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 Phase 3 Multicenter, Open-label, Switchover Trial to Assess the Safety and Efficacy of Plant Cell Expressed Recombinant Human Glucocerebrosidase (Taliglucerase alfa) in Patients with Gaucher Disease Treated with Imiglucerase (Cerezyme®) Enzyme Replacement Therapy

Investigators:

Site #	Principal Investigators	Affiliations
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Study centre(s): Eleven (11) study centers from nine (9) countries

Publication (reference): Not applicable

Studied period (years): Date of first enrolment: 15Dec2008 Date of last completed: 14Jan2013	**Phase of development:** Phase 3

Objectives: The objective of this study was to assess the safety and efficacy of prGCD (taliglucerase alfa) in patients with Gaucher disease who were currently being treated with imiglucerase (Cerezyme®) enzyme replacement therapy (ERT).

Methodology: This multi-center, open-label, switchover trial was designed to assess the safety and efficacy of taliglucerase alfa in patients, 2 years or older, with Gaucher disease who have been receiving imiglucerase (Cerezyme®) ERT for at least 2 years at a stable maintenance regimen (dose unchanged) for at least the last six months. Up to 30 patients were to be enrolled at 5-8 investigational centers.

Eligible patients entered a 12-week Baseline Stability Evaluation Period to establish the stability of their disease. During the Stability Evaluation Period the patients continued imiglucerase treatment. If the patient's imiglucerase was discontinued due to drug shortage, the patient could start receiving taliglucerase alfa infusions based on historical data on disease stability. The screening visit was conducted more than 5 days from an imiglucerase infusion to ensure an accurate baseline evaluation. Hemoglobin and platelet count were measured by the local laboratory every two weeks for a total of 6 measurements. Patients with stable disease were then switched from their imiglucerase to IV infusions of taliglucerase alfa. Infusions were performed every two weeks for a total of 20 infusions.

The starting dose of taliglucerase alfa was equivalent to each patient's imiglucerase dose in the past 6 months or to the dose prior to the shortage of imiglucerase. The infusions were administered at the selected medical center, infusion center, or at the patient's home. The total duration of treatment was nine months (38 weeks). At the end of the 9-month treatment period eligible patients were offered enrollment in an extension study (PB-06-003).

Number of patients (planned and analyzed): Up to 30 patients were planned to be enrolled into the study. Forty six (46) patients were screened, of these, 33 were eligible for enrollment. Two patients voluntarily withdrew from the study prior to treatment; 31 patients, 26 adults and 5 pediatric, received treatment. One adult patient discontinued the study after he experienced a moderate severity allergic reaction during the first infusion and declined to continue infusions with premedication. Thirty (30) patients, 25 adults and 5 pediatric patients completed the study. Thirty one (31) treated patients were evaluated for safety and 30 patients who completed the study were evaluated for efficacy.

Diagnosis and main criteria for inclusion:

1. Males and females, 2 years or older
2. Diagnosis of Gaucher disease with leukocyte GCD activity level ≤3 nmol/mg*hr (≤30 % of the mean activity of the reference range)
3. Stable Gaucher disease, defined as:
   a. Hemoglobin during Stability Evaluation Period is stable with no value more than 15% below or above the mean value of the Stability Evaluation Period measurements
   b. Platelets count during Stability Evaluation Period stable with no values more than 40% below or above the mean value if the mean value is > 120,000, or more than 20% below or above the mean value if the mean value is ≤ 120,000
   c. No major surgery in the last year
   d. No blood transfusion or major bleeding episode in the last year
   e. No acute avascular necrosis event in the last year
   f. No evidence of spleen or liver enlargement as detected by palpation, ultrasound, or MRI over the last year while being treated with enzyme replacement therapy
4. Receiving imiglucerase therapy for at least 2 years and on a stable maintenance regimen (dose unchanged except for drug shortage) for at least last six months
5. Able to provide written informed consent

Test product, dose and mode of administration, batch number: Taliglucerase alfa dosage was equivalent to the patient's imiglucerase dose at screening or before imiglucerase shortage. 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. The rate of infusion could be increased to up to 2.25 mL/min if the infusion was tolerated by the patient and approved by the Sponsor's Medical Director.

Duration of treatment: 38 weeks

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

Criteria for evaluation:

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

- Platelet count
- Hemoglobin
- Spleen volume
- Liver volume
- Biomarkers (chitotriosidase and PARC/CCL18)

Safety:

- Adverse events
- Anti-taliglucerase alfa antibodies
- Clinical laboratory (hematology, biochemistry, urinalysis)
- Electrocardiogram
- Echocardiogram
- Pulmonary function tests

Exploratory Growth and Development Assessments (patients < 18 years old)

- Height and weight for growth evaluation
- Tanner Stage for sexual development
- Bone age by X-ray of left hand and wrist

Statistical methods: Three interim analyses were performed. The first interim analysis was performed based on monitored data as of 30 April 2010. The second interim analysis was performed based on the monitored data when the first 15 patients who received treatment with taliglucerase alfa and completed or prematurely withdrew from the study. The third interim analysis was performed based on monitored data as of 1 May 2011.

Descriptive statistics for continuous variables, sample size (n), mean, standard deviation and range were presented; for categorical variables, number and percentage of patients were presented. All analyses were performed by age (adult patients, ≥18 years; pediatric patients, <18 years), dose (≤15 units/kg, >15 - ≤30 units/kg and >30 units/kg) and overall. The median dose of each patient was used for categorizing the dose group.

The safety population was defined as all patients who received at least one dose of study medication. All analyses were performed on the safety population except for measurements specifically for adult and pediatric patients.

Descriptive statistics were presented for organ volumes (spleen and liver), hemoglobin, platelet count and biomarkers (chitotriosidase and PARC/CCL18). Change from Baseline was summarized by visit.

Multiples of normal (MN) of spleen and liver volumes, change and percent change from baseline were also summarized by descriptive statistics.

The main effectiveness criteria were based on whether the clinical status of the patient was maintained over the treatment period with taliglucerase alfa after switching from Cerezyme®. Clinical disease deterioration was defined as follows:

- Platelet counts – a decrease of >20% from the mean of six Stability Evaluation Period values of ≤120,000 or a decrease of >40% from the mean of six Stability Evaluation Period values of >120,000 was considered a clinically relevant deterioration.
- Hemoglobin – a decrease of >20% from the mean of six Stability Evaluation Period was considered a clinically relevant deterioration
- Spleen volume – a 20% increase in spleen volume by MRI from Baseline to Month 9 (or the time of premature withdrawal) was considered a clinically relevant deterioration
- Liver volume – a 10% increase in liver volume by MRI from Baseline to Month 9 (or the time of premature withdrawal) was considered a clinically relevant deterioration

The arithmetic mean of the six Stability Evaluation Period values for hemoglobin or platelet count was used in the evaluation. If less than six values were available during Stability Evaluation Period, the available values were used to estimate the mean.

If the patient's treatment with imiglucerase was temporarily discontinued due to shortage of the drug at the time of enrolment, historical data on hemoglobin and platelet count were used to determine clinical deterioration.

The Medical Dictionary for Regulatory Activities (MedDRA) version 15.0 was used to classify all adverse events. Coded AEs were displayed by frequency, severity, and relationship for each treatment group.

Hypersensitivity reactions and specific bone events related to Gaucher disease (osteonecrosis, bone infarction, pathological fractures and bone pain) were analyzed as adverse events of special interest using descriptive statistics. Hypersensitivity reactions were further evaluated in the context of antibody formation.

All central and local laboratory measurements were displayed for each visit, and compared to Baseline measurements. Descriptive statistics were presented for the value and abnormality (e.g., low, normal, high) of each of the clinical laboratory results by visit. Shift tables describing abnormality shifts from Baseline to post treatment were provided.

Growth and development analysis was performed on the group of patients <18 years of age. The height (cm) and weight (kg) at baseline (Visit 1) and all post-treatment visits were summarized by descriptive statistics. Based on WHO 2007 standards, height and weight measured at baseline and month 9 visit were converted to standard deviation scores (SDS). Two sets of the SDS were generated, one was based on Chronological Age (CA) in Months and the other was based on bone age (BA) in months. Additionally growth velocity, i.e. growth per year, was summarized from baseline to month 9 visit.

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

Summary – Conclusions

Efficacy Results: In this study, of the 26 adult and 5 pediatric patients who received treatment, 25 adult

and 5 pediatric patients completed 9 months treatment of taliglucerase alfa. One adult patient (13-228) discontinued the study after he experienced a moderate severity allergic reaction with the first infusion and declined to continue infusions with pretreatment.

All 30 patients who completed 9 months of treatment had stable hemoglobin within -10.2% to 15.2% of the Baseline value at the end of study.

Platelet count in adult and pediatric patients remained stable during 9 months treatment with taliglucerase alfa following switching from Cerezyme®. Patients who received >30 units/kg of taliglucerase alfa showed a mean 10.9% increase from Baseline at Month 9 in platelet count. One adult patient (18-219) showed a clinically relevant deterioration with a sustained >20% reduction in platelet count from Baseline after 22 weeks of treatment with taliglucerase alfa. This patient was on a very low dose of taliglucerase alfa, after doubling the dose, the patient's platelet level increased to Baseline level. The patient completed the study receiving all 38 weeks of treatment.

Among the 25 adult patients who completed 9 months of treatment, 23 had an abdominal MRI for spleen and liver volume evaluation, 23 had measurable liver volume, and 20 had measurable spleen volume (three patients had no spleen volume readings due to splenectomy). All patients remained stable except for two patients who had clinically relevant deterioration based on the protocol definitions. One patient (10-203) with a >20% increase in spleen volume from Baseline to Month 9, and spleen volume per multiple of normal increased 17.4% from 5.43 MN at Baseline to 6.37 MN at Month 9. The second patient (10-205) with a >20% increase in liver volume from Baseline to Month 9, and liver volume per multiple of normal increased 16.1% from 0.90 MN at Baseline to 1.04 MN at Month 9. None of these changes were evaluated as clinically significant. These two patients did not show deterioration in any other disease parameter. The organ volume increases do not appear to be a clear representation of an increase in Gaucher disease activity.

All 5 pediatric patients remained stable with spleen volume change from Baseline between -21.0% to 14.0% (from mean 4.1 MN at Baseline to 3.3 MN at Month 9) and liver volume change from Baseline within -6.0% to 11.0% (from mean 1.3 MN at Baseline to 1.2 MN at Month 9) of Baseline value at the end of study. A slightly higher mean reduction in spleen volume from Baseline was observed at Month 9 in patients who received >15 units/kg compared to patients who received ≤15 units/kg of taliglucerase alfa.

Of the 28 patients who had available Baseline biomarker data, 22 (19 adult and 3 pediatric patients) showed a decrease in chitotriosidase activity and 17 (14 adult and 3 pediatric patients) showed a decrease in CCL18 activity from Baseline after 9 months of treatment with taliglucerase alfa. Of these, five adult patients showing > 50% reduction in chitotriosidase activity and three of these adult patients also had reduction in CCL18 activity (~40%) after switching to taliglucerase alfa. A dose response was observed in the decrease of chitotriosidase activities from Baseline after 9 months of treatment with taliglucerase alfa (≤15 units/kg, 6.5%; >15 - ≤30 units/kg, 10.5%; >30 units/kg, 18.4%). A greater mean reduction in CCL18 activity from Baseline was also observed at Month 9 in the >30 units/kg dose group (21.1%) compared to the ≤30 units/kg dose groups (≤15 units/kg, 2.6% reduction; >15 - ≤30 units/kg, 5.8% increase). It was noted the highest activities of chitotriosidase and CCL18 at Baseline were in the ≤15 units/kg dose group, while the >30 units/kg dose group had the lowest activity of chitotriosidase and CCL18.

Safety Results: Of 31 taliglucerase alfa treated patients, 25 adults experienced 136 AEs and 4 pediatric patients experienced 9 AEs. Of these, 10 adult patients experienced 24 AEs that were considered treatment related by the investigator. All AEs were mild or moderate in intensity except for two adult patients who experienced three AEs (hematuria, renal stone, prolapsed rectum bladder and cervix,

respectively) which were severe. The majority of the events resolved by the end of the study. Nineteen (19) Gaucher disease-related bone events were reported during the study, none of the events were considered related to treatment by the investigators.

Three (3) adult patients developed anti-taliglucerase alfa IgG antibody with the highest titer of 2768, 3542 and 23045, respectively. Of these, one patient with a titer of 23045 had neutralizing antibody activity with the *in vitro* assay but not in the cell based assay. Additionally, 4 patients were also found to have anti-taliglucerase alfa IgG antibody, one adult and two pediatric patients had positive IgG sample at Visit 1 prior to treatment with taliglucerase alfa and one adult with a very low titer of 82 at Visit 5.

Three (3) patients each experienced an SAE (epistaxis, renal stone and prolapsed rectum bladder and cervix, respectively) during the study. All three events were considered definitely not or probably not related to treatment by the investigator and reported as being resolved or resolving.

Bone age of left hand and wrist by X-ray in 5 pediatric patients showed that bone age increased proportionally to age from Baseline to Month 9. The mean height velocity for the 5 pediatric patients is estimated at 4.2 cm growth per year.

No deaths occurred and no patients discontinued from the study due to an AE. One patient voluntarily withdrew after experiencing hypersensitivity (a grade 2 allergic reaction - urticaria) during the first infusion of taliglucerase alfa and declined to continue infusions with pretreatment.

Conclusion: At the end of the nine months of treatment with taliglucerase alfa in this study, all 30 patients, 25 adults and 5 pediatric, remained clinically stable at all dose groups ranging from a median of 9 to 60/units/kg in adults and ranging from a median of 26 to 60/units/kg in pediatric patients. These patients had platelet and hemoglobin values within expected parameters, and there was also a mean reduction of 7.4% in spleen volume (8.8% in MN) and 2.4% in liver volume (3.7% in MN) from Baseline. The mean reduction of 12.2% in chitotriosidase and 6.2% in CCL18 biomarker level support the stability of Gaucher disease in these adult and pediatric patients after switching from Cerezyme® to taliglucerase alfa.

There was no evidence of increased safety concerns in patients switched from Cerezyme to taliglucerase alfa. Taliglucerase alfa administration every 2 weeks for 9 months was safe and well tolerated in adult and pediatric patients previously treated with Cerezyme. No unexpected safety risk was identified. There were no deaths, treatment-related SAEs or discontinuations due to AEs in this study. The most commonly experienced AEs were nasopharyngitis, infusion related reaction, arthralgia and headache.

This study shows that taliglucerase alfa is a safe and effective alternative to Cerezyme®.