2. SYNOPSIS

Name of Sponsor/Company: Protalix Ltd. 2 Snunit Street Science Park POB 455 Carmiel 20100, Israel Ph: 972-4-988-9488 Fax: 972-4-988-9489	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Taliglucerase alfa [plant cell expressed recombinant human glucocerebrosidase (prGCD)]		
Name of Active Ingredient: Taliglucerase alfa		

Title of Study: A Multicenter Extension Study of Taliglucerase alfa in Pediatric Subjects with Gaucher Disease

Investigators:

Site #	Principal Investigators	Affiliations
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Study centre(s): 6 study centers from 6 countries

Publication (reference): Not applicable

Studied period (years): Date of first enrolment: 30Oct2011 Date of last completed: 07Jul2014	**Phase of development:** Phase 3

Objectives: The objective of study PB-06-006 was to extend the assessment of the efficacy and safety of taliglucerase alfa in pediatric patients between 2 to < 18 years old with Gaucher disease who completed treatment in Protocols PB-06-002 (switchover study from imiglucerase) or PB-06-005 (treatment naïve with taliglucerase alfa).

Methodology: This multi-center, extension trial was designed to extend the assessment of the efficacy and safety of taliglucerase alfa in up to 16 patients between 2 to < 18 years old with Gaucher disease who completed 12 months of treatment in study PB-06-005 (Group I: randomly assigned to either 30 or 60 units/kg) or 9 months of treatment in study PB-06-002

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(Group II: switchover from a maintenance dose of imiglucerase).

- Group I includes patients who enrolled after completion of Protocol PB-06-005
- Group II includes patients who enrolled after completion of Protocol PB-06-002

Patients continuing from PB-06-005 remained blinded for a total of 24 months (12 months of PB-06-005 and 12 months in PB-06-006). Patients continuing from PB-06-002 remained on the same dose (unblinded) in PB-06-006.

Patients received IV infusion of taliglucerase alfa every two weeks for 24 additional months. Home therapy was implemented or continued, when feasible, for patients who were able to tolerate the infusions well based on approval of the investigator and the Medical Director.

The protocol was amended to obtain pharmacokinetic data at the first infusion following obtaining a modified informed consent. Blood samples were obtained at time 0 (before start of infusion) and at 45, 70, 110, 125, 135, 150, 175, 200 and 225 minutes after the start of the infusion. An additional sample for measurement of anti-taliglucerase alfa antibody was collected at time 0 if not already scheduled for the visit.

Number of patients (planned and analyzed): Of the 16 pediatric patients who completed studies PB-06-005 (11) and PB-06-002 (5); 15 were enrolled into this extension study PB-06-006. All patients in study PB-06-006 had Type 1 Gaucher disease except patient [redacted] (PB-06-005) who had Type 3 Gaucher Disease in the 30 units/kg treatment group. As a result, 2 sets of analyses were performed; an analysis was done including all patients (Type 1 Gaucher disease and Type 3 Gaucer disease) and a second analysis was done for patients with Type 1 Gaucher disease only. Thirteen (13) patients (PB-06-005, 9; PB-06-002, 4) completed the study; included were two patients ([redacted] and [redacted]) from PB-06-002 who completed 18 months treatment; due to closure of the study by the sponsor, both patients continued treatment under a compassionate use program. One patient ([redacted]) from Study PB-06-002 discontinued the extension study due to lost to follow up. One patient ([redacted]) from Study PB-06-005 voluntarily withdrew from the extension study due to personal reasons ([redacted]).

Diagnosis and main criteria for inclusion: For inclusion into the study, patients were required to fulfill all of the following criteria:

1. Successful completion of Protocol PB-06-002 or PB-06-005
2. The patient, parent(s) or legal guardian(s) signed informed consent and/or assent

Test product, dose and mode of administration: The initial infusions of taliglucerase alfa for all patients were the same infusion rate and the same volume administered at Visit 20 of Study PB-06-002 or Visit 27 of Study PB-06-005 every 2 weeks (+/- 4 days). The tolerability of the infusion was determined by signs and symptoms during the infusion and for one hour post-infusion in the clinic. The rate of infusion could be adjusted according to individual subject symptoms and signs.

Duration of treatment: The total duration of treatment was 24 months in this protocol, although two patients ([redacted] and [redacted]) from PB-06-002 completed 18 months treatment.

Reference therapy, dose and mode of administration, batch number: Not applicable

Criteria for evaluation:
Efficacy Endpoints: Efficacy was determined by evaluation of the following parameters for clinical deterioration:

1. Spleen volume

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2. Liver volume
3. Platelet count
4. Hemoglobin

Additional efficacy endpoints included:

1. Change in height and weight
2. Change in Pubertal status (by Tanner stage)
3. Change in bone age by X-ray of left hand and wrist
4. Change in bone mineral density by DEXA (only for patients coming from PB-06-005 Study)
5. Occurrence of bone crises
6. Quality of Life using the Child Health Questionnaire™ (CHQ) PF-28 (valid for patients aged 5 to 18 years coming from PB-06-005 Study)

Safety:

1. Adverse events
2. Vital signs
3. Physical examination
4. Concomitant medications
5. Laboratory test results
   - Hematology
   - Biochemistry
   - HbA1c (valid for subjects coming from PB-06-002 Study)
   - Protein Electrophoresis (valid for subjects coming from PB-06-002 Study)
   - Urinalysis
   - Anti-taliglucerase alfa antibodies
6. Echocardiogram
7. Hypersensitivity reactions: Patients experiencing severe or recurrent hypersensitivity reactions are analyzed for IgE antibody formation, Tryptase and complement.
8. Bone events

Statistical methods: Descriptive statistics for continuous variables, sample size (n), mean and its standard error, standard deviation, median and range are presented; for categorical variables, count and percentages are presented. The time points in the summary tables were counted continuously from studies PB-06-005 (12 months) and PB-06-002 (9 months) and denoted by months relative to baseline. The end of study for patients from PB-06-002 was a total of 33 months treatment and for patients from PB-06-005 was a total of 36 months treatment.

No inferential statistics was performed for testing the change from baseline and/or for comparing between or among treatment groups.

Summary – Conclusions

Efficacy Results: Results of this extension study demonstrate that taliglucerase alfa maintains effectiveness throughout the dosing period of 36 months in pediatric patients from PB-06-005 study. Continued improvement was observed in spleen and liver volumes and in hematological parameters in pediatric patients naïve to enzyme replacement therapy with both dose groups.

Pharmacokinetic Results: Exposure to taliglucerase alfa, as measured by C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, was proportional to the dose expressed in units/kg or mg/kg. Mean and median values for T_{max}, k_e, and $t_{1/2}$ are similar for the 30 and 60 units/kg treatment groups. At 30 units/kg, mean $t_{1/2}$ was 34.8 min (range of 12.9 to 56.8 min), and at 60 units/kg, mean $t_{1/2}$ was 31.5 min (range of 18.0 to 42.9 min). After normalization for body weight, clearance and volume of distribution were similar at 30 and 60 units/kg,

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indicative of linear pharmacokinetics.

Safety Results: Taliglucerase alfa was well tolerated with long term (33-36 months) administration in pediatric Gaucher disease patients either naïve to enzyme replacement therapy or who were switched from commercially available imiglucerase.

Safety analyses in patients with Type 1 Gaucher disease also showed no change regardless of whether one patient with Type 3 was included or not in the overall conclusion on long-term safety findings.

Conclusion: This extension study of two Phase 3 studies evaluated the efficacy and safety of taliglucerase alfa as enzyme replacement therapy in pediatric patients with Gaucher disease. Ten (10) pediatric patients continued treatment from Study PB-06-005, a double-blind, randomized study comparing two dose levels of taliglucerase alfa, 30 and 60 units/kg, in patients naïve to enzyme replacement therapy. Five (5) patients continued from Study PB-06-002, a switchover study in pediatric patients previously treated with the commercially available enzyme replacement therapy, imiglucerase (Cerezyme®).

Data from treatment naïve pediatric patients treated for 12 months in Study PB-06-005 and a total of 36 months of treatment, including 24 months in the extension study, showed continued improvement for both the 30 units/kg and 60 units/kg doses of taliglucerase alfa and demonstrate the tolerability and efficacy of taliglucerase alfa. Pediatric patients switched from ERT to taliglucerase alfa in Study PB-06-002 for 9 months remained stable after 24 months in the extension study as shown by clinically relevant parameters (e.g., organ volume size, hematological parameters, biomarker measurements).

Overall, these data indicate that taliglucerase alfa was well tolerated and effective during administration of up to 36 months.

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