Long-Term Safety and Efficacy Data of Taliglucerase Alfa, a Plant Cell–Expressed Recombinant Glucocerebrosidase, in the Treatment of Naïve Gaucher Disease Patients: 36-Month Results

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Abstract

Taliglucerase alfa is a beta-glucocerebrosidase enzyme replacement therapy (ERT) that is approved in the USA, Israel, and Uruguay for the treatment of Gaucher disease (GD) in adults, and is the first approved plant cell–expressed biotherapeutic. Pivotal study PB-06-001 was a 9-month, randomized, double-blind, dose-ranging (30 and 60 U/kg) trial to assess the safety and efficacy of taliglucerase alfa in treatment-naïve GD patients. Primary outcome measure was change from baseline in spleen volume, while secondary outcome measures included change from baseline in liver volumes, platelet counts, hemoglobin levels, and chitotriosidase activity. Key inclusion criteria were splenomegaly >8 multiples of normal (MN) and platelet counts <120,000/mm^3. At the completion of the 9-month study, patients were eligible to enter an open-label extension study, PB-06-003, with taliglucerase alfa given every 2 weeks at the same dose as in study PB-06-001.

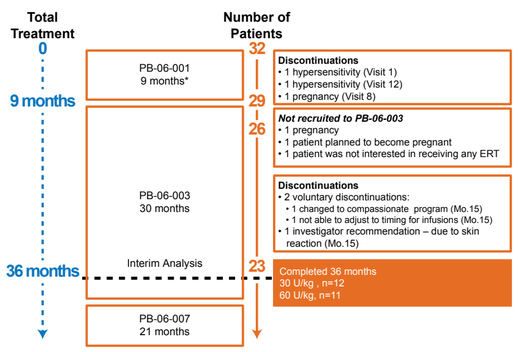
Twenty-six treatment-naïve GD patients from study PB-06-001 continued double-blind treatment in study PB-06-003. This interim analysis presents results for 23 patients that completed 27 months in PB-06-003 for a total of 36 months of taliglucerase alfa treatment. Mean spleen volume was reduced from 16.4/17.8 MN to 8.1/5.6 MN, liver volume was reduced from 1.7/1.5 to 1.3/1.1 MN, and chitotriosidase activity was reduced by 73.5% and 83.0% for 30 U/kg and 60 U/kg, respectively. Hemoglobin concentration and platelet counts were also improved. All treatment-related adverse events were mild or moderate in severity and transient in nature.

Introduction

- Taliglucerase alfa is a plant cell–expressed enzyme replacement therapy (ERT) approved for treatment of adult patients with type 1 Gaucher disease (GD) in the USA, Israel, and Uruguay.
- Pivotal study PB-06-001 was a 9-month, randomized, double-blind, dose-ranging (30 and 60 U/kg) trial that established the safety and efficacy of taliglucerase alfa in treatment-naïve GD patients.[1]
- The present interim report examines the 36-month safety and efficacy results for taliglucerase alfa in treatment-naïve GD patients from extension study PB-06-003.

Methods

Figure 1. Study Design and Disposition of Patients



*Zimran et al; *Blood* 2011;118:5767-73

Study Design

- Study PB-06-001 was a 9-month, double-blind, randomized trial with 2 dose groups, taliglucerase alfa 30 U/kg and 60 U/kg.[1]
- At the completion of PB-06-001, patients were eligible to enter a 30-month extension study, PB-06-003, with taliglucerase alfa given in double-blind fashion every 2 weeks at the same dose as in study PB-06-001 (**Figure 1**).
- Interim results for 27 months (36 total months of treatment with taliglucerase alfa) are presented here.

Efficacy Endpoints

- Primary endpoint: Percent change in spleen volume from baseline
- Secondary endpoint: Change from baseline in liver volume, platelet counts, hemoglobin concentration, and chitotriosidase activity
- Organ volume determined by magnetic resonance imaging (MRI) evaluation based on a validated method[2] using 2 blinded readers with intra-reader variability ≤0.5% and inter-reader variability ≤1.0%

Safety Endpoints

- Clinical laboratory findings, electrocardiography, echocardiography, adverse events (AEs), and anti–taliglucerase alfa antibody titers

Patients

- Main inclusion criterion for PB-06-003: Successful completion of study PB-06-001. Main inclusion criteria for PB-06-001 were ERT treatment-naïve adult patients [>18 years of age] with GD, splenomegaly ≥8 times the expected normal volume, and thrombocytopenia with platelet counts <120,000 per mm^3 with or without anemia.
- Patients were excluded from study PB-06-003 if they exhibited severe neurological signs and symptoms, were taking another experimental medication, or were judged to have any condition that would interfere with compliance or study requirements.

Results

Patient Disposition and Characteristics

- This is an interim report from study PB-06-003 summarizing data for the 23 patients that completed 36 months of taliglucerase alfa treatment (**Figure 1**).
- **Tables 1** and **2** describe the demographic, genetic, and baseline disease characteristics of these patients.

Table 1. Demographics (n=23)

Parameter	30 U/kg (n=12)	60 U/kg (n=11)
Age, mean ± SD, y (Range)	38.9 ± 12.1 (24–74)	34.5 ± 11.3 (19–53)
Male, n Female, n	7 5	6 5
Ashkenazi Jewish, n Non-Jewish, n	4 8	2 9
N370S homozygous, n Other genotype, n	4 8	3 8

SD=standard deviation.

Table 2. Baseline Clinical Characteristics (n=23)

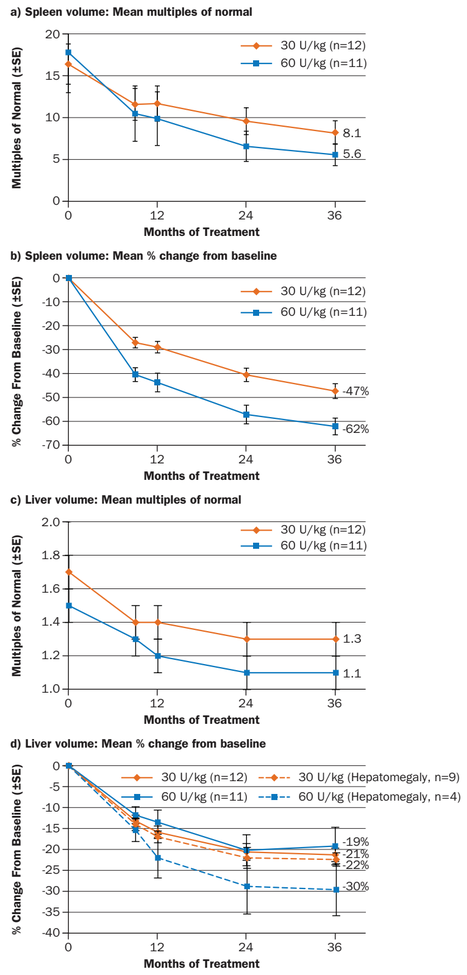
Disease Parameter (Mean Values)	30 U/kg (n=12)	60 U/kg (n=11)
Spleen volume, MN (Range)	16.4 ± 8.3 (8–35)	17.8 ± 16.0 (8–54)
Liver volume, MN (Range)	1.7 ± 0.4 (1.4–2.9)	1.5 ± 0.4 (0.9–2.6)
Hemoglobin, g/dL (Range)	12.4 ± 1.9 (7.9–14.6)	11.0 ± 2.9 (5.5–16.0)
Platelets, /mm^3 (Range)	64,900 ± 30,133 (27,000–112,000)	73,055 ± 30,362 (39,000–134,000)

MN=multiples of normal volume.

Efficacy (n=23)

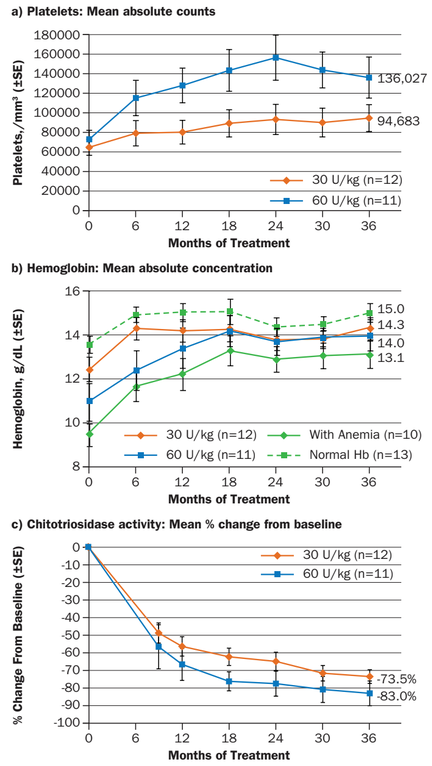
- Improvements in spleen volume, liver volume, hemoglobin concentration, platelet counts, and chitotriosidase continued through 36 months of treatment with taliglucerase alfa (**Figures 2** and **3**).

Figure 2. Organ Volume



Mean percent changes in spleen and liver volumes were calculated from absolute organ volumes in mL. Hepatomegaly=patients with liver volume >1.5 MN (1 MN=2.5% of body weight) at baseline; SE=standard error.

Figure 3. Hematologic Parameters



Anemia=patients with Hb <11.0 g/dL for women and <12.0 g/dL for men; SE=standard error.

Safety

Adverse Events (Table 3)

- All AEs were transitory and resolved without change in dose.
- All SAEs (immune thrombocytopenia, right hip arthrosis, hemangioma in knee, pulmonary embolism after surgical intervention, tonsillectomy, multiple tooth extraction, polypectomy of vocal chords) were not related to treatment.
- One event of hypersensitivity (reported as a non-serious AE) occurred at month 10; the patient continues to receive treatment under premedication.
- Related AEs (number of patients):
  - Headache (2)
  - Pruritus (2)
  - Hypersensitivity (1)
  - Abdominal pain (1)
  - Arthralgia (2)
  - Fixed-drug eruption (1)
  - Infusion-related reactions (1; dizziness, chills, nausea)

Table 3. Adverse Events

	30 U/kg No. of Events (No. of Patients)	60 U/kg No. of Events (No. of Patients)	Total No. of Events (%)
	n=12	n=11	n=23
AEs	179 (12)	167 (10)	346 (100)
Non-related Related	150 (12) 29 (6)	139 (10) 28 (6)	289 (82.5) 57 (16.5)
Mild or moderate	177 (12)	164 (10)	341 (98.6)
Severe or very severe	2 (1)	3 (3)	5 (1.4)
SAEs	5 (2)	2 (2)	7 (2.0)

AEs=adverse events; SAEs=serious adverse events.

Immunogenicity

- Two patients treated with 60 U/kg/infusion were found to have neutralizing IgG antibody activity in an *in vitro* assay.
- Overall, there were no changes in efficacy or safety parameters for these 2 patients.

Conclusions

- This interim report of the safety and efficacy of taliglucerase alfa in 23 ERT treatment-naïve patients with GD demonstrated continuous improvement through 36 months of treatment with 30 U/kg or 60 U/kg in the main GD parameters.
- All treatment-related AEs were mild or moderate in severity and transient in nature.
- This 36-month, long-term evaluation demonstrated that taliglucerase alfa is a safe and effective treatment for Gaucher disease.

References

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DISCLOSURE:

Ari Zimran, MD, receives consulting fees from and has options in Protalix Biotherapeutics, and is a member of their Scientific Advisory Board; receives support from Genzyme for participation in the International Collaborative Gaucher Group Registry; and receives honoraria from Shire HGT, Actelion, and Pfizer.

Atul Mehta, MD; Pilar Giraldo, MD; Hanna Rosenbaum, MD; Fiorina Giona, MD; Dominick J. Amato, MD; Milan Petakov, MD; Eduardo Terreros Muñoz, MD; Sergio Eduardo Solorio-Meza, MD; and **Gloria Durán, MD,** are study investigators.

Deborah Elstein, PhD, has no relevant conflicts of interest to disclose.

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

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