but there is a possibility that patients in studies 002 and 004 were not optimally treated with ERT at baseline. Bone crises were among the most important concerns identified by patients with GD in the patient input, but this outcome could not be interpreted for efficacy. Efficacy was based on surrogate outcomes such as hemoglobin level and platelet counts, although these are routinely measured in clinical practice in order to wholly assess patients' clinical status.

In addition to the studies that met the inclusion criteria for the review, evidence from a manufacturer-submitted extension study (Study 003) and three systematic reviews of ERTs for GD are summarized and critically appraised in APPENDIX 5: SUMMARY OF THE EXTENSION STUDY) and APPENDIX 6: SUMMARY

OF SYSTEMATIC REVIEWS), respectively. Study 003 was an extension study that enrolled 45 patients from studies 001 and 002 and reported end points after 36 and 39 months of ERT.

4.2 Interpretation of Results

4.2.1 Efficacy

Hemoglobin levels were improved from baseline when treatment-naive patients were treated with TALI at 30 U/kg and 60 U/kg doses for nine to 12 months. This increase from baseline was found to be statistically significant in Study 001, the only study that conducted statistical analyses. After 39 months, the improvement from baseline increased up to 2.8 g/dL in the extension Study 003. At end points, previously untreated patients met the normal hemoglobin values of > 11 g/dL for women and children and > 12 g/dL that were expected as per guidelines.[6,12] However, many patients in studies 001 and 005 were only very mildly anemic at baseline. When patients were switched from imiglucerase to TALI, hemoglobin levels remained stable after nine months (studies 002 [redacted]) and 39 months (Study 003). None of the patients in Study 002 had a clinically relevant deterioration for hemoglobin after switching to TALI for nine months.

Platelet counts improved from baseline in treatment-naive patients treated with TALI for nine to 12 months. Increases were numerically higher in pediatric patients (increases of 30.9% to 73.7%) than in adults (increases of 15.2% to 63.8%). In Study 001, the only study to conduct statistical analyses, the increase from baseline to nine months was statistically significant only in the 60 U/kg group, and a statistically significant difference was observed between the two dosing groups. After 39 months, changes from baseline in adult patients were numerically higher (57% to 118% increase) than at nine months and reached near normal values in the highest dose. As mentioned in the clinical practice guidelines,[6,12] treatment goals for platelet counts depend on baseline values. Because adult patients had lower platelet counts at baseline, an increase of 50% was expected, but, on average, they were still thrombocytopenic after nine months. Pediatric patients had higher values at baseline and reached normal values after 12 months. Most of the patients in studies 002 [redacted] who were switched from imiglucerase to TALI had maintenance or numerical increase in platelet counts in the range of normal values, but 8% of patients in Study 002 had a clinically significant deterioration.

Patients who were previously untreated had decreases in spleen volume from baseline ranging from 26.9% to 41.1% after nine to 12 months. In Study 001, the decrease from baseline was statistically significant for the two groups. After 36 months, patients had changes in spleen volume from baseline ranging from –47% to –62%. These values are in line with the expected decreases of 30% to 50% in spleen volume after one year and 50% to 60% after two to five years, as per guidelines[6,12] for treatment of patients with GD. In patients who were previously treated with imiglucerase and then switched to TALI, spleen volume was maintained over nine months (< 8% change) and numerically decreased over 36 months (–21% change). In Study 002, 5% of adult patients had a clinically relevant deterioration over nine months.

Previously untreated patients who were treated with TALI had liver volume change from baseline ranging from –6.3 % to –14.0% after nine to 12 months. In Study 001, the decrease from baseline was statistically significant for both dose groups. After 36 months, liver volumes were decreased from baseline by approximately 25%. These results are below the therapeutic target of normalization of volume (1.0 to 1.5 times normal) or a decrease of 20% to 30% within 12 months and 30% to 40% over two to five years.[6,12] Patients switched from imiglucerase to TALI had their liver volume maintained after nine and 36 months. In Study 002, 6.5% of patients had a clinically significant deterioration after nine months.

Child growth was measured in Study 005 with a very small sample size, including two patients with type 3 GD. Although patients had numerical increases in height and weight from baseline after 12 months, changes from baseline in height and weight SD scores based on chronological age and bone age were not significant. Changes in bone age from baseline varied from 1.9 to 1.4 years after 12 months. As acknowledged by the clinical expert involved in the review, the few patients in that study were heterogeneous for age at baseline. Thus, it is difficult to draw conclusions for these growth-related end points.

Chitotriosidase and CCL18 were measured as biomarkers for GD. Treatment-naive patients had improvements from baseline in both biomarkers after nine to 12 months, and this response was numerically better after 39 months. Chitotriosidase activity was reported to correlate with disease severity,[36] but no specific therapeutic targets were identified for biomarkers. In patients who switched from imiglucerase to TALI, numerical improvements from baseline were observed in chitotriosidase activities, and CCL18 levels were stable after nine months. After 39 months, both biomarkers appeared improved from baseline. These results indicate that TALI had a biological effect per its mechanism of action, as expected.

HRQoL was assessed in pediatric patients with the CHQ-PF28, a questionnaire completed by parents for patients aged between five and 18 years. The standardized score for general health numerically increased from baseline at 12 months, but the validity of this instrument for patients with GD has not been demonstrated in the literature. This type of outcome is also very sensitive to bias introduced due to lack of patients and/or investigator blinding to study treatment, which had a high risk for Study 005.

Bone disease was evaluated with z score, t score, BMD, and QCSI scores at nine, 12, and 36 months. In treatment-naive patients, z scores and t scores had small numerical increases from baseline for lumbar spine and femoral neck, but had small numerical decreases for total hip. QCSI scores also had a small numerical increase from baseline. According to the consulting clinical expert, these differences were too small to be clinically relevant. BMD was more or less stable for all bone sites. Results from Study 005 were too heterogeneous to be interpreted. The clinical expert consulted for this review questioned the value of DEXA and QCSI scores for short-term clinical trials in GD, especially in children.

In Study 001, the comparison of the 30 U/kg dose with the 60 U/kg dose for TALI did not show a statistically significant difference, except for platelet counts. Hence, it is uncertain whether the 60 U/kg TALI dose added clinical benefits to the 30 U/kg TALI dose, except for platelet counts. The clinical expert agreed that a higher dose did not add benefits, although a more rapid response may be achieved with a higher dose.

Two patients with type 3 GD were included in the population under review; both patients were enrolled in Study 005. The individual results for these patients showed no or very few benefits for hemoglobin, platelet counts, spleen volume, and liver volume. Therefore, the efficacy data to support the use of TALI for patients with type 3 GD are very limited, even though the clinical expert involved in the review felt the 30 U/kg TALI dose could have been too low.

The outcomes assessed in the included trials were the surrogate outcomes typically used for GD clinical trials. However, the clinical expert consulted for this review mentioned that clinicians use overall health to evaluate patients with GD, taking into account hematological and organ size outcomes, child growth, and bone manifestations collectively to assess a patient's status. Overall clinical benefits were not explored in the studies. HRQoL was assessed in only 11 patients with a questionnaire that was not

designed for use in patients with GD, and with no evidence for studies validating its use in this population. Bone crises were considered a primary issue by a patient group and by the clinical expert involved in the review. However, because bone crisis was reported as an AE, and due to the size of the included population and lack of comparator group, this outcome could not be interpreted for efficacy purposes.

Due to the numerous major limitations identified for the included trials, particularly their non-comparative nature, uncertainty remains with respect to the meaning of the efficacy results. Most of the identified limitations were likely to bias the results in favour of the apparent efficacy of TALI, or to impair the scientific validity of the results. In addition, the non-inferiority or superiority of TALI compared with other ERTs available in Canada could not be assessed by direct or indirect comparison. TALI appeared to generally improve hematological (and organ) manifestations of GD; and, while these outcomes are objective measures, they remain surrogate markers of disease status. The extent to which these improvements affect patients in a clinically important way is not clear from the TALI data. Although the context of a rare disease might be argued as being a limitation affecting the design and protocol of clinical trials, comparative randomized controlled pivotal trials have been conducted for other drugs used in GD.[48-50] In consideration of this, when assessing the value of the submitted pivotal trials for TALI for health technology assessment purposes, the trials are considered to be of limited quality.

Notwithstanding all the limitations of the trials, based on a naive side-by-side comparison with results of three systematic reviews on ERTs for GD, the efficacy results observed for TALI do not appear to be different from efficacy results reported for other ERTs (see APPENDIX 6: SUMMARY OF SYSTEMATIC REVIEWS). However, there are numerous limitations with naive or informal indirect comparisons, meaning there is a high degree of uncertainty with respect to this type of comparison between ERTs.

4.2.2 Harms

The small population under review and the lack of power to detect changes in AEs rendered improbable the chance to detect infrequently occurring AEs. Overall rates for AEs ranged from 68.8% to 100%. Incidence rates of AEs did not appear to be associated with a specific dose of TALI. The most common AEs were headache (total occurrence of 19.7%), arthralgia (16.7%), upper respiratory tract infection (14.4%), and nasopharyngitis (12.9%), which are often reported AEs in clinical trials. Bone pain occurred in 3.8% of patients. SAEs occurred in 4.5% of patients. Neither a trend in the nature of SAEs nor an association with a dosing regimen was observed. WDAEs occurred in 3.0% of all patients. All of them were related to hypersensitivity or infusion-related reactions. No deaths occurred during the trials.

Notable harms were a priori included in our review protocol based on input from the clinical expert involved in the review, on safety warnings from regulatory agencies, and on product monographs for other ERTs. Specifically, hypersensitivity reactions, particularly anaphylaxis, infusion-related reactions, and positive detections of anti-TALI antibodies were identified. No cases of anaphylaxis were reported. Hypersensitivity and infusion-related reactions each occurred in approximately 5% of patients. In comparison, the Food and Drug Administration (FDA) reported that 29% of patients who were infused biweekly with TALI had hypersensitivity.[51] A positive anti-TALI antibody test was observed in approximately 23% of all patients. It was also observed that patients who had imiglucerase for a prolonged period, such as more than two years, could develop antibodies for TALI when they switched to this drug. The clinical expert consulted for this review was surprised by this finding, given that the amino acid sequence of these two drugs are very similar, while the cell line from which the enzyme is produced is different. Although the clinical consequence of immunogenicity is unclear, the proportion of

patients who developed anti-TALI antibodies appeared numerically higher than rates reported for imiglucerase (15%) or velaglucerase alfa (2%).[13] According to the clinical expert involved in the review, the high immunogenicity of TALI is a concern and should be further monitored during post-marketing studies.

As for efficacy, safety data could not be directly or indirectly compared with placebo or another ERT given the single-arm design of the TALI studies. A naive side-by-side comparison with few safety data of two systematic reviews (see APPENDIX 6: SUMMARY OF SYSTEMATIC REVIEWS) did not show obvious differences for safety data between ERTs. However, as mentioned previously, there are numerous limitations to such a comparison between treatments, and there therefore remains a degree of uncertainty with respect to the comparative safety of TALI versus other ERTs.

Safety was monitored for 39 months in the extension study, Study 003, and no additional safety signals or obvious increases in the frequency of AEs were observed compared with the pivotal trials (APPENDIX 5: SUMMARY OF THE EXTENSION STUDY).

5. CONCLUSIONS

Results from four phase 3, multi-centre trials suggest that TALI biweekly IV infusions improved hemoglobin levels, platelet counts, and spleen and liver volumes from baseline; however, only one study conducted a statistical analysis showing a statistically significant improvement in outcomes from baseline. Efficacy results for these outcomes generally met clinical targets defined in clinical practice guidelines for GD, with the exception of liver volume. It is uncertain whether the 60 U/kg TALI dose added clinical benefits to the 30 U/kg TALI dose, except for platelet counts. The evidence for the use of TALI in type 3 GD patients is extremely limited and is based on changes in hematological factors in only two patients. Safety data revealed no important AEs other than hypersensitivity and infusion-related reactions, and a somewhat high rate of immunogenicity to TALI. An extension study provided longer-term safety and efficacy data for TALI after three years, which were in line with results observed at nine and 12 months. HRQoL and bone crises were identified as key end points by the clinical expert involved in the review and a patient group, respectively, but HRQoL was not assessed in most of the trials and the bone crises could not be interpreted given the limitations of the data. A key limitation of the reviewed data is the lack of a head-to-head comparison with another ERT or a formal indirect comparison between ERTs. Neither patients nor investigators were blinded to the administration of TALI, rendering studies prone to related bias, such as the Hawthorne effect. For these reasons, the superiority or non-inferiority of TALI compared with other ERTs could not be assessed and the comparative results reported by the pivotal trials are associated with a high degree of uncertainty.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One group, the National Gaucher Foundation of Canada (NGFC), provided the patient input information for this review. NGFC is a non-profit organization of volunteers that support the Gaucher community through advancement in awareness, education, and research. The NGFC, a registered charity since 1992, has continued to support and represent Canadians living with Gaucher disease (GD) for the past 20 years. The NGFC is governed by a voluntary Board of Directors, which consists of Gaucher patients and their family members from across Canada. The NGFC hosts a well-attended national conference once every 18 months, drawing participation from all regions of Canada. The last patient meeting was held in Ottawa in October 2013.

The NGFC has directly received unrestricted educational grants from manufacturers including Actelion, Shire, Genzyme, and Pfizer Canada, which have been used to hold a national patient conference.

2. Condition and Current Therapy-Related Information

This information was gathered by means of direct one-on-one conversation with patients with GD via telephone and email, and in person. Interviewed patients are currently being treated with Cerezyme, velaglucerase alfa (VPRIV), and Zavesca, whereas some patients were untreated. Some information was collected for a previous submission to CADTH.

It was reported that people living with GD face a wide variety of physical, emotional, and social challenges. Each patient experiences the symptoms of this chronic condition differently, and disease manifestations range from mild to very severe. Bone pain is a common experience of patients with GD. Some patients often experience bone crisis. Bone crises are excruciating, and during a crisis even the slightest movements can cause severe pain. Bone crises can severely limit a patient's day-to-day functioning, and in some cases require hospitalization to manage the pain. Bone crisis has been described as having a "heart attack of the bone." Other serious skeletal involvement includes degeneration of joints, spontaneous fractures, and bone necrosis. In addition, pronounced liver and spleen enlargement is also reported. Enlarged organs can cause patients' stomachs to protrude and have an effect on their body image. Children and adolescents may be particularly conscious of their appearance. Being teased about a large "tummy" can have a serious impact on a child's self-esteem. Children are often prevented from participating in physical activities that other children may take for granted, such as contact team sports and downhill skiing. Children can also be absent frequently from school as families and doctors learn how to best support the health needs of the individual child. One patient described the disease-on-bone impact as follows: "The most troubling aspect of this disease, to me, is its effects on my bones. I have restricted mobility, chronic bone pain and have suffered through bone crises which are extremely painful and devastating. By 2002, my disease had progressed to the point where it was now inevitable my hip would collapse. The bone pain became so sharp I would often fall. I stopped working at that point and went on disability." The psychological impact of GD can be great. Decreased stamina, frequent pain, and immobility can all have a major impact on patients and their caregivers, families, careers, and social lives. Dealing with exhaustion on a daily basis leaves little room for patients to participate in some of the more enjoyable things in life.

The NGFC indicated that the ultimate goal of treatment for GD is to manage the more serious symptoms and complications by managing bone pain, preventing bone crisis, reducing liver and spleen volumes, increasing platelets, reducing or eliminating anemia, and preventing delayed growth and development in children. For many years, patients with GD have benefited from enzyme replacement therapy (ERT) with Cerezyme and, most recently, with VPRIV. ERT reverses or controls many of the symptoms of GD. However, as with any medication, there are side effects. Most are mild, and while some patients develop antibodies, most are able to continue treatment. In Canada, we know of one patient who has had an anaphylactic reaction to Cerezyme. Some Canadian patients are being treated with Zavesca, a substrate reduction therapy (SRT), but Zavesca is generally not a front-line therapy because of the serious side effects experienced by some patients. One of the biggest unmet needs is the lack of alternative options for patients who experience severe adverse effects of currently available medications.

Balancing caregiving responsibilities with the demands of a job can be difficult. Tasks such as calling doctors, arranging services, and scheduling appointments take place during daytime hours. In addition, there are many financial implications such as out-of-pocket expenses for food, transportation, and co-pays. Caring for children can also be a burden in trying to navigate a balance between home and work. The parent must coordinate medical appointments with treatment and school schedules, as well as dealing with non-affected siblings. Caregivers experience both emotional and financial burdens and a great deal of worry, stress, and anxiety.

3. Related Information About the Drug Being Reviewed

Currently, no Canadians are receiving Elelyso. The information provided here was gathered via one-on-one conversation with a patient who has been treated with Elelyso in the United States with good clinical outcome in the United States.

Elelyso is made from carrot cells rather than the more complex, mammalian cell-based system that current therapies use, which will reduce the risk of viral transmission. The NGFC stated that having access to Elelyso is likely to reduce life-threatening risk to patients and provide a new option to those who currently cannot receive the available therapies due to adverse reactions or shortages. The NGFC believes that currently untreated patients will be able to lead much fuller and healthier lives once they receive the ERT Elelyso.

In summary, the NGFC indicated that patients with GD face a wide variety of physical, emotional, and social challenges. They are also a burden to their family members and caregivers. Current ERT treatments do not work for everyone, and sometimes have serious adverse events, including one case of an anaphylactic reaction. One of the biggest unmet needs is the lack of alternative options for patients who experience these severe adverse effects with current medications. The NGFC expects that Elelyso will be made accessible to patients with Gaucher disease.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 25, 2015
Alerts:	Biweekly (twice monthly) search updates until July 15, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
	MEDLINE search
1	(37228-64-1 or C582473).rn,nm.
2	(Elelyso* or taliglucerase* or uplyso or UNII-0R4NLX88O4).ti,ab,rn,nm,sh,hw,ot.
3	or/1-2
4	3 use pmez
	Embase search
5	*taliglucerase alfa/
6	(Elelyso* or taliglucerase* or uplyso or UNII-0R4NLX88O4).ti,ab.
7	or/5-6
8	7 use oemezd
9	4 or 8
	Remove non-human studies and duplicates
10	exp animals/
11	exp animal experimentation/ or exp animal experiment/
12	exp models animal/
13	nonhuman/
14	exp vertebrate/ or exp vertebrates/
15	animal.po.
16	or/10-15
17	exp humans/
18	exp human experimentation/ or exp human experiment/
19	human.po.
20	or/17-19
21	16 not 20
22	9 not 21
23	conference abstract.pt.
24	22 not 23
25	remove duplicates from 24

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	March 2015
Keywords:	Elelyso (taliglucerase alfa), Gaucher disease & synonyms
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug & Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: DETAILED OUTCOME DATA

TABLE 14: CONCOMITANT MEDICATIONS

	Study 001		Study 004	Study 005	
	TALI 30 U/kg N = 16	TALI 60 U/kg N = 16	Safety Set [redacted]	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Patients with concomitant drug use,[a] n (%)					
Analgesics	5 (31.3)	6 (37.5)	[redacted]	1 (16.7)	2 (40.0)
Antianemic preparations	0	4 (25.0)	[redacted]	1 (16.7)	2 (40.0)
Antibacterials (systemic)	6 (37.5)	4 (25.0)	[redacted]	3 (50.0)	1 (20.0)
Antihistamines (systemic)	4 (25.0)	1 (6.3)	[redacted]	1 (16.7)	3 (60.0)
Anti-inflammatory and antirheumatic products	2 (12.5)	2 (12.5)	[redacted]	1 (16.7)	0
Cough and cold preparations	2 (12.5)	3 (18.8)	[redacted]	0	1 (20.0)
Drugs for acid-related disorders	1 (6.3)	0 (0.0)	[redacted]	NR	NR
Vitamins	NR	NR	[redacted]	2 (33.3)	0 (0.0)

NR = not reported; TALI = taliglucerase alfa; U = unit.
[a] Used by at least 12% of the patient population.
Source: Clinical Study Reports for Study 001,[14] Study 004,[16] and Study 005.[17]

TABLE 15: CLINICAL DETERIORATION IN STUDY 002 AFTER 9 MONTHS

	Study 002	
	Adults N = 26	Pediatric Patients N = 5
Hb Levels		
n (%)	25 (96.2)	5 (100)
Clinically relevant deterioration,[a] n (%)	0	0
Platelet Counts		
n (%)	25 (96.2)	5 (100)
Clinically relevant deterioration,[b] n (%)	2 (8.0)	0 (0.0)
Spleen Volume		
n (%)	20 (76.9)	5 (100)
Clinically relevant deterioration,[c] n (%)	1 (5.0)	0 (0.0)
Liver Size		
n (%)	23 (88.5)	5 (100)
Clinically relevant deterioration,[d] n (%)	1 (4.3)	1 (20.0)

Hb = hemoglobin.
[a] Clinically relevant deterioration is defined as per cent change < –20% in hemoglobin.
[b] Clinically relevant deterioration is defined as per cent change < –20% for patients with baseline platelet counts ≤ 120,000 or per cent change < –40% for patients with baseline platelet counts > 120,000.
[c] Clinically relevant deterioration is defined as per cent change ≥ 20% in spleen volume.
[d] Clinically relevant deterioration is defined as per cent change ≥ 10% in liver volume.
Source: Clinical Study Report for Study 002.[15]

TABLE 16: EFFICACY OUTCOMES AT LAST FOLLOW-UP IN STUDY 004

	Study 004
	Efficacy Set [redacted]
Hb Levels (g/dL)	
n (%)	[redacted]
Baseline, mean (SD)	[redacted]
Mean at last follow-up (SD)	[redacted]
Change from baseline, mean (SD)	[redacted]
Platelet Counts (/mm^3)	
n (%)	[redacted]
Baseline, mean (SD)	[redacted]
Mean at last follow-up (SD)	[redacted]
Change from baseline, mean (SD)	[redacted]

Hb = hemoglobin; SD = standard deviation.
Source: Clinical Study Report for Study 004.[16]

TABLE 17: EFFICACY OUTCOMES AT 9 MONTHS IN STUDY 005

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Hemoglobin Levels (g/dL)		
n (%)	6 (100)	5 (100)
Baseline, mean (SD)	11.3 (1.7)	10.6 (1.4)
Mean at 9 months (SD)	12.2 (1.4)	11.9 (1.4)
Change from baseline, mean (SD)	1.0 (1.9)	1.3 (0.7)
Percentage change from baseline: mean (SD), median (interquartile range)	 9.3 (10.0) 7.8 (13.9)	 13.1 (7.9) 14.2 (3.2)
Chitotriosidase Levels (nmol/mL/h)		
n (%)	6 (100)	4 (80.0)
Baseline, mean (SD)	24,820 (17,902)	34,961 (22,080)
Mean at 9 months (SD)	12,589 (12,441)	17,301 (17,049)
Change from baseline, mean (SD)	–12,231 (8,449.5)	–17,660 (6,567.1)
Percentage change from baseline, mean (SD)	–57.2 (18.7)	–58.9 (21.8)
CCL18 Levels (ng/mL)		
n (%)	6 (100)	5 (100)
Baseline, mean (SD)	1,139.3 (781.3)	1,339.4 (617.9)
Mean at 9 months (SD)	630.8 (599.5)	784.4 (530.3)
Change from baseline, mean (SD)	–508.5 (290.7)	–555.0 (284.1)
Percentage change from baseline, mean (SD)	–49.9 (13.0)	–46.5 (22.4)

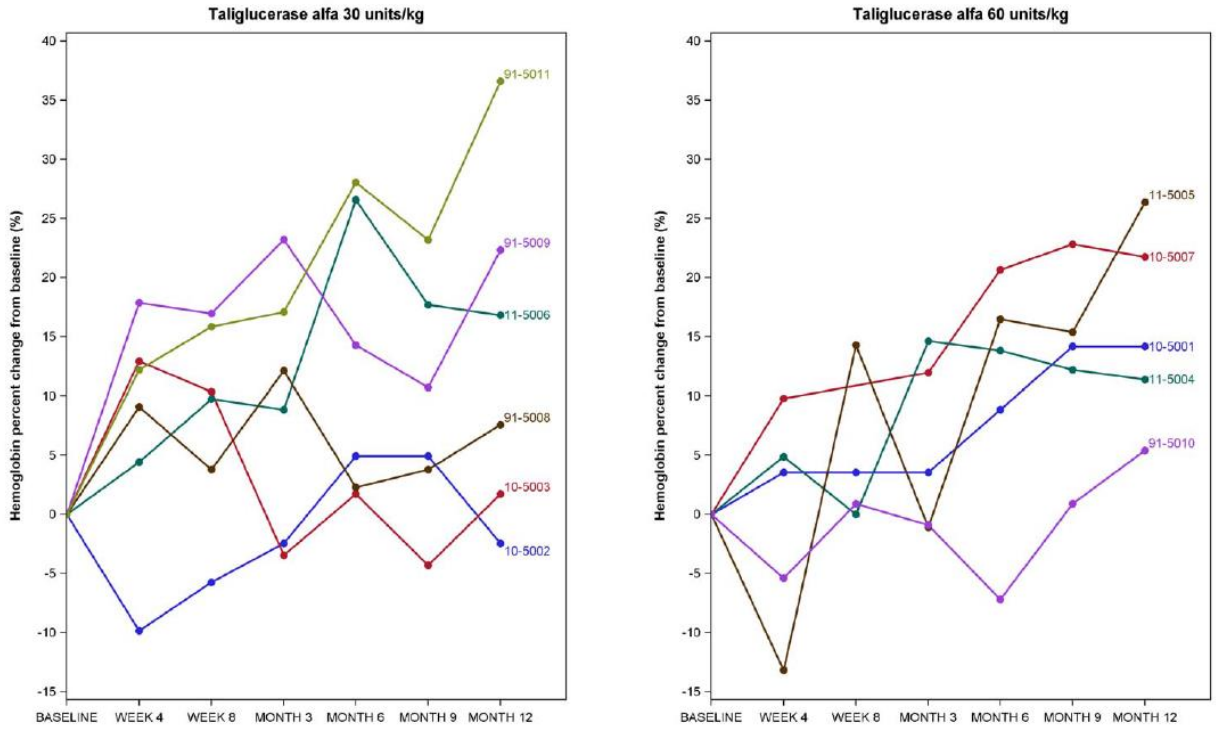
CCL18 = Chemokine (C-C motif) ligand 18; Hb = hemoglobin; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 005.[17]

TABLE 18: HEMOGLOBIN AFTER 12 MONTHS FOR PATIENTS WHO WERE ANEMIC AT BASELINE IN STUDY 005 (POST-HOC ANALYSIS)

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Hb Levels (g/dL)		
N	4 (66.7)	4 (80.0)
Baseline (SD)	10.6 (1.6)	10.2 (1.2)
Mean at 12 months (SD)	12.5 (1.2)	11.8 (0.7)
Change from baseline, mean (SD)	1.4 (1.3)	1.6 (0.7)
Percentage change from baseline, mean (SD), median (interquartile range)	19.4 (14.4) 19.6 (20.2)	16.9 (9.2) 17.9 (14.3)

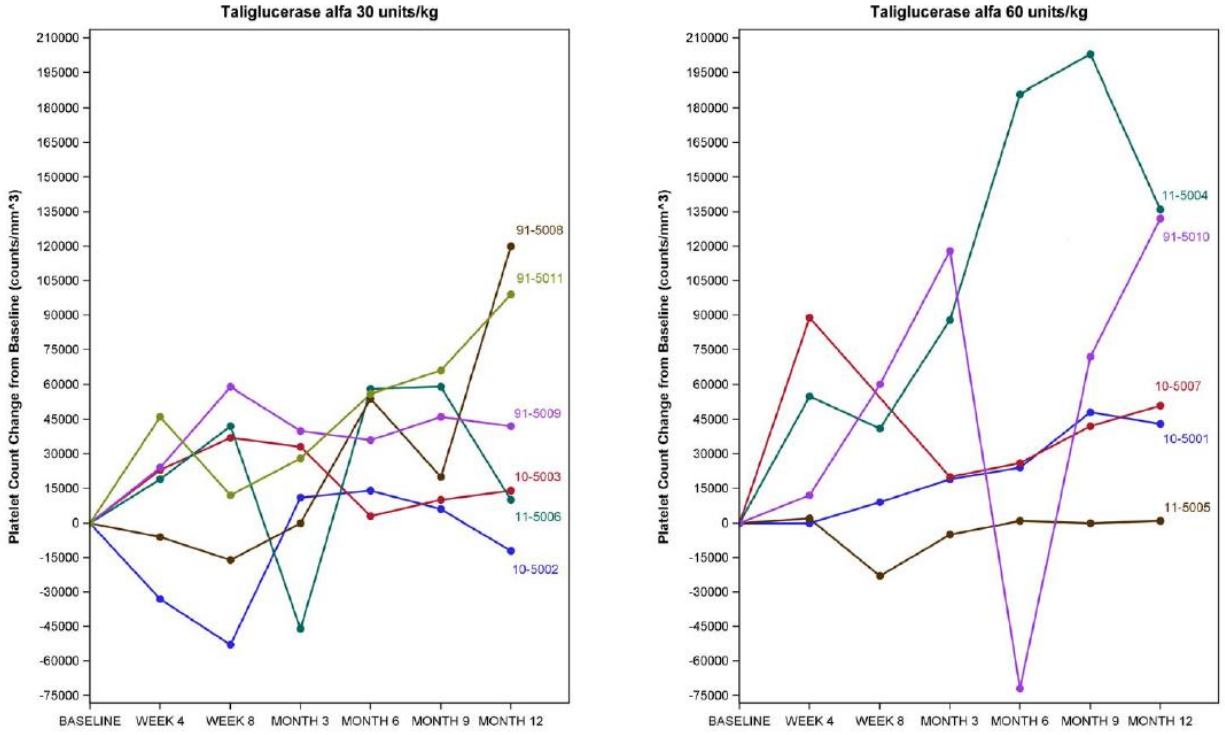
Hb = hemoglobin; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 005.[17]

FIGURE 2: INDIVIDUAL PERCENTAGE CHANGES IN HEMOGLOBIN FROM BASELINE IN STUDY 005



Source: Clinical Study Report for Study 005.[17]

FIGURE 3: INDIVIDUAL CHANGES IN PLATELET COUNTS FROM BASELINE IN STUDY 005 (/MM^3)



Source: Clinical Study Report for Study 005.[17]

TABLE 19: PLATELET COUNTS AFTER 12 MONTHS FOR PATIENTS WHO WERE THROMBOCYTOPENIC AT BASELINE IN STUDY 005 (POST-HOC ANALYSIS)

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Platelet Counts (/mm^3)		
n (%)	2 (33.3)	4 (80.0)
Baseline (SD)	91,000 (35,355)	80,500 (4,654.7)
Mean at 12 months (SD)	147,500 (95,459)	138,250 (54,279)
Change from baseline, mean (SD)	56,500 (60,104)	57,750 (56,588)
Percentage change from baseline, mean (SD)	53.3 (45.3)	73.4 (71.5)

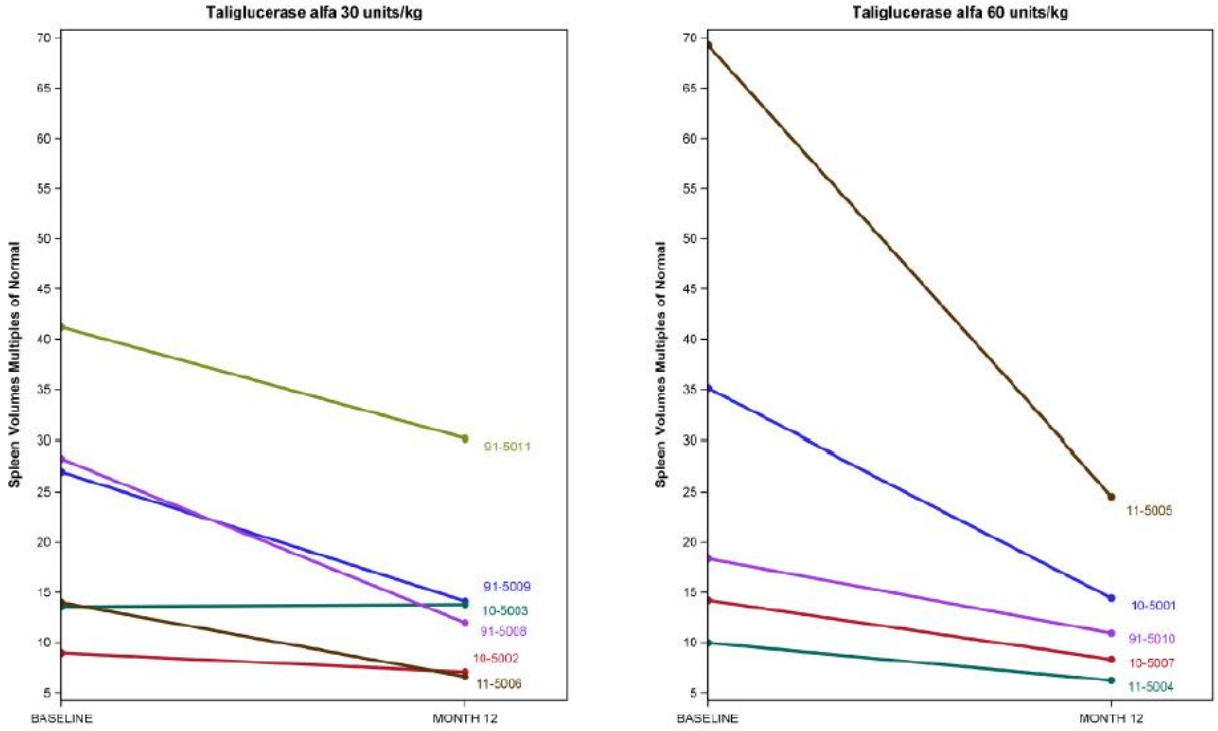
SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 005.[17]

TABLE 20: PROPORTION OF PATIENTS WITH ≥ 10% REDUCTION IN SPLEEN VOLUME AT 9 MONTHS IN STUDY 001

	Study 001	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16
n (%)	15 (100)	16 (100)

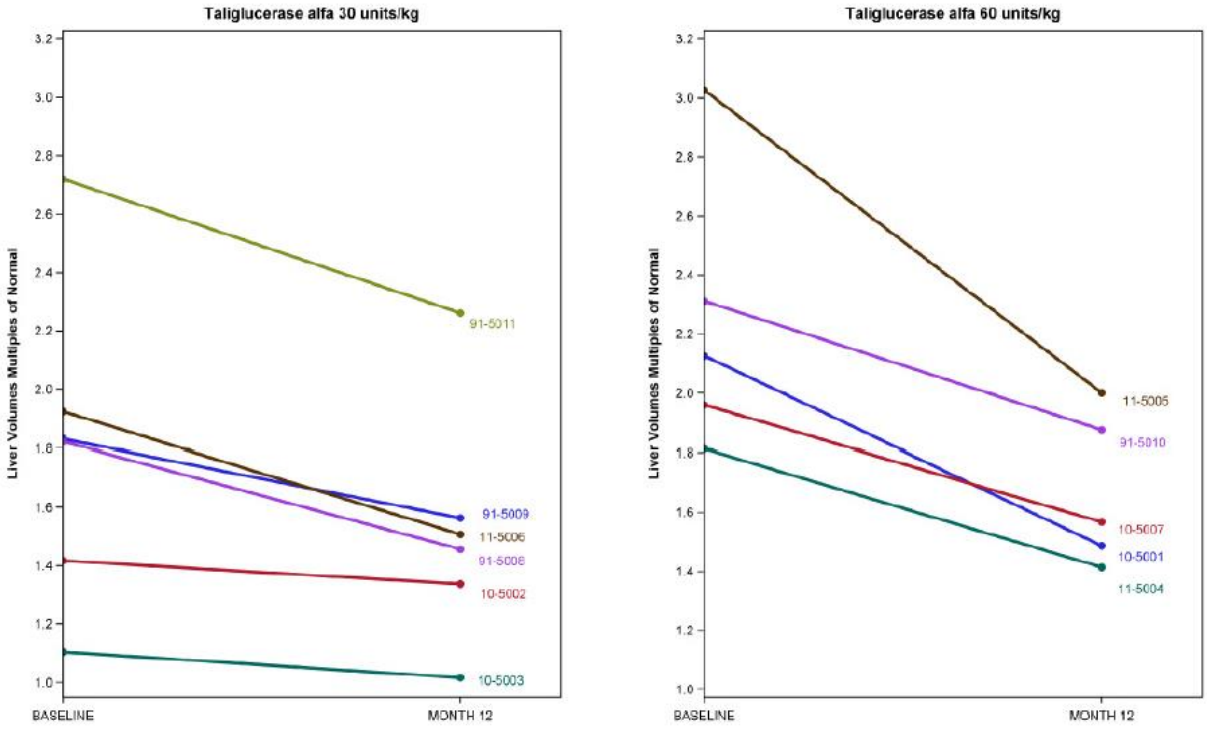
TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 001.[14]

FIGURE 4: INDIVIDUAL CHANGES IN SPLEEN VOLUMES IN STUDY 005 (MULTIPLES OF NORMAL)



Source: Clinical Study Report for Study 005.[17]

FIGURE 5: INDIVIDUAL CHANGES IN LIVER VOLUMES IN STUDY 005 (MULTIPLES OF NORMAL)



Source: Clinical Study Report for Study 005.[17]

TABLE 21: BIOMARKERS LEVELS

	Study 001 (9 Months)		Study 002 (9 Months)		Study 005 (12 Months)	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16	Adults N = 26	Pediatric Patients N = 5	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Chitotriosidase Levels (nmol/mL/h)						
n (%)	14 (93.3)	15 (93.8)	23 (88.5)	5 (100)	6 (100)	4 (80.0)
Baseline, mean (SD)	28,158 (11,686)	24,702 (17,428)	6,934 (9,651)	7,947 (9,790)	24,820 (17,902)	34,961 (22,080)
Mean at end point[a] (SD)	14,548 (8,025.8)	12,538 (14,489)	5,555 (8,269)	6,070 (7,385)	11,610 (11,916)	14,433 (14,534)
Change from baseline, mean (SD)	–13,264 (8,378.2)	–12,165 (12,064)	–1,206 (1,685)	–1,877 (2,425)	–13,210 (9,811.6)	–20,528 (8,715.4)
P value	< 0.0001	0.0016	NR	NR	NR	NR
Percentage change from baseline, mean (SD)	NR	NR	–21.3 (28.3)	–29.7 (81.6)	–58.5 (17.5)	–66.1 (20.1)
CCL18 Levels (ng/mL)						
n (%)	NR	NR	23 (88.5)	5 (100)	6 (100)	5 (100)
Baseline, mean (SD)	NR	NR	316.3 (284.3)	306.4 (316.7)	1,139.3 (781.3)	1,339.4 (617.9)
Mean at end point[a] (SD)	NR	NR	285.9 (287.8)	217.6 (198.5)	641.2 (697.9)	702.4 (498.4)
Change from baseline, mean (SD)	NR	NR	–18.8 (63.9)	–88.8 (127.0)	–498.2 (326.9)	–637.0 (315.4)
Percentage change from baseline, mean (SD)	NR	NR	–6.6 (19.3)	–4.4 (37.3)	–50.6 (19.4)	–52.6 (22.5)

CCL18 = Chemokine (C-C motif) ligand 18; NR = not reported; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
[a] The time of end point was 9 months for Study 001 and 002, and 12 months for Study 005.
Source: Study 001,[14] Study 002,[15] and Study 005.[17]

TABLE 22: QUALITY OF LIFE — CHILD HEALTH QUESTIONNAIRE PARENT FORM 28 (STUDY 005)

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Question 1.1, General Health (Standardized Score)		
n (%)	6 (100)	5 (100)
Baseline, mean (SD)	56.7 (25.8)	61.0 (31.7)
Mean at 12 months (SD)	67.5 (22.1)	71.0 (40.2)

SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 005.[17]

TABLE 23: DUAL-ENERGY X-RAY ABSORPTIOMETRY SCORES FOR LUMBAR SPINE AT 9 MONTHS IN STUDY 001

	Study 001	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16
Z score		
At Screening		
n (%)	14 (93.3)	15 (93.8)
Mean (SD)	–0.5 (1.2)	–1.2 (1.0)
At 9-month Visit		
n (%)	13 (86.7)	14 (87.5)
Mean (SD)	–0.1 (1.0)	–1.0 (1.2)
T score		
At Screening		
n (%)	13 (86.7)	15 (93.8)
Mean (SD)	–0.9 (0.8)	–1.2 (1.0)
At 9-month Visit		
n (%)	13 (86.7)	15 (93.8)
Mean (SD)	–0.6 (0.8)	–1.1 (1.4)
BMD		
At Screening		
n (%)	15 (100)	16 (100)
Mean (SD)	1.0 (0.1)	1.0 (0.1)
At 9 month Visit		
n (%)	11 (73.3)	13 (81.3)
Mean (SD)	1.1 (0.1)	1.0 (0.2)

BMD = bone mineral density; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Study 001.[14]

TABLE 24: DUAL-ENERGY X-RAY ABSORPTIOMETRY SCORES FOR LUMBAR SPINE AT 12 MONTHS IN STUDY 005

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Z score		
At Screening		
n (%)	6 (100)	5 (100)
Mean (SD)	–1.6 (1.6)	–2.6 (1.4)
At 12-month Visit		
n (%)	6 (100)	4 (80.0)
Mean (SD)	–1.8 (1.3)	–2.5 (1.6)
Change From Baseline		
Mean (SD)	–0.20 (0.49)	0.27 (0.10)
T score		
At Screening		
n (%)	3 (50.0)	1 (20.0)
Mean (SD)	–4.0 (1.1)	–5.9 (none)
At 12-month Visit		
n (%)	3 (50.0)	1 (20.0)
Mean (SD)	–3.9 (0.9)	–5.4 (none)
Change From Baseline		
Mean (SD)	0.17 (0.15)	0.50 (none)
BMD		
At Screening		
n (%)	6 (100)	5 (100)
Mean (SD)	0.6 (0.1)	0.4 (0.1)
At 12-month Visit		
n (%)	6 (100)	4 (100)
Mean (SD)	0.6 (0.1)	0.5 (0.1)
Change From Baseline		
Mean (SD)	0.01 (0.03)	0.04 (0.02)

BMD = bone mineral density; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 005.[17]

TABLE 25: DUAL-ENERGY X-RAY ABSORPTIOMETRY SCORES FOR FEMORAL NECK AT 9 MONTHS IN STUDY 001

	Study 001	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16
Z score		
At Screening		
n (%)	14 (93.3)	15 (93.8)
Mean (SD)	–0.1 (1.6)	–0.6 (1.4)
At 9-month Visit		
n (%)	13 (86.7)	14 (87.5)
Mean (SD)	0.6 (1.8)	–0.2 (2.3)
T score		
At Screening		
n (%)	13 (86.7)	15 (93.8)
Mean (SD)	–0.7 (1.6)	–0.8 (1.4)
At 9-month Visit		
n (%)	13 (86.7)	15 (93.8)
Mean (SD)	–0.1 (2.0)	–0.5 (2.3)
BMD		
At Screening		
n (%)	15 (100)	16 (100)
Mean (SD)	0.9 (0.2)	0.9 (0.2)
At 9-month Visit		
n (%)	11 (73.3)	13 (81.3)
Mean (SD)	1.0 (0.3)	0.9 (0.4)

BMD = bone mineral density; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 001.[14]

TABLE 26: DUAL-ENERGY X-RAY ABSORPTIOMETRY SCORES FOR FEMORAL NECK AT 12 MONTHS IN STUDY 005

	Study 005	
	TALI 30 U/kg N = 6	TALI 60 U/kg N = 5
Z score		
At Screening		
n (%)	5 (83.3)	4 (80.0)
Mean (SD)	–0.4 (0.5)	–1.9 (0.8)
At 12-month Visit		
n (%)	5 (83.3)	4 (80.0)
Mean (SD)	–0.7 (0.2)	–1.7 (0.9)
Change From Baseline		
Mean (SD)	–0.30 (0.62)	0.20 (0.42)
T score		
At Screening		
n (%)	3 (50.0)	1 (20.0)
Mean (SD)	–1.3 (0.7)	–3.4 (none)
At 12-month Visit		
n (%)	3 (50.0)	1 (20.0)
Mean (SD)	–1.3 (0.3)	–3.1 (none)
Change From Baseline		
Mean (SD)	0.07 (0.38)	0.30 (none)
BMD		
At Screening		
n (%)	6 (100)	4 (80.0)
Mean (SD)	0.7 (0.2)	0.5 (0.1)
At 12-month Visit		
n (%)	6 (100)	4 (80.0)
Mean (SD)	0.8 (0.1)	0.6 (0.1)
Change From Baseline		
Mean (SD)	0.01 (0.08)	0.03 (0.03)

BMD = bone mineral density; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 005.[17]

TABLE 27: DUAL-ENERGY X-RAY ABSORPTIOMETRY SCORES FOR TOTAL HIP AT 9 MONTHS IN STUDY 001

	Study 001	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16
Z score		
At Screening		
n (%)	10 (66.7)	9 (56.3)
Mean (SD)	–0.1 (1.5)	–0.6 (1.3)
At 9-month Visit		
n (%)	5 (33.3)	6 (37.5)
Mean (SD)	–0.2 (0.9)	–0.8 (0.4)
T score		
At Screening		
n (%)	8 (53.3)	8 (50.0)
Mean (SD)	–0.7 (1.8)	–0.7 (1.2)
At 9-month Visit		
n (%)	4 (26.7)	6 (37.5)
Mean (SD)	–1.2 (0.9)	–1.1 (0.5)
BMD		
At Screening		
n (%)	10 (66.7)	9 (56.3)
Mean (SD)	1.0 (0.2)	0.9 (0.2)
At 9-month Visit		
n (%)	5 (33.3)	6 (37.5)
Mean (SD)	0.9 (0.2)	0.9 (0.1)

BMD = bone mineral density; SD = standard deviation; TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 001.[14]

TABLE 28: QUANTITATIVE CHEMICAL SHIFT IMAGING SCORES (FAT FRACTION) AT 9 MONTHS (STUDY 001)

	Study 001	
	TALI 30 U/kg N = 15	TALI 60 U/kg N = 16
n (%)	4 (26.7)	4 (25.0)
Baseline	0.1675	0.2375
At 9 months	0.2375	0.3600
Change from baseline	0.0700	0.1225

TALI = taliglucerase alfa; U = unit.
Source: Clinical Study Report for Study 001.[14]

APPENDIX 4: THERAPEUTIC GOALS FOR ENZYME REPLACEMENT THERAPY IN GAUCHER DISEASE AND VALIDITY OF OUTCOME MEASURES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

1. Objective

To summarize the therapeutic goals of ERT treatment in GD and assess the validity of key outcomes reported in the included studies.

2. Findings

The therapeutic goals of ERT for GD are identified in two documents below. Pastores et al.[12] reported the therapeutic goals for the treatment of GD that were established in 2004 by an international panel of physicians with extensive clinical experience in this condition. The panel convened for the purpose of reaching consensus on evidence-based treatment goals for each organ system, in order to guide clinicians treating patients and serve as reference standards for clinical trials. In 2011, experts in Ontario established a similar guideline[6] for the ERT treatment in GD based mainly on Pastores et al.'s report. The therapeutic goals for GD are described below and summarized in Table 29. In addition, the validity information for outcomes reported in the included studies is also discussed.

Anemia

Anemia is defined as a hemoglobin concentration < 12.0 g/dL in males 12 years of age and older, and < 11.0 g/dL in females and children between the ages of two and 12 years. Therapeutic goals for treating anemia include improving hemoglobin concentration to normal levels, eliminating dependency on blood transfusions, and alleviating symptoms associated with anemia.[6,12] A rapid and sustained increase in hemoglobin concentration was observed in data from the ICGG Registry[12] after patients received ERT. During the first 12 months of ERT, patients' hemoglobin showed a steady rise to normal levels, and these were maintained during a second year of follow-up.[12] According to the clinical expert involved in this review, however, there is no MCID specified for hemoglobin improvement.

Thrombocytopenia

The normal range of platelet counts is ≥ 150 × 10^9/L or 150,000/µL). The immediate therapeutic goal of ERT is to sufficiently increase platelet counts to prevent spontaneous, surgical, and obstetrical bleeding. Other goals include avoiding splenectomy for the purpose of improving thrombocytopenia, and normalizing platelet counts (for patients with splenectomy) or increasing counts by 1.5 to 2-fold (for patients with intact spleen) during the first year of treatment. [6,12] It is indicated that the magnitude and time to platelet response depends on the baseline severity of thrombocytopenia and whether patients have an intact spleen. Although platelet responses have been observed in patients with moderate (< 120,000/µL and > 60,000/µL) and severe (< 60,000/µL) thrombocytopenia, patients with moderate thrombocytopenia reached a higher mean platelet count. Patients with an intact spleen who had extremely low platelet counts at baseline continued to be somewhat thrombocytopenic with ERT, although their counts doubled with treatment.[12] According to the clinical expert involved in this review, however, there is no MCID specified for platelet count improvement.

Splenomegaly

Splenomegaly is defined as a mass exceeding the normal 0.2% of total body weight. Therapeutic goals for ERT include a reduction in spleen volume and alleviation of discomfort due to splenomegaly, such as abdominal distension, early satiety, and new splenic infarction. Patients with severe baseline splenomegaly (> 15 times normal) are not expected to achieve normalized volume.[12,32] Data have demonstrated significant decreases in spleen volume with ERT, with a 30% to 50% decrease by one year and 50% to 60% decrease over two to five years.[12]

Hepatomegaly

Hepatomegaly is defined as a liver mass that exceeds 1.25 times the normal 2.5% of total body weight. The goal of ERT is to decrease and maintain liver volume to 1.0 to 1.5 times normal.[6,12] In the ICGG Registry, [12] patients with moderate (> 1.25 times normal) or severe (> 2.5 times normal) hepatomegaly demonstrated a decrease of 20% to 30% within 12 months and 30% to 40% over two to five years. Normalization of liver volume was more likely among patients with moderate hepatomegaly compared with severe hepatomegaly (50% to 58% versus 6% to 9% by two years). [12]

Spleen and liver volumes were measured with magnetic resonance imaging (MRI). According to the CDR clinical expert involved in this review, MRI is the standard and reliable method used to measure organ size in clinical research, due to its accuracy and reproducibility. However, there is no MCID specified for hepatosplenomegaly reduction.

Skeletal Pathology and Growth

Skeletal pathology associated with GD is multifaceted and can result in irreversible complications. Manifestations can include bone pain and crises, osteopenia, osteoporosis, avascular necrosis, and fractures. Treatment goals focus on preventing bone pain, bone crises, and osteonecrosis, and improving bone mineral density.[6,12] Data from the ICGG Registry found that bone pain resolved in 50% of symptomatic patients within two years of ERT.[12] Overall bone involvement showed improvement in 30% to 40% of pediatric patients and 20% to 30% of adult patients after two to four years of treatment. ERT has also been shown to improve bone mineral density (BMD); however, this may take at least two years.[27]

Children with GD often have growth retardation and delayed onset of puberty.[42] Goals of treatment include normalizing height within three years and achieving normal onset of puberty.[6,12] Studies have shown growth normalization with ERT.[43,44]

Bone Mineral Density

A BMD test is used to determine bone health. The test can be used to identify osteoporosis, determine risk for fractures, and measure response to osteoporosis treatment. Similar to regular X-rays, it is painless. The most widely recognized BMD test is done by DEXA.[38] BMD is measured by DEXA and compared to that of an established norm or standard. Although no bone density test is 100% accurate, the DEXA test is the single most important predictor of whether a person will have a fracture in the future.[38] T scores and z scores are also commonly used in the clinical research. T score is calculated by comparing a DEXA test result to the ideal or peak BMD of a healthy 30-year-old adult.[38] Based on the World Health Organization (WHO) definition, a t score of 0 means that BMD is equal to the norm for a healthy young adult.[38] Differences between the BMD of a person with GD and that of a healthy young adult norm are measured in units of SDs. The more SDs units below 0, , the higher the risk of fracture is.[38] A t score between +1 and −1 is considered to be normal or healthy. A t score between −1 and −2.5 indicates low bone mass, although not low enough to be diagnosed with osteoporosis. A t score of −2.5 or lower indicates osteoporosis. The greater the negative number, the more severe the osteoporosis. [38]

However, it is believed that WHO diagnostic categories for normal, osteopenia, and osteoporosis, based on t scores, are not applicable to children and adolescents who have not yet reached peak bone mass. [39] Few published pediatric reference values for BMD measured with DEXA include factors that are known to affect the results, besides age and gender. [39] Z score is calculated by comparing the DEXA results with age and sex-matched groups. [38,40] Because a low BMD level is common among older adults, comparisons with the BMD of a typical individual whose age is matched to patient can be misleading. Therefore, the diagnosis of osteoporosis or low bone mass is usually based on t score. However, a z score can be useful for determining whether an underlying disease or condition is causing bone loss.[38] No MCID was specified for t score or z score. The clinical expert involved in this review indicated that the value of DEXA in trial for GD is not clear. The expert did not expect any improvement in t score and z score in these trials. In addition, the t score used in children was not appropriate.

Quantitative Chemical Shift Imaging

Quantitative chemical shift imaging (QCSI) is a methodology for quantifying bone marrow response (fat fraction content) to ERT in GD.[41] The mean fat fraction value in a healthy population is 0.37 (normalization value), and a fat fraction of ≤ 0.23 is an indication of bone complications and bone at risk.[41] The fat fraction of the lumbar spine when measured with Dixon QCSI is associated with the occurrence of bone complications. It may, therefore, be a clinically useful parameter. QCSI is considered to be a sensitive and valuable tool for the evaluation of bone marrow (fat fraction) responses to individualized doses of ERT in type 1 GD. [52,53] However, no validity information was identified and no MCID in GD is specified. The CDR clinical expert involved in this review indicated that the value of QCSI in trial for GD is not clear. The expert does not expect any improvement in QCSI in these trials.

Child Health Questionnaire Parent Form 28

The Child Health Questionnaire Parent Form 28 (CHQ-PF28) is a survey questionnaire used to assess the quality of life (QoL) for children based on the recall of the last four weeks. CHQ-PF28 assesses four dimensions, including family cohesion, global health, physical functioning, and self-esteem. Items are scored and summed to produce scales (standardized scores) that range from 0 to 100; 0 is the worst possible and 100 the best possible health state.[45] Question 1.1 addresses the general health of the child and no index or overall score is available. The CHQ-PF28 is considered to be valid for patients aged five to 18 years.[17] It has been reported that the questionnaire is acceptable to parents and school nurses for school children,[42,45] and children with asthma or allergy,[46,47] but neither validity information nor MCID is found in children with GD.

Biomarkers

Circulating biomarkers such as chitotriosidase and CCL18 are important surrogates for monitoring disease activity in type 1 GD,[54] and have been used in clinical trials in patients with GD.[36,37] Progressive storage of glucosylceramide in mononuclear cells and macrophages results in elevated levels of chitotriosidase and CCL18. It was reported that there was a similarly strong correlation of chitotriosidase with disease severity in individual patients monitored serially over many years (chitotriosidase $r = 0.96$ to 0.98, $P < 0.001$).[36] The less severely affected patients are more likely to normalize their chitotriosidase activities after long-term ERT.[55] One of the limitations reported is that chitotriosidase activities cannot be analyzed in at least 6% of patients with GD due to a null mutation in the corresponding gene.[36] Furthermore, no validity and MCID information on the biomarkers is found for ERT treatment in GD.

TABLE 29: THERAPEUTIC GOALS FOR THE TREATMENT OF GAUCHER DISEASE

Symptom	Therapeutic Goals
Anemia	• Elevate Hb levels to ≥ 11.0 g/dL for women and children and ≥ 12.0 g/dL for men within 1 to 2 years; maintain improved Hb values • Eliminate need for blood transfusion • Reduce fatigue, dyspnea, and angina
Thrombocytopenia	• Increase platelet counts sufficiently to prevent bleeding within first year • *Patients with splenectomy*: normalize platelet counts within 1 year • *Patients with intact spleen*: increase platelet count by 1.5- to 2-fold by year 1; approach low-normal level (patients with moderate baseline) or continue slight increase in count (patients with severe baseline) during year 2; avoid splenectomy; maintain stable platelet count
Hepatomegaly	• Reduce and maintain liver volume to 1 to 1.5 times normal • Reduce volume by 20% to 30% in first year, and by 30% to 40% in years 3 to 5
Splenomegaly	• Reduce and maintain spleen volume to ≤ 2 to 8 times normal • Reduce spleen volume by 30% to 50% in first year, and by 50% to 60% in years 2 to 5 • Relieve symptoms associated with splenomegaly (e.g., abdominal distension, early satiety, new splenic infarction) • Eliminate hypersplenism
Two episodes of severely symptomatic splenic infarcts	• Reduction of spleen volume by 50% • Prevention of further splenic infarcts
Acute bone crises	• Prevent bone crises
Spontaneous fractures	• Prevention of further fractures
Radiographic or MRI evidence of incipient destruction of any major joint	• Improvement in imaging parameters (MRI, QCSI, or BMD)
Major joint replacement surgery	• Optimize surgical outcome
Skeletal pathology	• Decrease or eliminate bone pain within 1 or 2 years • Prevent subchondral joint collapse and osteonecrosis • Improve BMD: *children*: reach normal or ideal peak skeletal mass, and increase cortical and trabecular BMD within 2 years; *adults*: increase trabecular BMD in 3 to 5 years
Significant liver dysfunction	• Improvement in hepatic function
Growth failure in children	• Return to normal range of growth parameters
Progressive pulmonary disease due to GD	• Reverse hepatopulmonary syndrome and oxygen dependency • Reduce pulmonary hypertension, functional status, and QoL • Prevent sudden deterioration and death • Prevent pulmonary disease by early initiation of ERT
Evidence from the rate of progression of symptoms, in both adults and children, that the disease is likely to become severe within a few years	• Improvement of those parameters as defined above
Functional health and well-being	• Improve ability to resume normal daily activities • Improve QoL scores within 2 or 3 years

BMD = bone mineral density; ERT = enzyme replacement therapy; MRI = Magnetic resonance imaging; QCSI quantitative chemical shift imaging;
Source: Pastores et al.,[12] Ontario guidelines for treatment of GD.[6]

3. Summary

The therapeutic goals of ERT for clinically important outcomes — such as hepatosplenomegaly, anemia, thrombocytopenia, growth failure in children and skeletal pathology in patients with GD —were established by a panel of international experts in 2004.[12] Similar guidelines for the treatment of GD with ERT were established by experts in Ontario in 2011. The treatment goals were created to help guide clinicians treating patients with GD and to serve as reference standards for clinical trials. The clinical expert involved in this review stated that any observed improvement (e.g., organ size, reduction in clinical symptoms, increase in hemoglobin and platelet counts) is a good indication of disease control although no actual MCID has been specified for the above outcomes. In addition, other outcomes — including DEXA for measuring BMD (t score, z score), QCSI for measuring bone marrow fat fraction, CHQ-PF28 for assessing QoL in children, and biomarkers (chitotriosidase and CCL18) — are commonly used in the clinical research in GD; however, neither validity nor MCIDs have been established for these outcomes in patients with GD.

APPENDIX 5: SUMMARY OF THE EXTENSION STUDY

Aim

To summarize the findings of Study 003,[56] a three-year extension of studies 001[14] and 002.[15]

Findings

Demographic Characteristics and Patient Disposition

The demographics of patients enrolled in Study 003 are summarized in Table 30. Briefly, ages ranged from 19 to 74 years and gender distribution was similar among the 30 units (U)/kg and 60 U/kg dosing as well as the switchover treatment groups. Among 59 patients who completed Study 001 (n = 29) and Study 002 (n = 30) at nine months, 45 patients (76.3%) from 14 study sites were enrolled in this extension study (Study 003). Forty-four received treatment and 38 completed the study (Table 31). Among the 26 treatment-naive patients from Study 001, two patients in the 60 U/kg group discontinued from the study. One patient was discontinued by the investigator's recommendation to assess a possible allergic reaction after 38 infusions, and one patient voluntarily withdrew from the study after 33 infusions. Of the 18 patients from Study 002, four discontinued from the study (Table 31).

TABLE 30: SUMMARY OF DEMOGRAPHIC INFORMATION

		Study 003		
		Study 001		Study 002
		30 U/kg	60 U/kg	
		N = 12	N = 14	N = 18
Age (years)	Mean (SD)	39.7 (12)	36.6 (12)	46.5 (14)
	Range	25 to 74	20 to 59	19 to 67
Gender, n (%)	Male	7 (58)	8 (57)	9 (50)
	Female	5 (42)	6 (43)	9 (50)
Religion, n (%)	Jewish — Ashkenazi	4 (33)	2 (14)	11 (61)
	Non-Jewish	8 (67)	12 (86)	7 (39)

SD = standard deviation; U = units.
Note: Data reported as full analysis population.
Source: Clinical Study Report, Study 003, p. 39.[56]

TABLE 31: PATIENTS' DISPOSITIONS

	Study 003		
	Study 001		Study 002
	30 U/kg	60 U/kg	
Enrolled, N	12	14	19
Treated, N	12	14	18
Completed 36 months of treatment, n (%)	12 (100)	11 (79)	10 (56)
Withdrew from study, n (%)	0 (0)	3 (21)	8 (44)
Reason for discontinuation, n (%)	0	2	4
Protocol violation, n (%)	—	0 (0)	1 (25)
Voluntary withdrawal, n (%)	—	1 (50)	3 (75)
By investigator, n (%)	—	1 (50)	0 (0)

SD = standard deviation; U = units.
Source: Clinical Study Report, Study 003, p. 37.[56]

Results: Efficacy and Harms

Efficacy

The outcomes reported in the extension period include spleen volume, liver volume, platelet counts, hemoglobin, and biomarkers (chitotriosidase and CCL18). Organ sizes were assessed after 36 months, while hematological parameters and biomarkers were assessed after 39 months. Bone mineral density (BMD) measured by DEXA (dual-energy X-ray absorptiometry) and quantitative chemical shift imaging (QCSI) were only reported in patients from Study 001 after 36 months. Thirty-three patients who completed the study (i.e., who had received 36 months of treatment) were included in the completer population (CP) analysis.

Spleen Volume

Of the 26 patients from Study 001, 12 patients in the 30 U/kg group showed a 47.3% mean reduction in spleen volume after 36 months of treatment. In 11 patients treated with 60 U/kg, a mean reduction of 62% in spleen volume was observed (see Table 32). A mean reduction (50% to 65%) from baseline in spleen volume in multiples of normal was observed for both treatment groups throughout the study. Patients from Study 002 were switched from a stable dose of imiglucerase to the equivalent dose of taliglucerase alfa (TALI) in Study 003. Seven patients had a mean reduction of 21.2% from baseline in spleen volume after 36 months of treatment. A mean 19.8% reduction in multiples of normal spleen volume was also observed (Table 32).

Liver Volume

Among the patients from Study 001, 12 patients on 30 U/kg completed 36 months of treatment, and their mean liver volume decreased 21.6%. In patients treated with 60 U/kg, a mean reduction of 19.2% in liver volume was observed in 11 patients after 36 months of treatment. The mean liver volume decreased from 1.7 multiples of normal at baseline to 1.3 multiples of normal after 36 months of treatment in patients on 30 U/kg. Of 14 patients treated with 60 U/kg, mean liver volume decreased from 1.5 multiples of normal at baseline to 1.1 multiples of normal in the patients who completed 36 months of treatment. Overall, there was a mean reduction of 0.4 multiples of normal from baseline in liver volume for patients treated with either TALI 30 U/kg or TALI 60 U/kg at month 36 (Table 32). Patients from Study 002 showed a slight mean decrease of 0.8% in liver volume from baseline to month 36 (Table 32).

TABLE 32: SUMMARY OF SPLEEN AND LIVER VOLUME CHANGE

	Study 003		
	Study 001		Study 002
	30 U/kg	60 U/kg	
	Mean (SD)		
Spleen volume			
Number of patients treated, N	N = 12	N = 14	N = 18
Patients with month 36 data, n (%)	12 (100)	11 (78.6)	7 (38.9)
At baseline (patients with month 36 data)	2,324 (1,209)	2,172 (1,618)	932 (584)
At month 36	1,237 (696)	761 (556)	735 (446)
Change from baseline to month 36	–1,087 (558)	–1,411 (1,206)	–198 (308)
% change from baseline to month 36	–47 (10)	–62 (12)	–21 (28)
Spleen volume in MN			
Baseline (patients with month 36 data)	16 (8)	18 (16)	6 (4)
Month 36	8 (4)	6 (5)	5 (3)
Change from baseline to month 36	–8 (4)	–12 (13)	–1 (2)
% change from baseline to month 36	–50 (8)	–65 (11)	–20 (26)
Liver volume			
n (%)	12 (100)	11 (78.6)	8 (44.4)
Baseline (patients with month 36 data)	3,000 (779)	2,475 (480)	2,018 (376)
Month 36	2,341 (553)	1,972 (405)	2,014 (517)
Change from baseline to month 36	–659 (277)	–503 (440)	–4 (323)
% change from baseline to month 36	–22 (5)	–19 (15)	–0.8 (17)
Liver volume in MN			
Baseline (patients with month 36 data)	1.7 (0.4)	1.5 (0.4)	1.1 (0.3)
Month 36	1.3 (0.2)	1.1 (0.2)	1.1 (0.2)
Change from baseline to month 36	–0.4 (0.2)	–0.4 (0.4)	–0.0 (0.2)
% change from baseline to month 36	–25.6 (5.1)	–24.4 (15.3)	0.9 (15.4)

MN = multiples of normal; SD = standard deviation; U = unit.
Note: Data reported as completer population.
Source: Study 003, p. 47 to p. 62.[56]

Platelet Counts

Patients from Study 001 showed an improvement in platelet counts throughout the study. At the end of the study, a 34,845/mm^3 (57%) mean increase was observed after 11 patients completed 39 months of treatment. A 74,582/mm^3 (118%) mean increase in platelets was observed after 11 patients completed 39 months of treatment. Of the 18 patients from Study 002, a 6,428.6/mm^3 (7.5%) mean increase in platelets was observed in the seven patients who completed 39 months of treatment (Table 33).

Hemoglobin

All patients from Study 001 showed a consistent improvement in hemoglobin levels throughout the study as well. A 1.7 g/dL (15%) mean increase was observed after 39 months of treatment in patients on 30 U/kg TALI (N = 9). Of the patients with 60 U/kg TALI, a 2.8 g/dL (33%) mean increase was observed after 39 months of treatment (n = 10). For patients from Study 001 who were anemic at baseline (n = 10), hemoglobin improvement was observed in both the 30 U/kg (n = 2) and 60 U/kg (n = 8) treatment

groups. Hemoglobin levels in patients from Study 002 remained stable after being switched from imiglucerase to TALI during the 39-month extension treatment (Table 33).

TABLE 33: SUMMARY OF PLATELET COUNT AND HEMOGLOBIN

	Study 003		
	Study 001		Study 002
	30 U/kg	60 U/kg	
	Mean (SD)		
Platelet counts (mm^3)	N = 12	N = 14	N = 18
Patients completed at month 39, n (%)	11 (92)	11 (79)	7 (39)
Baseline (patients with month 39 data)	65,709 (31,466)	73,055 (30,362)	132,286 (75,439)
Month 39	100,555 (48,983)	147,636 (59,852)	138,714 (79,774)
Change from baseline to month 39	34,845 (27,723)	74,582 (56,946)	6,428.6 (11,450)
% change from baseline to month 39	57 (43)	118 (110)	8 (17)
Hb, n (%)	9 (75)	10 (71)	7 (39)
Baseline (patients with month 39 data)	12.3 (2.0)	11.1 (3.1)	13.9 (1.4)
Month 39	14.0 (1.8)	13.9 (2.4)	13.1 (1.1)
Change from baseline to month 39	1.7 (1.6)	2.8 (2.7)	–0.8 (1.1)
% change from baseline to month 39	15.1 (15.6)	32.9 (39.7)	–5.0 (8.0)

Hb = hemoglobin; SD = standard deviation.
Note: Data reported as completer population.
Source: Study 003, p. 75 and p. 211.[56]

Biomarkers: Chitotriosidase and CCL18

In Study 001, one patient (TALI 60 U/kg dose) was found to have no chitotriosidase activity; therefore, only 25 patients were analyzed for chitotriosidase. Mean chitotriosidase activity decreased throughout the extension study. At month 39, a mean reduction in chitotriosidase activity from baseline was observed in the 30 U/kg group (–17,881 nmol/mL/h, 74% reduction, N = 11 patients) and also in the 60 U/kg group (–15,581 nmol/mL/h, 84% reduction, N = 9 patients). In study 002, a 53% mean reduction (–2,686 nmol/mL/h) in chitotriosidase activity from baseline was observed in patients who completed a total of 39 months of treatment (N = 7). In terms of Chemokine (C-C motif) ligand 18 (CCL18) levels, mean reductions of 60%, 70%, and 34% were observed in the 30 U/kg and 60 U/kg groups in Study 001 as well as in Study 002, respectively, in patients who completed 39 months of treatment (Table 34).

TABLE 34: BIOMARKERS — CHITOTRIOSIDASE AND CHEMOKINE (C-C MOTIF) LIGAND 18

		Study 003		
		Study 001		Study 002
		30 U/kg	60 U/kg	
		Mean (SD)		
Chitotriosidase (nmol/mL/h)	**Baseline (patients with month 39 data), n (%)**	**11 (92)**	**9 (64)**	**7 (39)**
	Baseline	25,150 (11,763)	20,172 (18,323)	5,604.6 (4,838.9)
	Month 39	7,269 (6,317)	4,591 (8,131)	2,919 (3,227)
	Change from baseline to month 39	–17,881 (8,054)	–15,581 (1,490)	–2,686 (2,259)
	% change from baseline to month 39	–74 (15)	–84 (20)	–53 (30)
CCL18 (ng/mL)	**Baseline (patients with month 39 data), n (%)**	**11 (92)**	**10 (71)**	**7 (39)**
	Baseline	874 (426)	801 (375)	277 (99)
	Month 39	350 (209)	233 (197)	182 (97)
	Change from baseline to month 39	–524 (278)	–568 (333)	–95 (92)
	% change from baseline to month 39	–60 (17)	–71 (18)	–34 (28)

CCL18 = Chemokine (C-C motif) ligand 18; SD = standard deviation; U = unit.
Source: Clinical Study Report for Study 003, p. 320 to p. 343.[56]

Bone Mineral Density by Dual-Energy X-ray Absorptiometry

Z score, t score, and BMD for lumbar spine, femoral neck, and total hip DEXA scans were obtained in patients from Study 001. DEXA was not performed in Study 002. A trend in improvement in scores was observed in the majority of patients over the course of treatment. The findings of DEXA on lumbar spine are presented in Table 35.

Quantitative Chemical Shift Imaging

Quantitative chemical shift imaging (QCSI) was used to measure bone marrow fat fraction content as an exploratory end point. Eight patients in Study 001 (N = 4 in each group) had QCSI performed at month 36. It was reported that, at baseline, six out of eight patients (75%) presented with a fat fraction of ≤ 0.23, which is considered "bone at risk". At 36 months, two of the three patients in the 30 U/kg treatment group had not reached healthy population fat fraction value of approximately 0.37, but their fat fraction continued to improve to a fat fraction higher than 0.23. Overall, an increase in fat fraction from baseline was observed in all patients treated with TALI using the QCSI technique. At baseline, only 25% (two of eight) of patients had a fat fraction > 0.23. After 36 months of treatment, 87.5% (seven of eight) of patients showed a fat fraction > 0.23, and 62.5% (five of eight) of patients reached healthy population fat fraction value (> 0.37).

TABLE 35: BONE MINERAL DENSITY BY DUAL-ENERGY X-RAY ABSORPTIOMETRY

		Study 001	
		30 U/kg	60 U/kg
		Mean (SD)	
Lumbar spine — z score	**Baseline (patients with month 36 data), n (%)**	**10 (83)**	**10 (71)**
	Baseline	–0.2 (1.2)	–1.1 (1.1)
	Month 36	0.0 (1.4)	–0.8 (1.0)
	Change from baseline to month 36	0.2 (0.5)	0.3 (0.8)
	% change from baseline to month 36	64.8 (130.2)	13.2 (87.2)
Lumbar spine — t score	**Baseline (patients with month 36 data), n (%)**	**11 (92)**	**10 (71)**
	Baseline	–0.8 (0.8)	–0.9 (0.9)
	Month 36	–0.4 (1.0)	–0.8 (1.1)
	Change from baseline to month 36, n	0.4 (0.5)	0.1 (0.6)
	% change from baseline to month 36	141.4 (267.4)	9.1 (86.0)
Lumbar spine — BMD	**Baseline (patients with month 36 data), n (%)**	**12 (100)**	**11 (79)**
	Baseline	1.0 (0.1)	1.0 (0.1)
	Month 36	1.1 (0.1)	1.0 (0.2)
	Change from baseline to month 36	0.1 (0.1)	0.0 (0.1)
	% change from baseline to month 36	5.5 (10.0)	4.2 (13.5)

BMD = bone mineral density; SD = standard deviation; U = unit.
Note: Data are reported as completer population.
Source: Clinical Study Report for Study 003, p. 422 to p. 439.[56]

TABLE 36: QUANTITATIVE CHEMICAL SHIFT IMAGING SUMMARY

	Baseline	36 Months	Change from Baseline at Month 36
TALI (30 U/kg)			
Patient 1	0.16	0.26	0.10
Patient 2	0.11	0.19	0.08
Patient 3	0.23	0.34	0.11
Patient 4	0.22	0.40	0.18
Mean	**0.18**	**0.30**	**0.12**
TALI (60 U/kg)			
Patient 5	0.35	0.40	0.05
Patient 6	0.33	0.49	0.16
Patient 7	0.14	0.40	0.26
Patient 8	0.13	0.42	0.29
Mean	**0.24**	**0.43**	**0.19**

TALI = taliglucerase alfa; U = unit.
Note: Standard deviations were not reported.
Source: Clinical Study Report for Study 003, p. 87.[56]

Harms

Extent of Exposure

In patients from Study 001, those in the TALI 30 U/kg group (N = 12) received an average dose of 33.7 U/kg (range: 29.8 U/kg to 47.5 U/kg); those in the TALI 60 U/kg group (N = 14) received an average dose of 60.3 U/kg (range: 55.2 U/kg to 66.6 U/kg). In patients from the switchover study (Study 002), the average dose of TALI was 32.4 U/kg (range: 12.0 U/kg to 59.0 U/kg).

Adverse Events

Treatment-emergent adverse events (TEAEs) are summarized in Table 37. No deaths were reported during the extension study. No patients were discontinued from the study due to an adverse event (AE). It was reported that 24 patients from Study 001 experienced 275 AEs, and 17 patients from Study 002 experienced 136 AEs. Four patients from Study 001 reported seven SAEs, which included head injury, immune thrombocytopenia, hemangioma, and pulmonary embolism. Three patients from Study 002 reported four SAEs, which included osteoarthritis, arthralgia, pneumothorax traumatic, and renal stone removal. No SAEs were considered to be related to the study drug. The AEs reported in ≥ 10% of patients are presented in Table 37. In addition, 13 patients tested positive for the presence of anti-TALI immunoglobulin G (IgG) antibodies on at least one visit, with peak titers ranging from 151 to 51,398. Four patients from Study 002 tested positive for anti-TALI IgG antibodies on at least one visit, with peak titers ranging from 573 to 121,869. Of note: three patients (6.8% of treated patients), one in each group, had an event of bone pain during the study.

Limitations

One of the limitations of the extension study is that not all patients who completed the original nine-month studies entered the extension, and it is not clear how the patients were selected. Whether the extension study had a selection bias cannot be determined. The selected reporting of outcomes due to missing data from the end points (such as week 39) could be perceived as another limitation. Furthermore, there was no control group included in the extension study. As a result, it is unknown whether the improvements observed can be attributed to the treatment, or whether treatment with TALI is more effective than current ERTs such as imiglucerase.

TABLE 37: TREATMENT-EMERGENT ADVERSE EVENTS

	Study 003		
	Study 001	Study 001	Study 002
	30 U/kg	60 U/kg	
	N = 12	N = 14	N = 18
Number of patient with ≥ 1 AE, n (%)	12 (100)	12 (86)	17 (94)
Number of patients with ≥ 1 SAE, n(%)	2 (17)	2 (14)	3 (17)
Number of patients with AE that occurred in ≥ 10% patients, n (%)			
Diarrhea	3 (25)	0 (0)	3 (17)
Gastroenteritis	2 (17)	1 (7)	1 (6)
Nasopharyngitis	2 (17)	3 (22)	7 (39)
Pharyngitis	2 (17)	0 (0)	1 (6)
Sinusitis	0 (0)	3 (21)	2 (11)
Upper respiratory tract infection	3 (25)	3 (21)	3 (17)
Urinary tract infection	0 (0)	0 (0)	2 (11)
Limb injury	1 (8)	2 (14)	0 (0)
Hypertriglyceridemia	0 (0)	2 (14)	0 (0)
Arthralgia	4 (33)	4 (29)	4 (22)
Back pain	2 (17)	2 (14)	2 (11)
Musculoskeletal pain	0 (0)	2 (14)	3 (17)
Pain in extremity	2 (17)	4 (29)	2 (11)
Headache	4 (33)	3 (21)	2 (11)
Cough	0 (0)	1 (7)	3 (17)
Endodontic procedure	0 (0)	2 (14)	0 (0)
Hypertension	2 (17)	3 (21)	1 (6)

AE = adverse event; SAE = serious adverse event; U = unit.
Source: Clinical Study Report for Study 003, p. 97 to p. 109.[56]

Summary

In the extension study, 44 patients continued TALI treatment for up to 39 months. The findings of this study showed that TALI maintains its effectiveness for as long as 39 months. Continued improvement was observed in spleen and liver volumes, platelet counts, and hemoglobin in patients naive to ERT in both dose groups. Patients who switched from imiglucerase to TALI remained stable for up to 39 months. TALI was also well tolerated during the extension period. No new serious AEs were reported. However, the results should be interpreted with caution due to the limitations associated with the lack of a control group.

APPENDIX 6: SUMMARY OF SYSTEMATIC REVIEWS

The randomized controlled trials (RCTs) included in the systematic review of clinical evidence for TALI were not designed to compare TALI to relevant active comparators. In addition, most pivotal studies conducted with ERTs as the intervention have been single-arm trials. According to the manufacturer, this lack of a common comparator between trials prevented an indirect comparison to be conducted. Instead, the manufacturer provided two systematic reviews of the available evidence for naive side-by-side comparison. The objective of this section is to summarize and critically appraise the systematic reviews of ERT for GD provided by the manufacturer,[57] as well as a recent systematic review retrieved from the published literature.[58]

1. Manufacturer-Submitted Systematic Reviews

1.1 First Systematic Review: Efficacy After Nine to 12 Months

The objective of the systematic review was to evaluate the efficacy of imiglucerase, velaglucerase alfa, and TALI as ERT for the treatment of GD based on clinical trial data.

a) Methods

The methods for conducting this systematic review were briefly described in a congress abstract[59] and in a document provided by the manufacturer after request.[60] Both journal articles and congress abstracts were included in the review. Electronic searches were performed on MEDLINE, Embase, and CENTRAL databases up to May 2011. Abstracts from major genetic and metabolic conferences up to March 2011 were reviewed. Two independent reviewers performed the selection. Two independent researchers assessed study quality using a modified version (12 items) of the Downs and Black checklist with a maximum score of 16. Studies with scores greater than 10 were considered to be good quality by the authors.

Inclusion Criteria

To be included, studies had to have a population of treatment-naive adults with an intact spleen. Interventions of interest were ERTs (30 U/kg to 60 U/kg) compared with other ERTs or placebo for a duration of up to 12 months. The clinical end points of interest were changes from baseline in spleen volume, liver volume, hemoglobin levels, and platelet counts.

b) Findings

Seven studies (six journal articles and one congress abstract) were identified in the systematic literature review for inclusion. Six publications, including one abstract, reported use of imiglucerase or velaglucerase alfa. The included studies received quality scores ranging from 11 to 16. The results of the six studies on imiglucerase or velaglucerase alfa were compared against one publication that reported use of TALI.

Population Characteristics

The baseline characteristics of the patients are shown in Table 38. The mean values for the baseline clinical measures of spleen volume, liver volume, hemoglobin, and platelet count were similar for the studies included.

TABLE 38: BASELINE CHARACTERISTICS OF PATIENTS

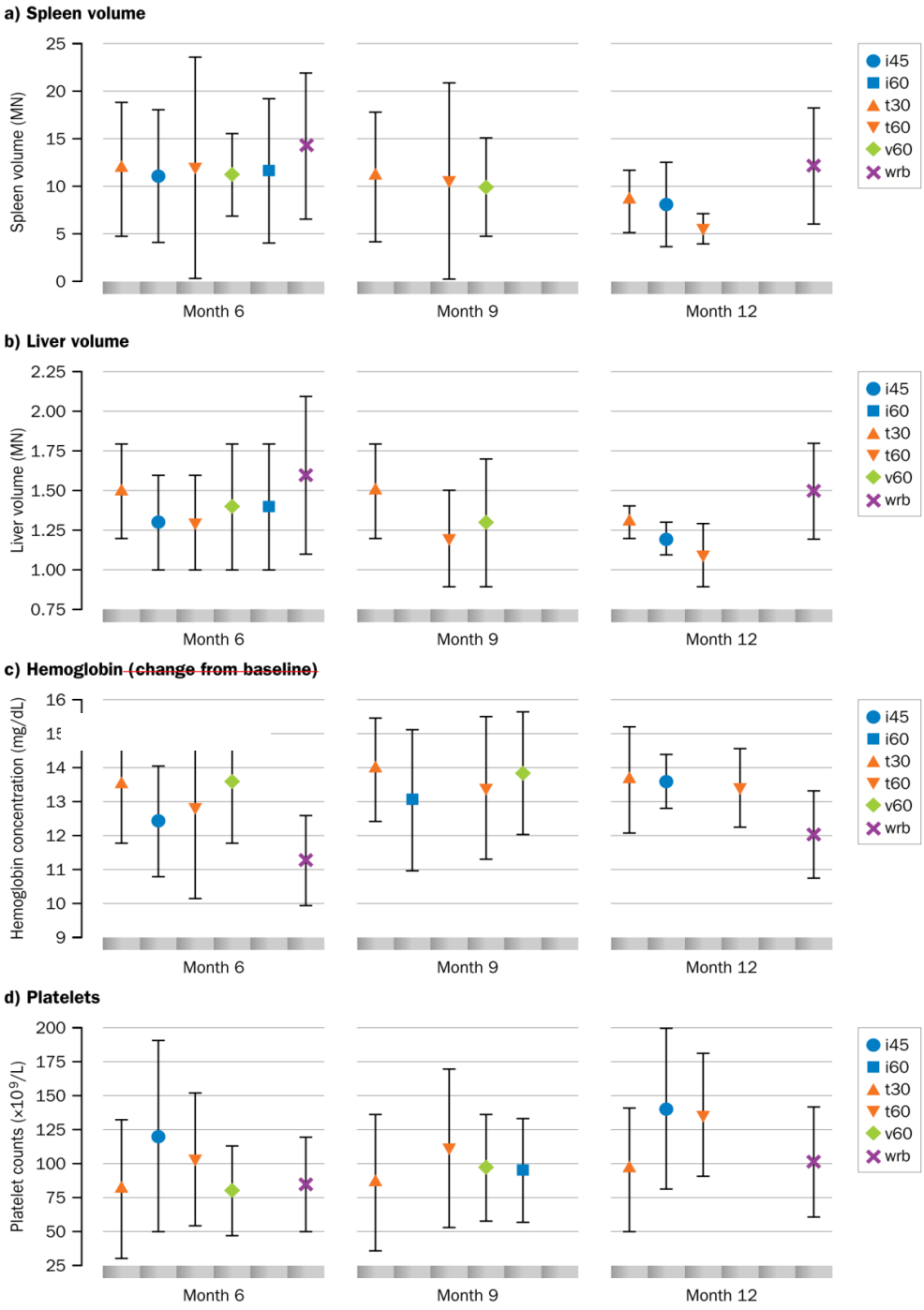
	Registry[a]	Registry[b]	Imiglucerase		Velaglucerase Alfa			TALI	
	Weinreb (2002)[23]	Giraldo (2000)[61]	Grigorescu-Sido (2010)[62]	Grabowski (1995)[63]	Zimran and Gonzalez (2010)[64]		Zimran (2010)[65]	Zimran (2011)[30] and Zimran (2012)[66]	
ERT dose (U/kg every other week)	Varied	Varied	45[c]	60	45	60	60	30	60
Spleen Volume (MN)									
N	96	94	21	12	13	12	11	12	12
Mean (SD)	20.2 (10.2)	11.7 (1.0)	14.4 (7.6)	18.3 (12.0)	14.5 (NR)	14.0 (NR)	19.4 (6.2)	15.1 (8.5)	17.3 (15.4)
Liver Volume (MN)									
N	94	94	28	12	13	12	11	NR	NR
Mean (SD)	2.0 (0.4)	5.5 (1.0)	1.5 (0.5)	1.6 (0.5)	1.4 (NR)	1.5 (NR)	1.6 (0.5)	1.7 (0.4)	1.5 (0.5)
Hb Levels (g/dL)									
N	135	94	11	12	13	12	11	12	12
Mean (SD)	9.6 (0.9)	11.8 (0.5)	9.5 (1.8)	10.7 (2.5)	10.6 (1.4)	10.7 (1.4)	11.6 (1.4)	12.5 (1.9)	11.3 (2.6)
Platelet Counts (10^9/L)									
N	222	94	22	12	13	12	11	12	12
Mean (SD)	69 (15)	110 (15)	76 (32)	67 (26)	84 (60)	113 (112)	58 (13)	75 (38)	72 (32)

ERT = enzyme replacement therapy; Hb = hemoglobin; ICGG = International Collaborative Gaucher Group; MN = multiples of normal; NR = not reported; SD = standard deviation; SGDG = Spanish Gaucher Disease Group; TALI = taliglucerase alfa; U = unit.
[a] ICGG Registry; varied doses of alglucerase or imiglucerase (dosage range not specified).
[b] SGDG Registry; varied doses of alglucerase or imiglucerase (84/94 [89.3%] received ≥ 30 U/kg every other week; 10 patients treated at low dose, high frequency).
[c] Dose represents the mean for patients treated with 30 U/kg to 60 U/kg.

Efficacy

As shown in Figure 6, the mean change from baseline in spleen volume, liver volume, hemoglobin, and platelet count for TALI (30 U/kg and 60 U/kg) showed overlap with that of velaglucerase alfa (45 U/kg and 60 U/kg) and imiglucerase (60 U/kg) at months 6, 9, and 12. Efficacy end point data for both dose groups of TALI fell within the range of data from the International Collaborative Gaucher Group (ICGG) Registry.

FIGURE 6: COMPARISON OF EFFICACY END POINTS AT 6, 9, AND 12 MONTHS FOR ENZYME REPLACEMENT THERAPIES



i45 = imiglucerase 45 U/kg; i60 = imiglucerase 60 U/kg; t30 = taliglucerase 30 U/kg; t60 = taliglucerase 60 U/kg; v60 = velaglucerase alfa 60 U/kg; wrb = Weinreb et al. (International Collaborative Gaucher Group Registry, weighted average).
Note: The end point data reported by Gonzalez et al. (2010) were available only as changes from baseline and are therefore not included in that figure.
Source: Manufacturer's pharmacoeconomic submission.[57]

A subgroup analysis of patients stratified by baseline severity of splenomegaly, anemia, or thrombocytopenia was similar to the findings of the primary analyses.

Safety

The safety data for TALI, imiglucerase, and velaglucerase alfa provided by the manufacturer were extracted from their respective product monographs. These data are presented in Table 39. Of note: imiglucerase safety data are based on a very small sample of 40 patients and the manufacturer of this drug reported only treatment-related adverse events (AEs) instead of all AEs, irrespective of cause. In that context, comparing with AEs of imiglucerase would be misleading. When compared with velaglucerase alfa, TALI has generally similar or numerically better safety outcomes.

TABLE 39: COMPARISON OF SAFETY END POINTS FOR ENZYME REPLACEMENT THERAPIES AFTER 9 TO 12 MONTHS

System Organ Class Preferred Term	TALI (N = 132)		Velaglucerase Alfa (N = 94)	Imiglucerase (N = 40)
	All Causality AEs[a]	Treatment-Related AEs[b]	All Causality AEs[c]	Treatment-Related AEs[d]
Cardiac disorder				
Tachycardia	—	—	2 (2.1%)	—
Gastrointestinal disorder				
Abdominal pain/abdominal pain upper/chest pain	16 (12.1%)	3 (2.3%)	16 (17.0%)	2 (5.0%)
Diarrhea	—	—	—	1 (2.5%)
Nausea	13 (9.8%)	4 (3.0%)	7 (7.4%)	2 (5.0%)
General disorders and administration-site conditions				
Fatigue/asthenia	15 (11.4%)	2 (1.5%)	13 (13.8%)	—
Fever/pyrexia/body temperature increase	—	—	19 (20.2%)	1 (2.5%)
Infusion site pain	4 (3.0%)	2 (1.5%)	—	—
Oedema peripheral	9 (6.8%)	2 (1.5%)	—	—
Immune system disorder				
Hypersensitivity	5 (3.8%)	5 (3.8%)	3 (3.2%)	1 (2.5%)
Injury, poisoning, and procedural complications				
Infusion-related reaction	10 (7.6%)	7 (5.3%)	37 (39.4%)	—
Infections and infestations				
Upper respiratory tract infections	—	—	29 (30.9%)	—
Investigations				
Activated partial thromboplastin, time prolonged	—	—	8 (8.5%)	—
Neutralizing Ab positive	—	—	1 (1.1%)	—
Weight increase	3 (2.3%)	3 (2.3%)	—	—

System Organ Class Preferred Term	TALI (N = 132)		Velaglucerase Alfa (N = 94)	Imiglucerase (N = 40)
	All Causality AEs[a]	Treatment-Related AEs[b]	All Causality AEs[c]	Treatment-Related AEs[d]
Musculoskeletal and connective tissue disorders				
Arthralgia	29 (22.0%)	2 (1.5%)	21 (22.3%)	—
Back pain	13 (9.8%)	2 (1.5%)	16 (17.0%)	—
Bone pain	7 (5.3%)	1 (0.8%)	14 (14.9%)	—
Pain in extremity	22 (16.7%)	2 (1.5%)	—	—
Nervous system disorders				
Dizziness	7 (5.3%)	2 (1.5%)	15 (16.0%)	1 (2.5%)
Headache	29 (22.0%)	8 (6.1%)	31 (33.0%)	4 (10.0%)
Paresthesia	—	—	—	1 (2.5%)
Psychiatric disorders				
Affect liability	—	—	—	1 (2.5%)
Nervousness	—	—	—	1 (2.5%)
Renal and urinary disorders				
Oliguria	—	—	—	1 (2.5%)
Respiratory, thoracic, and mediastinal disorders				
Throat irritation	4 (3.0%)	3 (2.3%)	—	—
Skin and subcutaneous tissue disorders				
Erythema	5 (3.8%)	3 (2.3%)	—	—
Pruritus	11 (8.3%)	7 (5.3%)	—	2 (5.0%)
Rash	5 (3.8%)	2 (1.5%)	3 (3.2%)	2 (5.0%)
Urticaria	—	—	3 (3.2%)	—
Vascular disorders				
Hypertension	—	—	7 (7.4%)	—
Hypotension	—	—	4 (4.3%)	1 (2.5%)
Flushing/vasodilation	5 (3.8%)	3 (2.3%)	1 (1.1%)	2 (5%)

Ab = antibodies; AEs = adverse events; TALI = taliglucerase alfa.
[a] TALI product monograph.
[b] TALI data in file.
[c] Velaglucerase alfa product monograph.
[d] Imiglucerase product monograph.
Source: Manufacturer's pharmacoeconomic submission.[57]

CDR Reviewer's Conclusion

The efficacy findings of the systematic review suggest a similar magnitude of effect size for hematological and visceral responses between TALI, imiglucerase, and velaglucerase alfa. For comparative safety, findings were very limited, but there was no obvious difference in safety profiles between TALI and other ERTs.

c) Critical Appraisal

The AMSTAR checklist[67] was used to appraise the quality of this systematic review.

Strengths

The authors followed a pre-specified protocol for their review. The literature search was extensive and grey literature was included. The study selection and quality evaluation was duplicated.

Limitations

In general, the methods and findings were not reported in a clear manner. The search strategy was not provided and the search was conducted up to May 2011, which is outdated for the present review of TALI. The list of excluded studies was not provided and the list of included studies does not match the number of publications included. The baseline characteristics of the included studies provided very minimal information on the population. The authors used a modified version of Downs and Black's checklist to assess the quality of the included studies. However, the validity of this modified version is uncertain and their assessments were not properly reported (i.e., unable to tell the score of a specific study). Therefore, it is unclear if limitations were adequately taken into consideration for their evaluation. The likelihood of publication bias has not been assessed. Conflicts of interest were not mentioned.

Indeed, the major limitation is the naive side-by-side comparison, which did not report formal statistics or estimates of relative effects. In addition, it is unclear how the heterogeneity of the studies was considered in the comparison. Moreover, it was not specified why the authors did not search for safety outcomes in the systematic review and preferred to extract safety data from product monographs. In terms of evidence, the safety data for imiglucerase could not be properly compared with other ERTs. This is problematic because, according to the clinical expert consulted for this review, imiglucerase is the standard of care in Canada with a market share of approximately 66%.

1.2 Second Systematic Review: Efficacy and Safety After 36 Months

The objective of the systematic review was to compare the efficacy and safety of TALI after 36 months with current Food and Drug Administration (FDA)–approved ERTs for GD.

a) Methods

Searches of electronic databases (OVID, BIOSIS, Embase) were conducted on March 2013. Data were extracted and changes from baseline were calculated when possible. When data were shown graphically, values were estimated from graphs.

The authors did not mention more specific inclusion criteria.

b) Findings

Of 251 citations, 109 were deemed potentially relevant. Thirteen publications were identified in the systematic literature review and met the inclusion criteria. Of these, nine reported data on imiglucerase and/or alglucerase and four reported data on velaglucerase alfa. Seven were prospective studies and four were registry reports. Studies that reported on use of TALI were not included in the systematic review, but were used for comparison by the manufacturer. The characteristics of the included studies are described in Table 40.

TABLE 40: CHARACTERISTICS OF INCLUDED STUDIES

Author, Year	Study Design	Population	Intervention	Comparator	Outcomes
Giraldo (2000)[61]	Retrospective cohort study of SGDG Registry.	155 patients with GD from 66 hospitals. 149 with type 1 GD; 72 were males, 42 were children. Mean age was 31.5 years. 95% had organomegaly, 62% had bone disease, 62% had decreased hematological parameters, and 19% were asymptomatic.	No intervention, or alglucerase and imiglucerase (10 with low dose/high frequency and 84 with high dose/low frequency).	None	• Distribution • Clinical characteristics • Genetics
Poll (2002)[68]	Prospective cohort study.	30 patients with type 1 GD from one centre in Germany. Mean age was 43 years; 11 males and 19 females.	Alglucerase, then imiglucerase after 1997. 60 U/kg every 2 weeks for 18 patients, 40 U/kg for 7 patients, 30 U/kg for 3 patients, and 20 U/kg for 2 patients.	None	• Hematological, visceral, and biochemical parameters • Bone marrow response
Weinreb (2002)[23]	Retrospective cohort study of ICGG Registry.	Non-splenectomized patients with type 1 GD and abnormal baseline values (between 12 and 170 patients per subset) were reported. Mean ages of diagnosis and start of ERT were 17 years and 30 years, respectively. Samples were taken from a population of 1,028 patients from 25 countries (53% from US).	Varying doses or ERT.	None	• Hematological, visceral, and biochemical parameters
Charrow (2007)[69]	Retrospective cohort study of ICGG Registry.	219 patients (91 males) with bone crises, and 244 patients (101 males) with bone pain. Samples were taken from a population of 2,153 patients from 52 countries.	Varying doses or ERT.	None	• Bone crises • Bone pain
Sims (2008)[70]	Prospective, non-randomized, multi-centre, OL study.	33 treatment-naive patients with type 1 GD and history of bone disorders. 19 were males; mean age was 43 years.	Imiglucerase: 60 U/kg every 2 weeks for the first 24 months, then could be decreased to	None	• Bone response

Author, Year	Study Design	Population	Intervention	Comparator	Outcomes
			either 45 U/kg or 30 U/kg every 2 weeks, depending on the degree of disease burden and improvement.		
Grabowski (2009)[24]	Retrospective cohort analysis of a subset of the ICGG Registry.	Three matched cohorts of N = 122 patients each. Sample was taken from a population of 4,434 patients. Splenectomy was an exclusion criterion. Mean age ranged from 22.1 years to 23.1 years.	Alglucerase (4.4% of patients) and imiglucerase (95.6% of patients) at the following doses (U/kg): Group A: 5 to < 29 Group B: 29 to < 48 Group C: 48 to < 75	None	• Hematological and visceral parameters
Grigorescu-Sido (2010)[62]	Prospective, observational study of the Romanian national experience with GD.	50 patients (including 14 children) with type 1 GD. 19 patients were males. Mean diagnostic age was 28.8 years.	Imiglucerase (N = 39): 18 with 60 U/kg every 2 weeks, 20 with 30 U/kg every 2 weeks and 1 with 45 U/kg every 2 weeks	Untreated patients (N = 11)	• Hematological, visceral, and biochemical parameters
Krug (2010)[71]	Retrospective, observational study of the Brazilian experience with GD.	25 patients with mean ages of 33.8 years at end point. 17 had type 1 GD; 10 were males.	19 patients with imiglucerase; 1 declined treatment. Mean dose was 48 U/kg every 2 weeks at baseline, 25 U/kg every 2 weeks at 1 year, and 23 U/kg every 2 weeks at 3 years.	None	• Hematological and visceral parameters
Zimran (2010)[65] and Zimran (2011)[72]	Prospective, OL, phase 1/2 study of 9 months followed by a 39-month extension	12 adult patients with type 1 GD treated at single site. Mean age of 41.7 years. 5 were males.	Velaglucerase alfa at 60 U/kg every 2 weeks for the first 15 to 18 months. Depending of	None	• Hematological and visceral parameters

Author, Year	Study Design	Population	Intervention	Comparator	Outcomes
	study.		response, the dose could be decreased to 45 U/kg and then 30 U/kg every 2 weeks.		
Elstein (2011)[73]	Prospective, OL, phase 1/2 study of 9 months followed by a 39-month extension study.	12 adult patients of which 8 were described with data. Mean age was 38.8 years. 5 of 8 patients were males.	Velaglucerase alfa at 60 U/kg every 2 weeks for the first 15 to 18 months. Depending of response, the dose could be decreased to 45 U/kg and then 30 U/kg every 2 weeks.	None	• Hematological and visceral parameters • BMD
Elstein (2011)[74]	Prospective, OL, phase 1/2 study of 9 months followed by a 39-month extension study.	12 adult patients of which 10 were described with data (2 patients discontinued during extension phase). Mean age was 35 years. 4 of 10 patients were males.	Velaglucerase alfa at 60 U/kg every 2 weeks for the first 15 to 18 months. Depending of response, the dose could be decreased to 45 U/kg and then 30 U/kg every 2 weeks.	None	• BMD
Mistry (2011)[75]	Retrospective cohort study of the ICGG Registry.	889 patients: ages 5 to 50, type 1 GD, treatment with imiglucerase/alglucerase, BMD evaluations done, no bisphosphonate treatment. 481 were males. Sample was taken from a population of 5,563 patients from 62 countries. Age groups: ≥ 5 to < 12 y, n = 156 ≥ 12 to < 20 y, n = 125 ≥ 20 to < 30 y, n = 185 ≥ 30 to < 50 y, n = 423	Imiglucerase and alglucerase at a mean dose ranging from 35.5 U/kg to 38.9 U/kg every 2 weeks.	None	• Lumbar spine BMD • Baseline characteristics were reported for hematological and visceral parameters and bone-related AEs

AEs = adverse events; BMD = bone mineral density; CDR = CADTH Common Drug Review; ERT = enzyme replacement therapy; GD = Gaucher disease; ICGG = International Collaborative Gaucher Group; OL = open-label; SGDG = Spanish Gaucher Disease Group; U = unit; y =year.
Source: Summarized by CDR reviewer based on manufacturer's pharmacoeconomic submission.[57]

Efficacy

Efficacy data reported by all of the included studies are presented in Table 41 to Table 54. These tables were used for naive side-by-side comparison with data reported for TALI.

TABLE 41: GIRALDO (2000) — EFFECTIVENESS DATA (N = 155)

Parameter	Baseline	36 Months[a]	Change[a]	Percentage Change[a]
Hb (g/dL)	11.4	12.9[a]	1.5	13%
Plt (x 10^6/mL)	110,500	173,000	62,500	57%
Spleen (MN)	11.7[a]	8[a]	–3.7	–32%
Liver (MN)	5.7[a]	2.4[a]	–3.3	–58%

Hb = hemoglobin; MN = multiples of normal; plt = platelet.
[a] Calculated by Pfizer.
Note: It was unclear whether values were means, medians, or modes.
Source: Giraldo, 2000;[61] manufacturer's pharmacoeconomic submission.[57]

TABLE 42: POLL (2002) — EFFECTIVENESS DATA (N = 30)

Parameter (means)	Baseline[a]	36 Months[a]	Change[b]	Percentage Change[b]
Hb (g/dL)	12.6	14.5	1.9	15%
Plt (x 10^6/mL)	116,100	205,300	89,200	77%
Chitotriosidase	14,463	2,892	–11,571	–80%
Spleen (MN)[b]	65.7	45.6	–20.1	–31%
Liver (MN)[b]	153.5	125	–28.5	–19%

Hb = hemoglobin; MN = multiples of normal; plt = platelet.
[a] Provided by Poll et al.
[b] Calculated by Pfizer.
Source: Poll (2002);[68] manufacturer's pharmacoeconomic submission.[57]

TABLE 43: GRABOWSKI (2009) — EFFECTIVENESS DATA (N = 366)

Parameter[b]	Baseline	Month 36[a]					
		30 U	Change	Percentage Change	60 U	Change	Percentage Change
Delta Hb	—	—	1.8	—	—	2.3	—
Plt (10^6/mL)	90,000	140,000	50,000	56%	175,000	85,000	94%
Spleen (MN)	11.8	6.1	–5.7	–48%	4.8	–7	–59%
Liver (MN)	1.5	1.12	–0.38	–25%	1.06	–0.44	–29%

Hb = hemoglobin; MN = multiple of normal; plt = platelet; U = unit.
[a] As estimated by Pfizer.
[b] It was unclear whether values were means, medians, or modes.
Source: Grabowski (2009);[24] manufacturer's pharmacoeconomic submission.[57]

TABLE 44: WEINREB (2002) — EFFECTIVENESS DATA (N = FROM 12 TO 170 PER SUBSET)

Parameter (Means)	Month 36 Response
Hb (g/dL)	2.6
Plt	80%
Spleen	36%
Liver	54%

Hb = hemoglobin; plt = platelet.
Source: Weinreb (2002);[23] manufacturer's pharmacoeconomic submission.[57]

TABLE 45: GRIGORESCU-SIDO (2002) — EFFECTIVENESS DATA (N = 50)

Parameter[a]	Baseline	36 Months	Change[b]	Percentage Change[b]
Hb (g/dL)	9.5	12.8	3.3	35%
Plt (x 10^6/mL)	76,000	163,000	87,000	114%
Spleen (MN)	14.4	3.8	–10.6	–74%
Liver (MN)	1.5	1.0	–0.5	–33%

Hb = hemoglobin; MN = multiple of normal; plt = platelet.
[a] It was unclear whether values were means, medians, or modes.
[b] As estimated by Pfizer.
Source: Grigorescu-Sido (2002);[62] manufacturer's pharmacoeconomic submission.[57]

TABLE 46: KRUG (2010) — EFFECTIVENESS DATA (N = 25)

Parameter[a]	Baseline	36 Months	Change[b]	Percentage Change[b]
Hb (g/dL)	12.3	12.8	0.5	4%
Plt (10^6/mL)	178,688	211,888	33,200	19%
Spleen (cm)	12.0[a]	15.0[a]	3.0	25%
Liver (cm)	10.6[a]	13.0[a]	2.4	23%

Hb = hemoglobin; plt = platelet.
[a] It was unclear whether values were means, medians, or modes.
[b] As estimated by Pfizer.
Source: Krug (2010);[71] manufacturer's pharmacoeconomic submission.[57]

TABLE 47: ZIMRAN (2010) — EFFECTIVENESS DATA (N = 12)

Parameter[a]	Mean Percentage Change at 36 Months[b]
Hb (g/dL)	25%
Plt (10^6/mL)	135%
Spleen	–75%
Liver	–37%

Hb = hemoglobin; plt = platelet.
[a] It was unclear whether values were means, medians, or modes.
[b] As estimated by Pfizer.
Source: Zimran (2010);[65] manufacturer's pharmacoeconomic submission.[57]

TABLE 48: MISTRY (2011) — BASELINE HEMATOLOGICAL AND VISCERAL CHARACTERISTICS (N = 889)

Parameter[a]	≥ 20 to < 30 Years	≥ 30 to ≤ 50 Years
Hb (g/dL)	11.8	12.3
Plt (10^9/mL)	77.8	87.4
Spleen (MN)	13	12
Liver (MN)	1.7	1.5

Hb = hemoglobin; MN = multiple of normal; plt = platelet.
[a] It was unclear whether values were means, medians, or modes.
Source: Mistry (2011);[75] manufacturer's pharmacoeconomic submission.[57]

TABLE 49: ELSTEIN (2011) — EFFECTIVENESS DATA (N = 8)

Parameter[a]	Baseline[b]	36 Months[b]	Change[b]	Percentage Change[b]
Hb (g/dL)	11.3	13.6	2.3	20%
Plt (10^6/mL)	59,125	131,750	72,625	123%
Spleen (MN)	18.8	4.6	–14.2	–76%
Liver (MN)	1.6	1.1	–0.5	–31%
BMD – Lumbar Spine	–1.5	–0.9	0.6	42%
BMD – Femoral Neck	–1.6	–1.1	0.5	31%

BMD = bone mineral density; Hb = hemoglobin; MN = multiple of normal; plt = platelet.
[a] It was unclear whether values were means, medians, or modes.
[b] As estimated by Pfizer.
Source: Elstein (2011);[73] manufacturer's pharmacoeconomic submission.[57]

TABLE 50: CHARROW (2007) — BONE EFFECTIVENESS DATA

	Pre-ERT	Year 1	Year 2	Year 3
Bone crises (N = 219)	38	10	1	6
% incidence of bone crises and bone pain	17%	5%	< 1%	3%
Bone pain (N = 244)	119	74	71	73
% incidence of bone pain	49%	30%	29%	30%

ERT = Enzyme replacement therapy.
Source: Charrow (2007);[69] manufacturer's pharmacoeconomic submission.[57]

TABLE 51: SIMS (2008) — BONE PAIN (N = 33 PATIENTS)

Parameter	Baseline[a]	36 Months[a]
Any	72%	37%
Moderate/severe/extreme	36%	8%

[a] As estimated by Pfizer.
Source: Sims (2008);[70] manufacturer's pharmacoeconomic submission.[57]

TABLE 52: SIMS (2008)[70] — BONE MINERAL DENSITY (N = 33)

Parameter[a]	Baseline[b]	36 Months[b]	Change[b]	Percentage Change[b]
Lumbar spine (z score)	–0.70	–0.30	0.4	57%
Femoral neck (z score)	–0.59	–0.18	0.4	69%

[a] It was unclear whether values were means, medians, or modes.
[b] As estimated by Pfizer.
Source: Manufacturer's pharmacoeconomic submission.[57]

TABLE 53: ELSTEIN (2011) — BONE MINERAL DENSITY (N = 8)

Parameter[a]	Baseline	33 Months	Change[b]	Percentage Change[b]
BMD — Lumbar spine	–1.59	–1.16	0.43	27%
BMD — Femoral neck	–1.46	–1.07	0.39	27%

BMD = bone mineral density.
[a] It was unclear whether values were means, medians, or modes.
[b] As estimated by Pfizer.
Source: Elstein (2011);[74] manufacturer's pharmacoeconomic submission.[57]

TABLE 54: MISTRY (2011) — LUMBAR SPINE BONE MINERAL DENSITY (Z SCORE) BY AGE (N = 889)

Age Group	Baseline[a]	36 Months[a]	Change[a]	Per Cent Change[a]
≥ 20 to < 30 Years	–2	–1.3	0.7	35%
≥ 30 to ≤ 50 Years	–1.8	–1.5	0.3	17%

[a] As estimated by Pfizer.
Note: It was unclear whether values were means, medians, or modes.
Source: Mistry (2011);[75] manufacturer's pharmacoeconomic submission.[57]

Safety

Safety data reported by all of the included studies are presented in Table 55 to Table 58. These tables were used for naive side-by-side comparison with data reported for TALI.

TABLE 55: SIMS (2008) — BONE ADVERSE EVENTS (N = 33)

AE	Baseline (or History)	Post-Baseline (Through 36 Months)
Medullary infarction	36%	12%
Osteoarticular necrosis	6%	15%
Lytic lesions	36%	9%
Fractures — long bones	3%	0%
Fractures — spinal	3%	6%
Bone crisis	39%	9%

AE = adverse event.
Source: Sims (2008);[70] manufacturer's pharmacoeconomic submission.[57]

TABLE 56: ZIMRAN (2010) — TREATMENT-RELATED ADVERSE EVENTS (> 10% OF PATIENTS) AFTER 9 MONTHS (N = 12)

AE	Number of Patients (%)
Dizziness	3 (25%)
Headache	2 (16.7%)
Nausea	2 (16.7%)
Back pain	2 (16.7%)
Bone pain	2 (16.7%)
Body temperature increased	2 (16.7%)

AE = adverse event.
Source: Zimran (2010);[65] manufacturer's pharmacoeconomic submission.[57]

TABLE 57: ZIMRAN (2010) — TREATMENT-RELATED ADVERSE EVENTS (> 10% OF PATIENTS) AFTER 39 MONTHS (N = 12)

AE	Number of Patients (%)
Epistaxis	2 (20%)
Abdominal pain	2 (20%)
Tremor	1 (10%)
Pain in extremity	1 (10%)
Fatigue	1 (10%)

AE = adverse event.
Source: Zimran (2010);[65] manufacturer's pharmacoeconomic submission.[57]

In the Zimran (2010)[65] study, no patients developed antibodies, no drug-related serious adverse events (SAEs) were observed regardless of infusion setting or duration of exposure, and no patient withdrew from the study because of AEs.

TABLE 58: MISTRY (2011) — BASELINE BONE-RELATED ADVERSE EVENTS BY AGE GROUP (N = 889)

AE	≥ 20 to < 30 Years	≥ 30 to ≤ 50 Years
Bone pain	59.0%	61.0%
Bone crisis	14.0%	11.0%
Avascular necrosis	36.9%	26.9%
Fractures	8.1%	11.8%
Infarction	40.8%	44.5%
Lytic lesion	45.7%	35.0%

AE = adverse event.
Source: Mistry (2011);[75] manufacturer's pharmacoeconomic submission.[57]

CDR Reviewer's Conclusion

Despite the fact that high heterogeneity was observed between studies and this could impair the comparison, the findings indicate TALI has similar efficacy versus other ERTs.

f) Critical Appraisal

The AMSTAR checklist[67] was used to critically appraise the systematic review.

Strengths
The search was made using many electronic databases, including grey literature. A list of included studies and the characteristics of the included studies was provided.

Limitations
The authors did not mention a pre-specified protocol, nor did they mention duplicated study selection and extraction. The literature search was performed in 2013 and is somewhat outdated. The list of excluded studies was not provided. Although some limitations of the included studies were discussed, the quality of the included studies was not systematically assessed. The likelihood of publication bias has not been assessed. Conflicts of interest were not discussed or mentioned.

The authors of the systematic review mentioned heterogeneity in the included studies — including the nature of the study (prospective versus retrospective;[23,24,69,75] interventional versus observational); the ages,[24,61,75] ethnicity, and homogeneity of the cohorts studied;[62,69,71,74] inclusion of an untreated cohort;[61] inclusion of splenectomized patients;[23] the dosage of ERT,[23,24,69,75] — as well as the method of analysis and expression of the values (e.g., organ volume expressed as length versus mass units versus multiples of normal).[61,68,71,73,75] Some studies had a high dropout rate or a high proportion of missing values at end point.[70,71] One study reported only AEs deemed to be related to treatment by the investigator, making comparison with other studies difficult.

As for the previous systematic review, the major limitation is the naive side-by-side comparison that did not report formal statistics or estimates of relative effects. It is unclear how the sources of heterogeneity were addressed in the comparison.

2. Systematic Review from Published Literature
An additional systematic review from the Cochrane Collaboration was identified in the published literature.[58] The objective of the systematic review conducted by Shemesh at al. was to summarize all available randomized controlled trial (RCT) study data on the efficacy and safety of ERTs and substrate reduction therapies (SRTs) for treating GD.

a) Methods
Databases (including grey literature) were comprehensively searched up to August 2014. Study authors were contacted when data were missing. If data were still unavailable, values were estimated from graphs.

b) Inclusion Criteria
All RCT and quasi-RCT studies (including open-label [OL] studies and crossover studies) assessing ERT or SRT, or both, in all types of GD were eligible for inclusion. Outcomes of interest included hemoglobin levels, platelet counts, hepatosplenomegaly, biomarker levels, skeletal outcomes, and AEs.

c) Findings
Eight publications reporting on 300 patients were identified for inclusion in the systematic review. Six studies compared different ERTs and two compared the combination of ERT and SRT versus ERT alone. Half of the included studies evaluated pre-treated or stabilized patients. Seven studies enrolled people with type 1 GD and one enrolled patients with type 3 GD.

d) Population Characteristics

TABLE 59: CHARACTERISTICS OF INCLUDED STUDIES

Author name, year	Study design	Population	Intervention	Outcomes
Ben Turkia (2013)[48]	Randomized, DB, multi-centre, parallel, non-inferiority trial	34 treatment-naive participants with type 1 GD (including children)	Velaglucerase alfa (N = 17) vs. imiglucerase (N = 17) for 9 months	Hb, plt, liver and spleen volumes, chitotriosidase, CCL18
De Frost (2007)[76]	RCT	11 pre-treated, stable, participants with GD	Imiglucerase every 2 weeks (N = 5) vs. every 4 weeks (N = 6); participants remained on the study for 12 months, or until study withdrawal	Hb, plt, ACE, chitotriosidase, ferritin, liver enzymes, lumbar bone marrow fat content, liver ratio, spleen volume
Elstein (2007)[77]	Randomized, phase 2, parallel group, OL study	36 adult, pre-treated, stable participants with type 1 GD	Miglustat (SRT; N = 12) vs. imiglucerase (ERT; N = 12) vs. the combination of both (N = 12); total study period was 6 months, after which participants could enter an extension protocol	Spleen and liver volume, QoL, chitotriosidase, imiglucerase assay, AEs, "routine laboratory tests"
Gonzalez (2013)[78]	Randomized, DB, multi-centre, phase 3 parallel group study	25 treatment-naive, anemic participants with type 1 GD	Velaglucerase alfa 45 U/kg (N = 13) vs. 60 U/kg (N = 12); study period was 12 months	Hb, plt, liver and spleen volume, chitotriosidase, CCL18, BMD (not defined as an end point)
Grabowski (1995)[63]	Randomized, DB, parallel study	30 treatment-naive participants with type 1 GD (including 4 children)	Imiglucerase 60 U/kg (N = 15) vs. alglucerase 60 U/kg (N = 15) for 9 months	Hb, plt, serum acid phosphatase, ACE, liver and spleen volumes, IgG Ab
Kishnani (2009)[79]	Randomized, multi-centre, OL trial, parallel study	102 pre-treated, stabilized, participants with type 1 GD	Imiglucerase every 2 weeks (N = 37) vs. every 4 weeks (N = 65) for 24 months	Hb, plt, liver and spleen volume, ACE, TRAP, chitotriosidase, AEs, bone disease progression, SF-36 health survey
Schiffmann (2008)[80]	Randomized, multi-centre, OL, phase 2, controlled study	30 pre-treated participants with type 3 GD	Addition of miglustat (SRT) to ERT (N = 21) vs. ERT alone (N = 9) for 24 months	Change in saccadic eye movements (horizontal and vertical) from baseline, neurological assessments (Purdue Pegboard test, Wechsler scale, Benton Visual Retention Test, Rey Auditory Verbal

Author name, year	Study design	Population	Intervention	Outcomes
				Learning Test, d2 Test of Attention, Continuous Performance Test, trail marking test, mental state, cranial nerves, motor skills), brain auditory-evoked potentials), pulmonary function tests, liver and spleen volumes, Hb, plt, chitotriosidase, hexosaminidase, glucosylceramide, AEs, tremor measurements
Zimran (2011)[30]	Randomized, DB, multi-centre, phase 3 parallel study	32 treatment-naive participants with type 1 GD	TALI 30 U/kg (N = 16) vs. 60 U/kg (N = 16) for 9 months	Spleen and liver volumes, Hb, plt, chitotriosidase, CCL18, BMD, bone marrow fat fraction

Ab = antibodies; ACE = angiotensin converting enzyme; AEs = adverse events; BMD = bone mineral density; CCL18 = Chemokine (C-C motif) ligand 18; double-bind = DB; ERT = enzyme replacement therapy; GD = Gaucher disease; Hb = hemoglobin; igG = immunoglobulin G; OL = open-label; plt = platelet; QoL = quality of life; RCT = randomized controlled trial; SF-36 = Short-Form 36-Item Health Survey; SRT = substrate reduction therapy; TALI = taliglucerase alfa; TRAP = tartrate resistant acid phosphatase; U = unit; vs. = versus.
Source: Shemesh et al. (2015).[58]

Quality of Studies

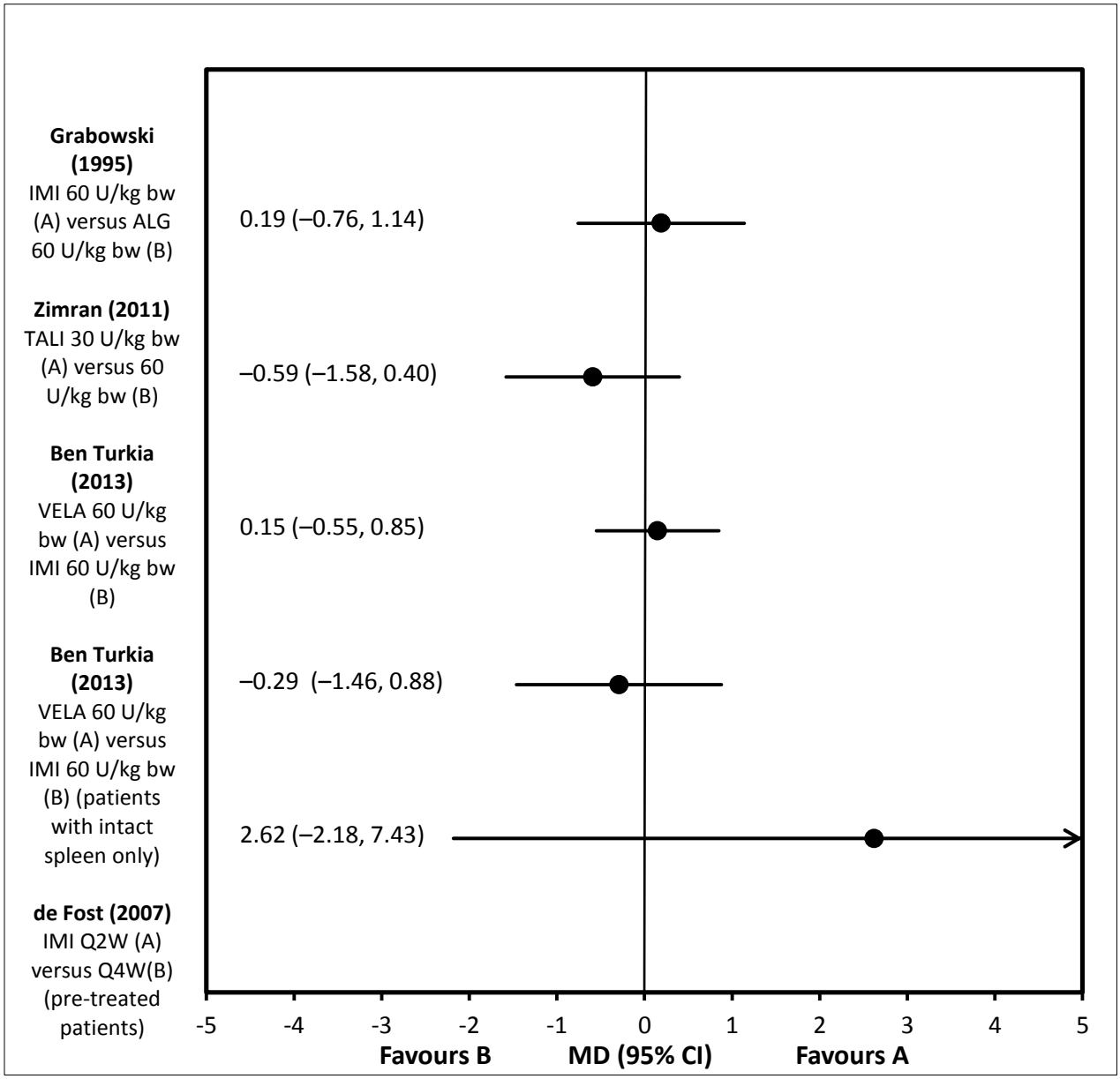
TABLE 60: RISK OF BIAS SUMMARY

Author Name, Year	Random Sequence	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias
Ben Turkia (2013)[48]	Unclear	Unclear	+	+	+	NR
De Frost (2007)[76]	Unclear	+	Unclear	+	+	+
Elstein (2007)[77]	+	—	—	Unclear	+	NR
Gonzalez (2013)[78]	+	+	+	+	+	—
Grabowski (1995)[63]	+	+	+	+	+	
Kishnani (2009)[79]	Unclear	Unclear	—	—	+	+
Schiffmann (2008)[80]	Unclear	Unclear	—	+	+	—
Zimran (2011)[30]	+	Unclear	+	+	+	+

NR = not reported.
Source: Shemesh et al. (2015).[58]

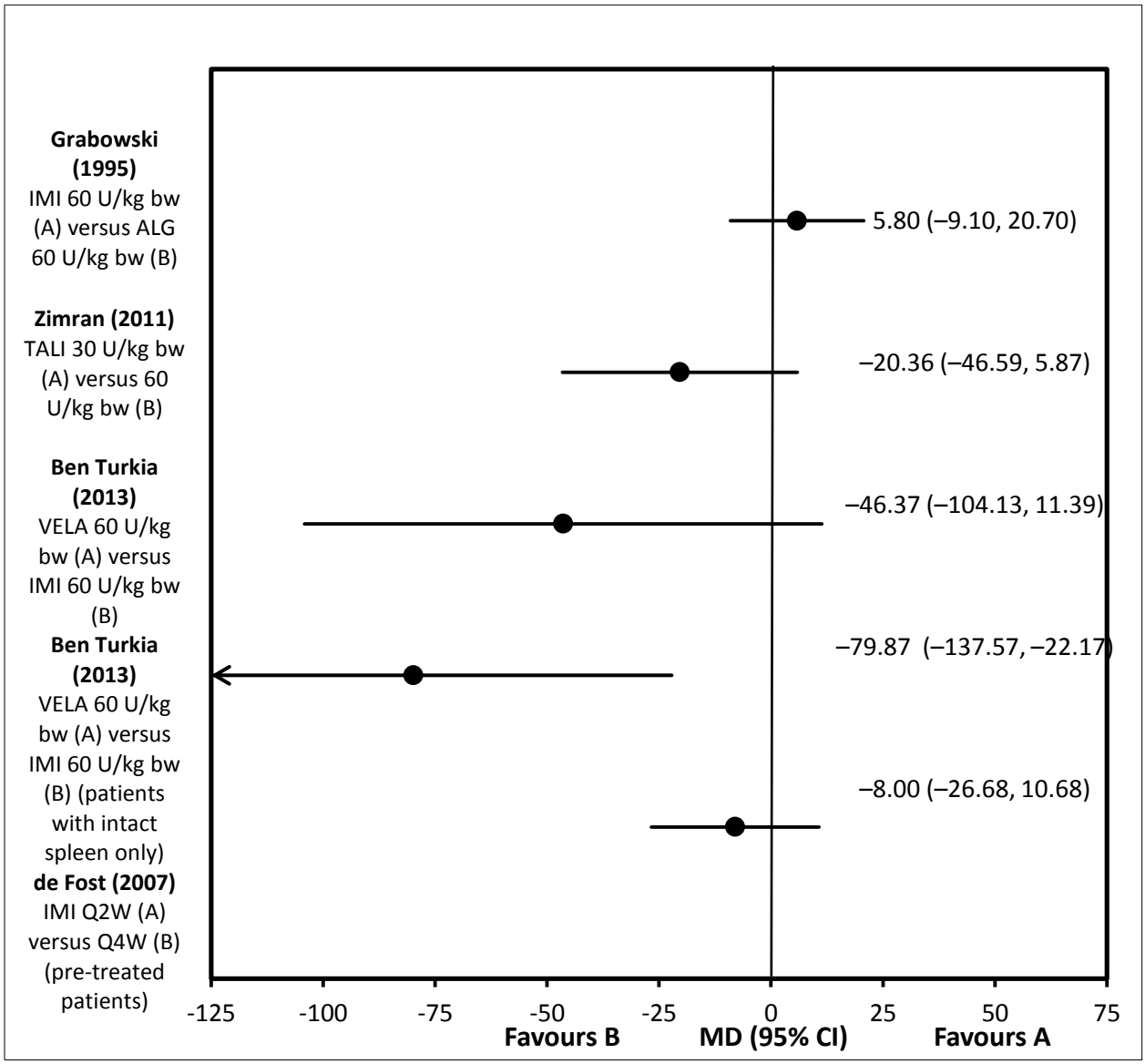
Efficacy

FIGURE 7: FOREST PLOT OF ENZYME REPLACEMENT THERAPY COMPARISON FOR HEMOGLOBIN LEVELS AT 9 MONTHS (SHEMESH ET AL. [2015])



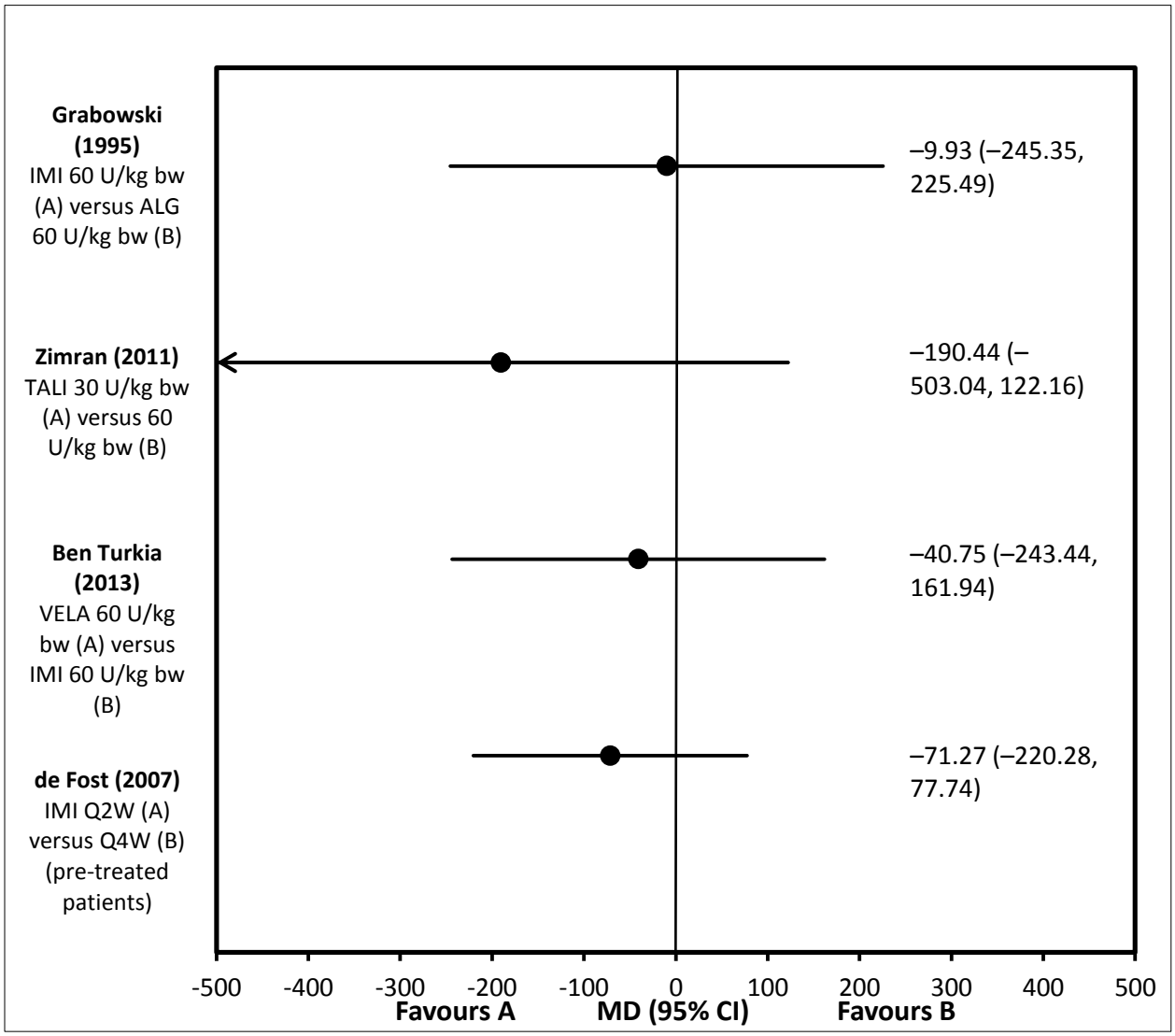
ALG = alglucerase; bw = biweekly; ERT = enzyme replacement therapy; IMI = imiglucerase; MD = mean difference; Q2W = every two weeks; Q4W = every four weeks; U = unit; TALI = taliglucerase alfa; VELA = velaglucerase alfa.
Source: The figure was made by the CADTH Common Drug Review based on results from Shemesh et al. (2015).[58]

FIGURE 8: FOREST PLOT OF ENZYME REPLACEMENT THERAPY COMPARISON FOR PLATELET COUNTS AT 9 MONTHS (SHEMESH ET AL. [2015])



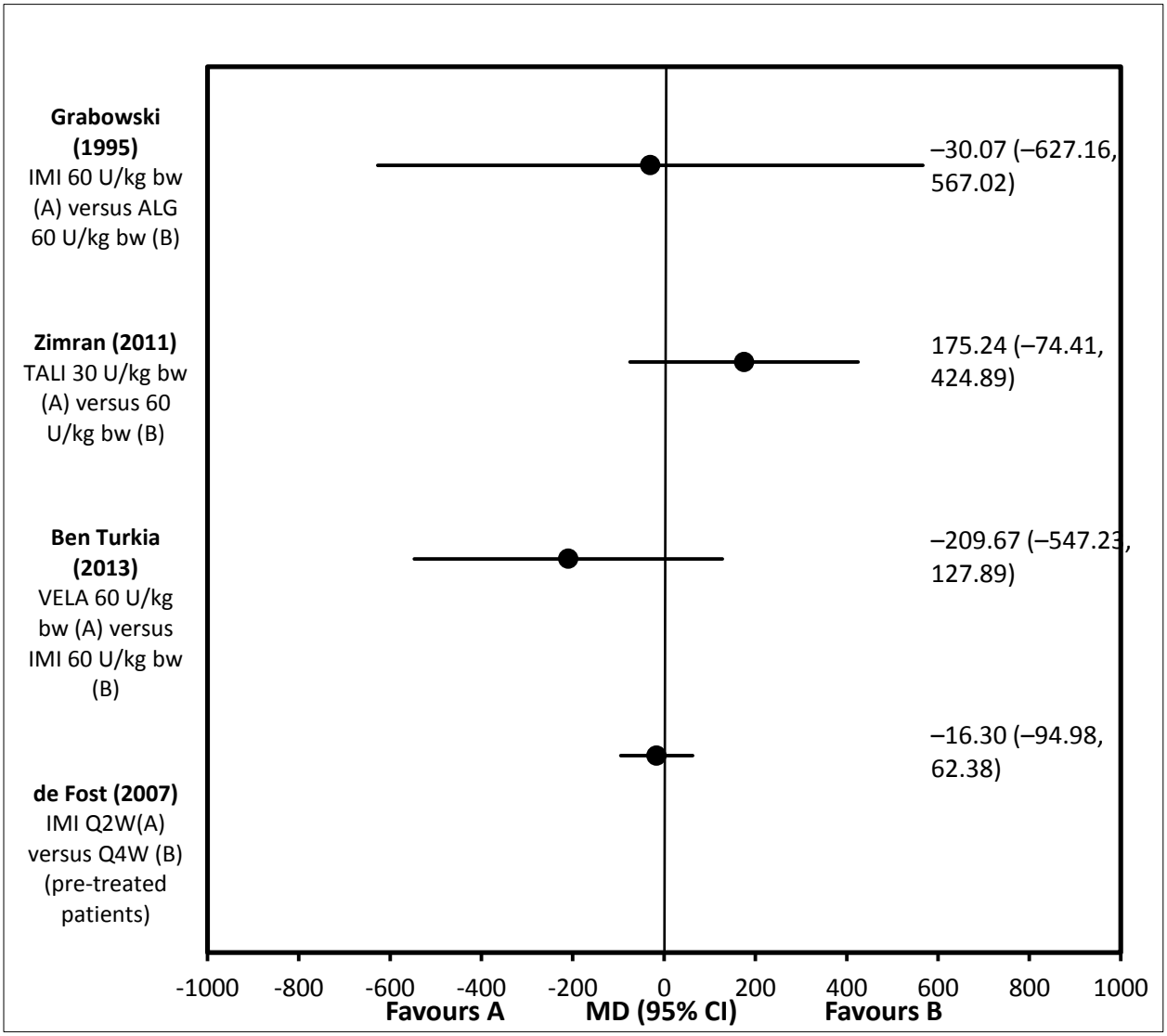
ALG = alglucerase; bw = biweekly; ERT = enzyme replacement therapy; IMI = imiglucerase; MD = mean difference; Q2W = every two weeks; Q4W = every four weeks; TALI = taliglucerase alfa; U = unit; VELA = velaglucerase alfa.
Source: The figure was made by the CADTH Common Drug Review based on results from Shemesh et al. (2015).[58]

FIGURE 9: FOREST PLOT OF ENZYME REPLACEMENT THERAPY COMPARISON FOR LIVER VOLUME AT 6 TO 9 MONTHS (SHEMESH ET AL. [2015])



ALG = alglucerase; bw = biweekly; ERT = enzyme replacement therapy; IMI = imiglucerase; MD = mean difference; Q2W = every two weeks; Q4W = every four weeks; TALI = taliglucerase alfa; U = unit; VELA = velaglucerase alfa.
Source: The figure was made by the CADTH Common Drug Review based on results from Shemesh et al. (2015).[58]

FIGURE 10: FOREST PLOT OF ENZYME REPLACEMENT THERAPY COMPARISON FOR SPLEEN VOLUME AT 6 TO 9 MONTHS (SHEMESH ET AL. [2015])



ALG = alglucerase; bw = biweekly; ERT = enzyme replacement therapy; IMI = imiglucerase; MD = mean difference; Q2W = every two weeks; Q4W = every four weeks; TALI = taliglucerase alfa; U = unit; VELA = velaglucerase alfa.
Source: The figure was made by the CADTH Common Drug Review based on results from Shemesh et al. (2015).[58]

e) Safety

Only a narrative description of the side effects was provided. Overall, AEs ranged from 5% (with imiglucerase and alglucerase) to 71.9% (with TALI). The most commonly reported AEs presumed to be related to the drug were infusion-related reactions and hypersensitivity. Withdrawals due to adverse events (WDAEs) were also motivated by these two causes.

CDR Reviewer's Conclusion

For safety and efficacy parameters, no evidence supports the choice of one ERT over another for the treatment of previously untreated patients with GD. In addition, no apparent efficacy difference was observed in patients who had a dose of 30 U/kg and those who had a dose of 60 U/kg.

f) Critical Appraisal

The AMSTAR checklist[67] was used to critically appraise the systematic review.

Strengths

A protocol was provided for conducting the systematic review. A comprehensive literature search was performed, including grey literature. Study selection, evaluation of quality, and data extraction was duplicated. The list of the included and excluded studies was provided. The quality of the studies was assessed using the Cochrane risk of bias assessment tool and the quality of the literature was reflected in the conclusions.

As sensitivity analysis was conducted excluding patients reported in one study who did not have GD.

Limitations

As the authors identified fewer than 10 studies, reporting biases were not discussed, as per their protocol. The authors' conflicts of interest were disclosed, but potential conflicts of interest in the included studies were not mentioned by the reviewers.

The authors noted other limitations, such as the small proportion of literature on RCTs, the external validity of patients enrolled in these trials, the enrolment of "treatment-naive" patients who were previously treated, the use of surrogate outcomes, the lack of data on skeletal manifestations, the potential lack of power to show difference between treatments, and the short duration of the studies compared to disease history.

3. Conclusion

This section summarized two systematic reviews conducted by the manufacturer, which reported a naive side-by-side comparison with results from TALI studies, and one systematic review retrieved from the published literature, which included TALI in its analysis. The three systematic reviews concluded that no difference for efficacy and safety could be observed between the different available ERTs, including TALI. However, the two systematic reviews provided from the manufacturer had numerous methodological limitations and the overall quality of the data provided by the three systematic reviews was limited by many factors, some of which were inherent to rare diseases. For these reasons, the uncertainty regarding the conclusions of the systematic reviews is deemed to be high.

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