A Multicenter, Double-Blind, Randomized Safety and Efficacy Study of Two Dose Levels of Taliglucerase Alfa in Pediatric Patients with Gaucher Disease*

Ari Zimran, MD,[1] Derlis Emilio Gonzalez-Rodriguez, MD,[2] Aya Abrahamov, MD,[1] Deborah Elstein, PhD,[1] Alona Paz, MD,[3] Einat Brill-Almon, PhD,[3] Raul Chertkoff, MD[3]

[1]Gaucher Clinic, Shaare Zedek Medical Center, Jerusalem, Israel; [2]Instituto Privado de Hematologia e Investigacion Clinica (I.P.H.I.C.), Asuncion, Paraguay; [3]Protalix Biotherapeutics, Carmiel, Israel

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Abstract

In the treatment of Gaucher disease (GD), early intervention with enzyme replacement therapy (ERT) is crucial in prevention of irreversible pathology. Taliglucerase alfa is a plant cell–expressed beta-glucocerebrosidase ERT that is approved in the USA, Israel, and Uruguay for treatment of GD in adults.

The aim of this multicenter, double-blind, dose-ranging (30 and 60 U/kg), 12-month study was to investigate the safety and efficacy of taliglucerase alfa in pediatric GD patients aged 2 to <18 years. Primary efficacy variable: median percent change in hemoglobin concentration from baseline. Secondary variables: percent changes in spleen/liver volumes, platelet counts, and chitotriosidase activity. After completion of the 12-month study, patients were eligible to enter a 2-year extension.

Eleven patients (nine, type 1; two, type 3) were randomized to taliglucerase alfa 30 or 60 U/kg. Progressive improvement was demonstrated in hemoglobin, spleen volume, liver volume, platelet count, and chitotriosidase activity. At 12 months, composite analysis of both dose groups revealed that mean hemoglobin and platelets were increased by 14.7% and 50.3%, respectively, from baseline, and absolute spleen and liver volumes were reduced 34.2% and 9.8%, respectively, from baseline. The majority (96.2%) of adverse events (AEs) were mild or moderate, 15.1% were reported as treatment related, and one related serious AE was reported (patient continues on treatment). There were no unexpected AEs and all treatment-related AEs were transient in nature.

Taken together, as previously seen for adult patients with GD, data suggest that taliglucerase alfa has the potential to provide an alternative therapy in pediatric patients.

Introduction

- Taliglucerase alfa is a plant cell–expressed enzyme replacement therapy (ERT) for the treatment of Gaucher disease.
  - The safety and efficacy of taliglucerase alfa were first established in adults with Gaucher disease[1]; it has been approved for treatment of adult patients with type 1 Gaucher disease in the United States, Israel, and Uruguay.
- Early treatment with ERT is recommended for pediatric patients with signs and symptoms of type 1 Gaucher disease because disease manifestation during childhood has been associated with a more severe and rapidly progressing disease course.[2]
- The objective of this study was to assess the efficacy and safety of taliglucerase alfa 30 and 60 U/kg in children with Gaucher disease.

Methods

Study Design

- This was a multicenter, randomized, double-blind trial comparing 2 doses of taliglucerase alfa (30 U/kg and 60 U/kg) in pediatric patients (aged 2 to <18 years) conducted at 3 centers (Shaare Zedek Medical Center, Jerusalem, Israel; Instituto Privado de Hematologia e Investigacion Clinica (IPHIC), Asuncion, Paraguay; University of the Witwatersrand, Johannesburg, South Africa).
- Patients received infusions of taliglucerase alfa every other week for 12 months.

Efficacy Endpoints

- Primary: Median (interquartile range) percent change in hemoglobin concentration from baseline
- Secondary: Percent change from baseline in spleen volume, liver volume, platelet count, and chitotriosidase or CCL18 activity
- Exploratory: Organ volumes expressed as multiples of normal (MN) where normal spleen volume = 2 mL/kg multiplied by body weight in kg and normal liver volume = 25 mL/kg multiplied by body weight in kg. Additional exploratory endpoints not reported here that will be the subject of a future publication include change in height, weight, Tanner stage, bone age, bone density, and quality of life

Safety Endpoints

- Clinical laboratory findings, echocardiography, adverse events, and anti-taliglucerase alfa antibody titers. Occurence of bone events and bone crises was part of the analysis of adverse events.

Patients

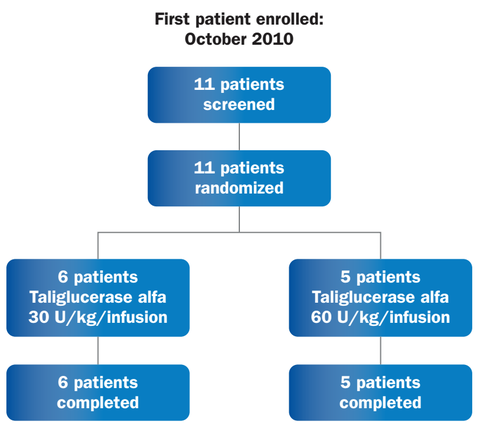
- Main inclusion criteria:
  - Treatment-naïve patients aged 2 to <18 years with Gaucher disease
  - Need for treatment with ERT based on clinical condition and opinion of the investigator
- Main exclusion criteria:
  - Presence of neurological signs and symptoms including complex neuronopathic features other than longstanding oculomotor gaze palsy
  - Unresolved anemia due to iron, folic acid, or vitamin B12 deficiency
  - Previous hypersensitivity reaction to other ERT for Gaucher disease or history of allergy to carrots

Results

Patient Disposition

- A total of 11 pediatric patients were randomized to taliglucerase alfa 30 or 60 U/kg (**Figure 1**).
- All 11 patients completed the study (**Figure 1**).

Figure 1. Patient Disposition



Demographics and Baseline Disease Parameters

- More than half of these pediatric patients were male, most were not of Ashkenazi Jewish ethnicity, and the majority consisted of Caucasian–non-Hispanic/Latino children (**Table 1**).
- Disease manifestations at baseline showed a wide variation between and within treatment groups (**Table 2**).

Table 1. Demographics

Patient Characteristic	30 U/kg (n=6)	60 U/kg (n=5)
Age, mean ± SD, y (Range)	9.5±4.0 (3–14)	6.6±3.1 (2–10)
Male, n (%) Female, n (%)	4 (66.7) 2 (33.3)	4 (80.0) 1 (20.0)
Ashkenazi Jewish, n (%) Non-Jewish, n (%)	0 6 (100.0)	2 (40.0) 3 (60.0)
Caucasian, n (%) Other, n (%)	6 (100.0) 0	4 (80.0) 1 (20.0)
Hispanic or Latino, n (%) Non-Hispanic or Latino, n (%)	3 (50.0) 3 (50.0)	1 (20.0) 4 (80.0)

Table 2. Gaucher Disease Parameters

	30 U/kg (n=6)		60 U/kg (n=5)	
Disease Parameter	Baseline	12 Months	Baseline	12 Months
Primary Endpoint				
Hemoglobin (g/dL) Mean±SD Range	11.3±1.7 8–13	12.7±1.2 11–14	10.6±1.4 9–12	12.2±1.1 11–14
Secondary Endpoints				
Spleen Volume (mL) Mean±SD Range	1,218±638.4 240–2,062	811.6±409.6 222–1,194	1,023±753.4 325–1,996	524.0±281.1 217–798
Liver Volume (mL) Mean±SD Range	1,214±424.7 475–1,750	1,116±366.9 525–1,642	991.7±301.3 612–1,295	849.1±271.9 584–1,219
Platelets (/mm³) Mean±SD Range	162,667±71,838 66,000–273,000	208,167±90,747 80,000–324,000	99,600±42,899 76,000–176,000	172,200±89,290 88,000–308,000
Chitotriosidase* (nmol/mL•h) Mean±SD Range	24,280±17,902 3,598–49,733	11,610±11,916 1,153–33,802	34,961±22,080 15,420–63,179	14,433±14,534 1,056–34,695
Exploratory Endpoints				
Spleen Volume (MN) Mean±SD Range	22.2±12.1 9.0–41.2	14.0±8.6 6.6–30.2	29.4±24.3 10.0–69.3	12.9±7.2 6.2–24.6
Liver Volume (MN) Mean±SD Range	1.8±0.5 1.1–2.7	1.5±0.4 1.0–2.3	2.2±0.5 1.8–3.0	1.7±0.3 1.4–2.0

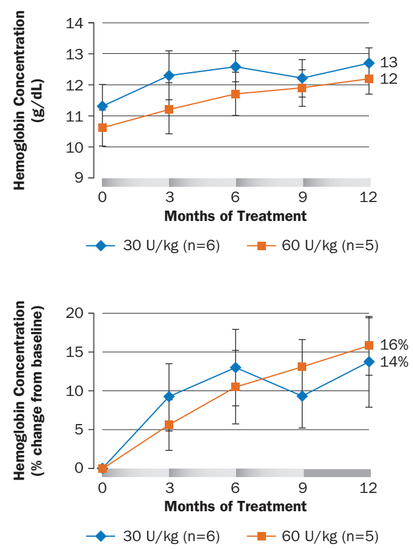
*One patient in the 60-U/kg dose group did not have measurable levels of chitotriosidase and was excluded from this analysis. MN=multiples of normal, where normal spleen volume is 2 mL/kg x body weight (kg) and the normal liver volume is 25 mL/kg x body weight (kg).

Efficacy

Primary Endpoint: Hemoglobin Concentration

- The median (interquartile range) percent change in hemoglobin concentration from baseline to 12 months was 12.2 (20.6) and 14.2 (10.4) for taliglucerase alfa 30 U/kg and 60 U/kg, respectively.
- Patients receiving taliglucerase alfa 30 and 60 U/kg demonstrated increases in mean hemoglobin levels from baseline at all time points (**Table 2, Figure 2**).

Figure 2. Hemoglobin Responses to Taliglucerase Alfa



Values are mean ± standard error.

- A post hoc analysis of patients (n=8) who had anemia at baseline showed that 6 of those patients no longer had anemia at study end; the 2 patients with anemia at study end had received taliglucerase alfa 30 U/kg and had a hemoglobin concentration that approached normal by study end (**Table 3**).

Table 3. Changes in Hemoglobin for Patients Who Had Anemia at Baseline

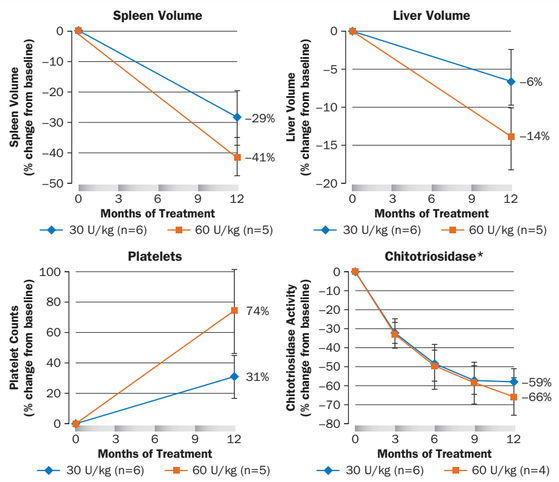
	Taliglucerase Alfa 30 U/kg (n=6)	Taliglucerase Alfa 60 U/kg (n=5)
Number of patients with anemia*	4	4
Mean hemoglobin concentration at baseline ±SE (g/dL)	10.6±0.8	10.2±0.6
Mean hemoglobin concentration at study end ±SE (g/dL)	12.5±0.6	11.8±0.4
Mean absolute change from baseline at study end ±SE (g/dL)	+1.4±0.5	+1.6±0.3

*Anemia was defined as a hemoglobin concentration <11.0 g/dL for patients 6 months to 4 years of age, <11.5 g/dL for patients 5 to <12 years of age, <12.0 g/dL for patients 12 to <15 years of age, <12.0 g/dL for females ≥15 years of age (<11.0 g/dL if pregnant) and <13.0 g/dL for males ≥15 years of age.

Secondary Endpoints: Spleen Volume, Liver Volume, Platelets, and Chitotriosidase

- From baseline to 12 months, improvements were observed in the absolute values and percent changes from baseline in key Gaucher disease parameters (**Table 2, Figure 3**).
  - At 12 months, for taliglucerase alfa 30 U/kg and 60 U/kg, respectively, spleen volume was reduced by 28.6% and 41.1% (**Figure 3**).
  - At 12 months, for taliglucerase alfa 30 U/kg and 60 U/kg, respectively, liver volume was reduced by 6.3% and 14.0% (**Figure 3**).

Figure 3. Percent Change in Spleen Volume, Liver Volume, Platelets, and Chitotriosidase in Response to Taliglucerase Alfa



Mean percent changes in spleen and liver volumes are calculated from absolute organ volumes in mL.
Values are mean ± standard error.
*One patient in the 60-U/kg dose group did not have measurable levels of chitotriosidase and was excluded from this analysis.

Safety

Adverse Events

- No new safety issues emerged during this trial as compared with the safety results for the pivotal trial in adult patients,[1] and the safety profiles for the 30- and 60-U/kg doses of taliglucerase alfa were similar.
- Most adverse events were mild-to-moderate in nature, transient, and not related to treatment (**Table 4**).
- No patient experienced a bone crisis during the trial.
- No patient withdrew from the study because of an adverse event.
- One patient experienced a treatment-related serious adverse event (gastroenteritis; reported as serious due to the need for hospitalization for rehydration) that resolved after 1 day of treatment; the patient continues on treatment.

Table 4. Adverse Events

	No. of AEs (No. of Patients [n=11])	Percentage of Total AEs
Total adverse events	53 (10)	100
Mild or moderate 30 U/kg 60 U/kg	51 (9) 21 (4) 30 (5)	96.2
Severe or very severe 30 U/kg[1] 60 U/kg[2]	2 (2) 1 (1) 1 (1)	3.8
Nontreatment-related	45 (10)	84.9
Treatment-related	8 (2)	15.1

AEs=adverse events.
[1]Pulmonary hypertension in a type 3c Gaucher disease patient; not treatment related. [2]Gastroenteritis; treatment related.

Echocardiography and Laboratory Test Results

- Abnormal echocardiography results at month 12 were reported for 2 patients:
  - One patient receiving the 60-U/kg dose had mild tricuspid regurgitation.
  - One patient in the 30-U/kg group had a baseline echocardiography that revealed abnormal atrioventricular and mitral valves and pulmonary hypertension with an abnormal tricuspid insufficiency gradient of 30 mm Hg which increased to 74 mm Hg at the study end; this patient was diagnosed with type 3c Gaucher disease and the deterioration in the echocardiographic parameter was deemed not related to study treatment.
- No clinically significant laboratory test abnormalities were noted.

Immunogenicity

- Serum samples of all 11 patients were screened for the presence of anti-taliglucerase alfa IgG antibodies (antidrug IgG antibodies; ADA).
- Two patients were found to have at least one IgG positive result of ADA post-treatment; both children improved clinically.
- One patient was found to have IgG positive result at the pretreatment sample and became negative as the trial progressed.
- All positive sample titers were low (<550).
- Neutralizing Ab testing for the above 3 patients were all found to be negative in both in vitro enzymatic inhibition assay and cell-based neutralizing assay.

Conclusions

- Children receiving treatment with taliglucerase alfa 30 and 60 U/kg every 2 weeks for 1 year demonstrated improvement in key Gaucher disease manifestations: hemoglobin concentration, spleen volume, liver volume, platelet counts, and chitotriosidase activity.
- Treatment was generally well tolerated, with nearly all adverse events being mild-to-moderate, unrelated to treatment, and transient in nature.
- After 1 year of treatment, the efficacy and safety profile of taliglucerase alfa in children appears to be similar to that of adult patients.
- Taken together, these results suggest that taliglucerase alfa has the potential to be a therapeutic treatment option for children with Gaucher disease.

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Derlis Emilio Gonzalez-Rodriguez, MD, is a study investigator.

Aya Abrahamov, MD, and **Deborah Elstein, PhD,** have no relevant conflicts of interest to disclose.

Alona Paz, MD, Einat Brill-Almon, PhD, and **Raul Chertkoff, MD,** are employees of Protalix Biotherapeutics.

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