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 Trial of Plant Cell Expressed Recombinant Human Glucocerebrosidase (Taliglucerase alfa) in Patients with Gaucher Disease

Investigators:

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Study centre(s): 14 study centers from 11 countries	
Publication (reference): Not applicable	
Studied period (years): Date of first enrolment: 19Jun2008 Date of last completed: 17May2013	**Phase of development:** Phase 3

Objectives: The objective of this study was to extend the assessment of the safety and efficacy of taliglucerase alfa in patients who had successfully completed 9 months treatment of taliglucerase alfa in studies PB-06-001 or PB-06-002 (adult patients) and continued to receive treatment at the dose assigned to each patient in study PB-06-001 or PB-06-002. Note that the pediatric patients from PB-06-002 entered a different extension study.

Methodology: This multi-center, extension trial with taliglucerase alfa was intended to extend the assessment of the safety and efficacy of taliglucerase alfa in patients with Gaucher disease, who completed 9 months of treatment in Studies PB-06-001 or PB-06-002. Patients received IV infusion of taliglucerase alfa every two weeks and had the option to receive their infusions at the selected medical center, infusion center, or at home. Local standard of practice, the investigator and the Medical Director determined the timing and method of infusion outside the medical center. The duration of the study was to be at least 15 months (Part A). The treatment was further extended by protocol amendment until marketing approval was obtained or for a total of no more than 30 months (Part B). If marketing approval was obtained while a patient was on treatment during part B, the earliest upcoming study visit was the final visit for this patient. Assessments for this visit were to be performed as in the Month 27 visit.

There were three treatment groups, with patients continuing to receive the allocated dose from Study PB-06-001, or the same dose they received at the completion of Study PB-06-002.

Treatment Group I (study PB-06-001): 30 units/kg every 2 weeks.
Treatment Group II (study PB-06-001): 60 units/kg every 2 weeks.
Treatment Group III (study PB-06-002): the same dose received at the completion of PB-06-002.

The following procedures were performed after each taliglucerase alfa infusion:

- The patients were observed clinically for a minimum of 1 hour after dosing
- Vital signs were evaluated before starting the infusion and 30, 60 and 120 minutes during the infusion.
- The injection site was evaluated.

Part A of the study consisted of 33 infusions and 6 Study Visits at which time efficacy parameters and clinical laboratory safety assessments were measured. Day 1 of this study was the final visit of Study PB-06-001 or the final visit of PB-06-002. Spleen and liver volumes were measured at Month 3 and Month 15 visits. Adverse events, concomitant medications and vital signs were recorded at each taliglucerase alfa infusion every 2 weeks. Physical exam (including body weight), laboratory safety tests (hematology, biochemistry and urinalysis), biomarkers, antihuman taliglucerase alfa antibodies and ECG were evaluated at Months 3, 6, 9, 12 and 15. Chest X-Ray, X-Ray skeletal evaluation, echocardiography and pulmonary function tests were performed at Month 15. TSH, transferrin, B12 and folic acid tests were also performed at Month 15. DEXA and QCSI were performed at Month 3 and Month 15 for patients who participated in the PB-06-001 study.

Part B of the study consisted of up to 33 infusions and up to 5 Study Visits at which time efficacy parameters and clinical laboratory for safety assessment were measured. Adverse events, concomitant medications, body weight and vital signs were recorded every 2 weeks at each taliglucerase alfa

infusion. Physical exam (including body weight), laboratory safety tests (hematology, biochemistry and urinalysis), biomarkers, antihuman taliglucerase alfa antibodies and ECG were evaluated at Months 18, 21, 24, 27, and 30. Echocardiography and pulmonary function tests were performed at Month 30. TSH, transferrin, B12 and folic acid tests were performed at Month 27. DEXA (for patients who participate in the PB-06-001 study), QCSI (when applicable) and MRI for organ evaluation were performed at Month 27.

The MRI systems at each center were calibrated and standardized following a standard protocol. All MRI volumetric analyses (spleen and liver) were analyzed by central reading experts and the reading was performed by radiological experts under the guidance and responsibility of the director of the reading center.

A Data Monitoring Committee (DMC) was constituted to monitor the safety of human taliglucerase alfa in this study as well as all other taliglucerase alfa studies. One responsibility of the DMC specific to this protocol was to review patients who completed the PB-06-002 study and who met clinical deterioration criteria and were being treated with the highest permissible dose of taliglucerase alfa of 60 units/kg.

Number of patients (planned and analyzed): Up to 60 patients were planned to be enrolled into the extension study. Forty five (45) patients (PB-06-001, 26; PB-06-002, 19) from 14 study sites were enrolled into this study. Forty four (44) patients (PB-06-001, 26; PB-06-002, 18) who received treatment were included in the full analysis population (FAP) and 33 (PB-06-001, 23; PB-06-002, 10) who completed 36 months of treatment were included in the completer population (CP). Efficacy analyses were performed in both FAP and CP, while safety analyses were performed in the FAP only.

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-06-001 or PB-06-002
2. Provide written informed consent

Test product, dose and mode of administration: The individual dose for each patient was prepared according to each patient's Treatment Group. Three treatment groups were evaluated in this study:

- Treatment Group I (Naïve): Taliglucerase alfa 30 units/kg body weight
- Treatment Group II (Naïve): Taliglucerase alfa 60 units/kg body weight
- Treatment Group III (Switch Over): Taliglucerase alfa at the same dose received at the completion of PB-06-002.

Taliglucerase alfa was administered every 2 weeks via IV infusion at the rate of approximately 1.3 mL/min. A total volume of 135 mL of taliglucerase alfa plus a line flush of 20 mL of normal saline was delivered over a 2 hour period.

Duration of treatment: The duration of the study was to be at least 15 months (Part A). The treatment was further extended by protocol amendment until marketing approval was obtained or for a total of no more than 30 months (Part B).

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
2. Liver volume
3. Platelet count
4. Hemoglobin

Additional efficacy endpoints included:

1. Biomarkers: chitotriosidase and PARC/CCL18
2. Bone mineral density by DEXA (dual-energy x-ray absorptiometry) (PB-06-001 only)
3. Quantitative Chemical Shift Imaging (QCSI) (Only in patients who had this test performed in Study PB-06-001

Safety:

1. Adverse events
2. Physical examination (changes in vital signs and body weight)
3. Concomitant medications
4. Laboratory test results
   - Hematology
   - Biochemistry
   - Urinalysis
   - Anti-taliglucerase alfa antibodies
   - Electrocardiogram
   - Echocardiogram
   - Pulmonary function tests
5. Hypersensitivity reactions: Patients experiencing severe or recurrent hypersensitivity reactions are analyzed for IgE antibody formation, Tryptase and complement.

Statistical methods: Descriptive statistics for continuous variables, sample size (n), mean and its standard error, standard deviation, median and range were presented; for categorical variables, count and percentages were presented. The time points in the summary tables were counted continuously from studies PB-06-001 and PB-06-002 (9 months) and denoted as baseline, 9 months, 12 months, 24 months, 36 months, and 39 months.

Descriptive statistics were presented for organ volumes (spleen and liver), hemoglobin, and platelet count. Several exploratory analyses were performed to examine the efficacy difference between the treatment groups. Pair-wise comparisons were made by a two-sample t-test.

Adverse events (AEs) were coded using the MedDRA dictionary to organ class by preferred term. Coded AEs were displayed by frequency, severity, and relationship for each treatment group in the interim population.

Hypersensitivity reactions and bone events (e.g., osteonecrosis, bone infarction, pathological fractures, and bone pain) were analyzed as AEs of special interest using descriptive statistics. Hypersensitivity reactions were further evaluated in the context of antibody formation.

All laboratory measurements were summarized by descriptive statistics by study visit and treatment. The change from Baseline to each post-treatment visit was presented. The frequency count and percentage were presented for abnormal laboratory results classified as low, normal or high. Shift tables describing shifts from Baseline to post treatment and follow-up were provided.

Descriptive statistics were also presented for electrocardiogram, echocardiogram and pulmonary function tests.

Data listings of the prior, concomitant medications, and class of medication were provided.

Summary – Conclusions

Efficacy Results: The efficacy results of this study provide evidence that taliglucerase alfa maintains effectiveness for as long as 39 months. Continued improvement was observed in spleen and liver

volumes and in hematological parameters in patients naïve to enzyme replacement therapy in both dose groups tested.

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

Conclusion: This study is an extension of two Phase 3 studies evaluating the efficacy and safety of taliglucerase alfa as enzyme replacement therapy in patients with Gaucher disease. Twenty six (26) patients continued treatment from Study PB-06-001, a double-blind, randomized study comparing two dose levels of taliglucerase alfa, 30 and 60 units/kg, in patients naïve to enzyme replacement therapy. Eighteen (18) patients continued from Study PB-06-002, a switchover study in patients previously treated with the commercially available enzyme replacement therapy, imiglucerase (Cerezyme®).

Data from treatment naïve patients treated for 9 months in Study PB-06-001 and a total of 39 months of treatment, including 30 months in the extension study, support a conclusion of continued improvement and that both the 30 units/kg and 60 units/kg of taliglucerase alfa demonstrate tolerability and efficacy, whereas patients switched from ERT to taliglucerase alfa in Study PB-06-002 remain stable as determined by clinically relevant parameters (e.g., organ volume size, hematological parameters, biomarker measurements).

Overall, these data support that taliglucerase alfa was well tolerated and effective with administration up to 39 months.