Plant Cell–Expressed Recombinant Glucocerebrosidase: Taliglucerase Alfa as Therapy for Gaucher Disease in Adult Patients Previously Treated With Imiglucerase: 24-Month Results

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Abstract

Taliglucerase alfa is an enzyme replacement therapy (ERT) approved in the USA, Israel, and Uruguay for adult patients with type 1 Gaucher disease (GD). Study PB-06-002 was a 9-month, phase 3, multicenter, open-label, switchover trial that evaluated safety and efficacy of taliglucerase alfa in patients with GD previously treated with imiglucerase for at least 2 years. Eligible patients entered a 12-week evaluation period to establish the stability of their disease based on hematologic parameters. For patients whose imiglucerase regimen was changed due to drug shortage, eligibility was based on historical data of disease stability. Patients with stable disease were then switched from imiglucerase to the same dose of taliglucerase alfa. Efficacy was determined by evaluation of platelet counts, hemoglobin levels, and spleen and liver volumes for clinical deterioration. The control for this study was each patient's previous historical clinical and stability laboratory measurements. At 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-06-002. This is an interim report for the 15 adult patients who have completed 24 total months of treatment.

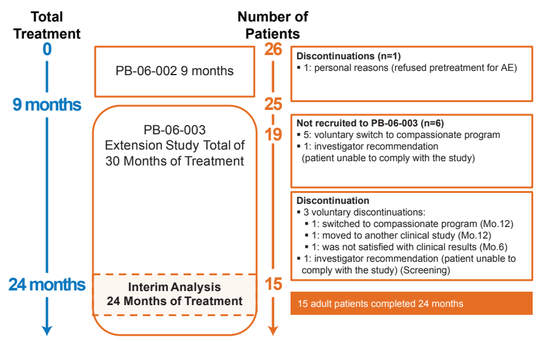
Following 24 months' treatment with taliglucerase alfa, efficacy parameters of spleen volume, liver volume, platelet counts, hemoglobin concentration, and chitotriosidase activity were maintained or improved in these patients following switchover to taliglucerase alfa. None of the patients met the criteria for clinically relevant deteriorations as specified by the study protocol. 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. It has been demonstrated to be safe and effective in treatment-naïve adults in study PB-06-001.[1]
- Study PB-06-002 was a 9-month, phase 3, open-label, switchover trial that evaluated the safety and efficacy of taliglucerase alfa in patients with GD who were previously treated with imiglucerase for at least 2 years. After completion of study PB-06-002, patients were eligible to continue into the extension study, PB-06-003.
- The present interim report examines the 24-month safety and efficacy results for GD patients previously treated with imiglucerase.

Methods

Figure 1. Study Design and Disposition of Patients



Study Design

- Study PB-06-002 was a 9-month, phase 3, worldwide, multicenter, open-label, switchover trial; PB-06-003 included a 30-month open-label extension of PB-06-002 (**Figure 1**).
- In PB-06-002, patients first entered a 12-week evaluation period to establish the stability of their disease. Taliglucerase alfa was then administered by intravenous (IV) infusion every 2 weeks starting at the same dose as previous imiglucerase treatment; in the extension study PB-06-003, patients continued at the same dose received at the completion of PB-06-002.
- Interim results for 15 months (24 total months of treatment with taliglucerase alfa) are presented here.

Efficacy Endpoints

- Hemoglobin concentration, platelet counts, spleen volume, liver volume, and chitotriosidase activity—the control for this study was each patient's previous historical clinical and stability laboratory measurements while treated with imiglucerase.
- Efficacy was determined by evaluation of the following clinically relevant deterioration criteria:
  - Sustained reduction of platelet count: A decrease of >20% from the mean value of the Stability Evaluation Period values of ≤120,000 or a decrease of >40% from the mean value of the Stability Evaluation Period values of >120,000
  - Sustained reduction of hemoglobin: A decrease of >20% from the mean value of the Stability Evaluation Period
  - Increase in spleen volume: A 20% increase in spleen volume by MRI from baseline to month 9
  - Increase in liver volume: A 10% increase in spleen volume by MRI from baseline to month 9

Safety Endpoints

- Adverse events (AEs), clinical laboratory tests, electrocardiogram, echocardiogram, pulmonary function test, and anti-human taliglucerase alfa antibody titers.

Patients

- Main inclusion criteria: Patients were eligible for study PB-06-002 if they were at least 2 years of age, had been receiving imiglucerase ERT for at least 2 years, were on a stable maintenance regimen for the last 6 months, and had stable GD (defined as stable hemoglobin and platelets, no major surgery, blood transfusions, bleeding episode, or avascular necrosis and no evidence of spleen or liver increased enlargement in the last year). Patients were eligible for PB-06-003 if they completed study PB-06-002.
- Main exclusion criteria: Patients were excluded from PB-06-002 if they had a history of allergy to carrots, previous infusion reaction to alglucerase or imiglucerase, or unresolved 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.
- Patients were evaluated for any change in disease state and enrolled in a 12-week evaluation period to establish stability of their hematologic parameters.

Study Amendments

- Due to imiglucerase shortage: Stability evaluation was based on 6 historical values of platelet count and hemoglobin concentration. This increased the number of patients from 15 to 30.
- As part of the Pediatric Investigational Plan (PIP), 5 out of 30 patients should be between 2 to 18 years of age.

Results

Patient Disposition and Characteristics

- This is an interim report from study PB-06-003 summarizing data for the 15 adult patients who had previously been treated with imiglucerase and have completed 24 months of taliglucerase alfa treatment (**Figure 1**).
- **Tables 1** and **2** describe the demographic, genetic, and baseline disease characteristics of these patients.
- Taliglucerase alfa dose (per infusion) distribution: 8 patients received ≥30 U/kg, 4 patients received >15 U/kg and <30 U/kg, and 3 patients received ≤15 U/kg.

Table 1. Demographics

Demographic Characteristics	Value
Age, mean ± SD, y (range)	45.8 ± 11.7 (22–63)
Male, n (%) Female, n (%)	7 (46.7%) 8 (53.3%)
Ashkenazi Jewish, n (%) Non-Jewish, n (%)	10 (66.7%) 5 (33.3%)
Splenectomized, n	1
Homozygous N370S, n Other genotypes*, n	7 11

SD=standard deviation.
*DNA sequencing, one patient result is missing.

Table 2. Baseline Clinical Characteristics

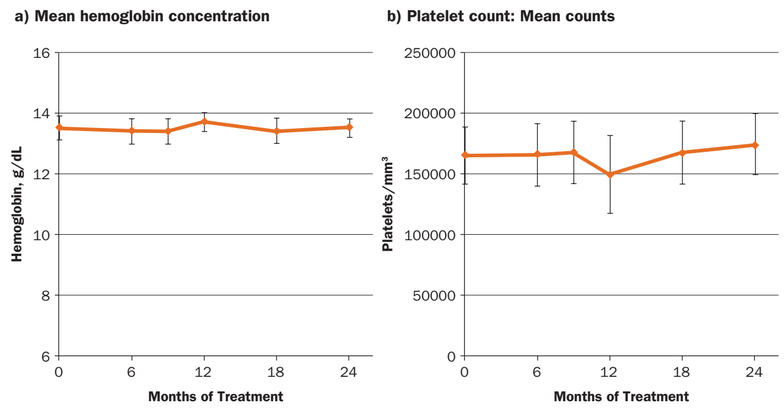
Baseline Disease Parameters	Mean ± SD (Range)
Spleen volume* (MN) (n=12)	4.8 ± 3.8 (0.1–11.7)
Liver volume* (MN) (n=13)	1.0 ± 0.3 (0.7–1.7)
Hemoglobin (g/dL)	13.5 ± 1.4 (10.7–15.8)
Platelets (/mm^3)	165,567 ± 92,659 (37,883–309,833)
Chitotriosidase (nmol/mL•h)	7,723.7 ± 11,111 (103–41,528)

MN=multiples of normal volume; MRI=magnetic resonance imaging; SD=standard deviation.
*Spleen and liver volumes were evaluated by MRI, 2 patients were evaluated by ultrasound and were not included.

Efficacy (n=15)

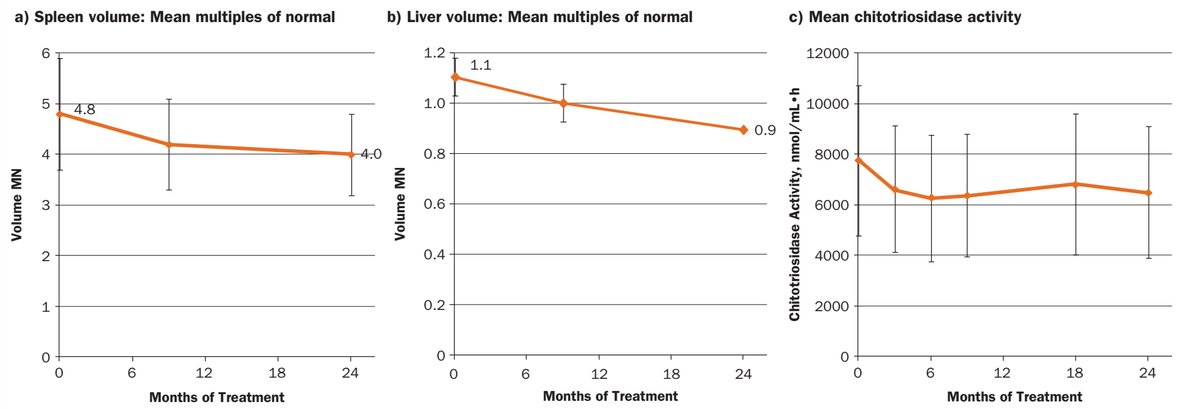
- Improvements in hemoglobin concentration, platelet count, spleen volume, liver volume, and chitotriosidase activity remained stable through 24 months of treatment with taliglucerase alfa (**Figures 2** and **3**).
- None of the patients met the criteria for clinically relevant deterioration as specified by the study protocol.

Figure 2. Hematological Parameters



Error bars represent standard errors.

Figure 3. Organ Volume and Chitotriosidase Activity



Error bars represent standard errors.

Safety

Adverse Events (Table 3)

- Four patients had serious adverse events (SAEs) due to hospitalization for non–treatment-related events: right knee replacement; left knee replacement; traumatic rib fracture and pneumothorax; prolapsed rectum, bladder, and cervix; renal stone extraction
- Related AEs (number of patients):
  - Flushing (1)
  - Weight increase (1)
  - ALT increase (1)
  - Infusion-related reactions (2; headache and fatigue after the infusion)
  - All were mild or moderate in severity
  - GGT increase (1)
  - Discomfort (1)
  - Skin tightness (1)

Table 3. Adverse Events

	No. of Events (No. of Patients)	Percentage of Total
AEs	174 (15)	
Mild or moderate	171 (15)	98.3
Severe or very severe*	3 (3)	1.7
Non-related	161 (15)	92.5
Related	13 (6)	7.5

AEs=adverse events; SAEs=serious adverse events.
*Three severe AEs not related to study treatment: hematuria and renal stone; prolapsed rectum, bladder, and cervix; and gonarthrosis of right knee.

Immunogenicity

- One patient treated with 28 U/kg/infusion was found to have neutralizing IgG antibody activity in an *in vitro* assay that was negative in a cell-based assay.
- At 24 months, hemoglobin concentration, platelet counts, spleen volume, and liver volume were stable or improved in this patient, but an increase in chitotriosidase activity was observed.

Conclusions

- This interim report of the safety and efficacy of taliglucerase alfa in 15 adult patients previously treated with imiglucerase demonstrated that the disease parameters of hemoglobin concentration, platelet counts, spleen volume, liver volume, and chitotriosidase activity remained stable through 24 months of treatment after switching from imiglucerase to the same dose of taliglucerase alfa.
- All treatment-related AEs were mild or moderate in severity and transient in nature.
- This 24-month evaluation demonstrated that taliglucerase alfa is a safe and effective alternative treatment for Gaucher disease in patients switched from imiglucerase to taliglucerase alfa.

Reference

1. Zimran A, Brill-Almon E, Chertkoff R, et al. Pivotal trial with plant cell-expressed recombinant glucocerebrosidase, taliglucerase alfa, a novel enzyme replacement therapy for Gaucher disease. *Blood*. 2011;118:5767-5773.

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