2. SYNOPSIS

Name of Sponsor/Company: Protalix Biotherapeutics 2 Snunit Street Science Park POB 455 Carmiel 20100, Israel Ph: [redacted] Fax: [redacted]	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 III Multicenter, Randomized, Double-Blind Trial to Assess the Safety and Efficacy of Two Parallel Dose Groups of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients with Gaucher Disease

Investigators:

Site #	Principal Investigators	Affiliations
10	[redacted] MD	[redacted] Israel
11	[redacted], MD	[redacted], South Africa
12	[redacted] MD	[redacted] UK
14	[redacted], MD	[redacted], Spain
15	[redacted], MD	[redacted], Israel
17	[redacted], MD	[redacted], Italy
22	[redacted], MD	[redacted] Ontario [redacted]
30	[redacted], MD	[redacted], Serbia
40	[redacted] Garcia, MD	[redacted] 06720
41	[redacted], MD	[redacted] 37320
42	[redacted], MD	[redacted] Chile

Study center(s): 11 study centers from 9 countries

Publication (reference): Not applicable

Studied period (years): Date of first enrolment: 5Aug2007 Date of last completed: 11Sep2009	**Phase of development:** Phase 3

Objectives: The objective of this study was to assess the safety and efficacy of taliglucerase alfa in

untreated patients with significant signs and symptoms of Gaucher disease.

Methodology: This was a multi-center, randomized, double-blind, parallel group, dose-ranging trial to assess the safety and efficacy of taliglucerase alfa in 30 untreated patients with Gaucher disease. Patients received IV infusion of taliglucerase alfa (Group I, 30 units/kg; Group II, 60 units/kg) every two weeks at the selected medical centers. The duration of treatment was nine months. At the end of the 9-month treatment period (21 visits, 38 weeks), eligible patients were offered enrollment in an open-label extension study.

Number of patients (planned and analyzed): Approximately 30 patients were planned to be enrolled so as to have 24 patients complete the study. Forty four (44) were screened, 33 were enrolled, 32 were evaluated for safety and 31 were evaluated for efficacy.

Diagnosis and main criteria for inclusion:

- Diagnosis of Gaucher disease with leukocyte GCD activity level ≤3 nmol/mg*hr (≤30 % of the mean activity of the reference range).
- Males and females, 18 years or older.
- Female patients of child-bearing potential or male patients with female partners of child bearing potential had to agree to use a medically acceptable method of contraception, which could not be the rhythm method.
- Splenomegaly defined as greater than eight times the expected volume [measured volume divided by estimated volume (0.2% of body weight)] as determined by MRI volumetric analysis.
- Thrombocytopenia (defined as platelet counts <120,000 per mm^3) with or without anemia (defined by hemoglobin at least 1 g/dL below normal range according to sex and age).
- Patients who have not received enzyme replacement therapy (ERT) in the past or patients who have not received ERT in the past 12 months and have a negative anti-glucocerebrosidase antibody test result.
- Patients who have not received substrate reduction therapy (SRT) in the past 12 months.

Test product, dose and mode of administration, batch number: Taliglucerase alfa 30 or 60 units/kg every 2 weeks by intravenous infusion over 1-2 hours.

	Batch#	Expiration date
Taliglucerase alfa	K-38743	April 2008
	K-39065	July 2008, October 2008
	K-40306	March 2009, June 2009 and October 2009
	PR2001	September 2009, December 2009 and April 2010
	PR2002	September 2010

Duration of treatment: 38 weeks

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

Criteria for evaluation:

Primary Efficacy Endpoints: Percent change from baseline in spleen volume measured by MRI at 9 months.

Major Secondary Efficacy Endpoints: Change from baseline in:

- Hemoglobin
- Liver volume (percent change)
- Platelet count

Other Secondary Efficacy Endpoints: Change from baseline in:

- Biomarkers [chitotriosidase and pulmonary and activation-regulated chemokine (PARC/CCL18)]
- Proportion of patients with greater than 10% reduction in spleen volume at 9 months

Tertiary Efficacy Endpoints: Change from baseline in:

- Quantitative Chemical Shift Imaging (QCSI)
- Dual-energy x-ray absorptiometry (DEXA)

Safety:

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

Statistical methods: This Phase 3 study had several analytical objectives. The primary objectives were to evaluate the efficacy and safety of taliglucerase alfa for the reduction of spleen volume in patients with Gaucher disease. The second objective was to determine changes in major secondary parameters of, hemoglobin, liver volume and platelet count. Other objectives were to evaluate changes in biomarkers of disease, QCSI and DEXA. The PK profile of taliglucerase alfa in patients with Gaucher disease was also determined.

All data obtained in this study and documented in the CRFs were tabulated with descriptive group statistics (mean, standard deviation, median, minimum, maximum, number of valid cases for continuous measures and counts and percentages for categorical measures) as appropriate.

Three study populations were defined in the analyses:

- Intent-to-Treat (ITT): patients who received at least one dose of study medication and had at least the Screening/Baseline MRI evaluation.
- Per Protocol (PP): all ITT patients who completed 9 months of the study and had no major protocol violations.
- Safety Population: patients who received at least one dose of study medication

The primary efficacy analysis was based on two one-sample t-tests (one for each treatment group) to determine if the percent change in spleen volume was different from zero using an alpha level of 0.025. The study was designed to test the null hypothesis that there was no percent change in spleen volume versus the alternative that the percent change in spleen volume was not equal to zero. Multiple imputation (MI) methodology was used as the primary efficacy analysis approach.

Three major secondary endpoints were selected to provide confirmatory evidence of efficacy: mean change in hemoglobin, percent change in liver volume, and mean change in platelet count. In order to examine these three secondary endpoints, a sequential (step-down) approach was used: First, the primary efficacy analysis was performed at each dose level. If spleen volume as the primary endpoint was shown to be significant for either one or both doses, mean change in hemoglobin was tested for that dose (or doses) using an alpha level of 0.025 to allow each dose to be tested. Next, if the percent change in hemoglobin was shown to be significant for either one or both doses, then the percent change in liver volume was tested for that dose (or doses) using an alpha level of 0.025 to allow each dose to be tested. Finally, if percent change in liver volume was shown to be significant for either one or both doses, then mean change in platelets was tested for that dose (or doses) using an alpha level of 0.025 to allow each dose to be tested.

For each of the secondary endpoints, a one-sample t-test (% change in liver volume, mean change in hemoglobin and platelet count) was examined first for each dose using the step-down approach.

For both the primary and major secondary efficacy analyses, a mixed effects model that included baseline, dose and time, with subject as a random effect, was fit to examine whether there was a difference between dose groups at months 6 and 9.

Patients who withdrew early were analyzed using last observation carried forward (LOCF) approach if early withdrawal not due to serious adverse event, "no-change from baseline" if due to serious adverse event, in order to examine the sensitivity of the study results to a different assumption concerning missing data.

Summary – Conclusions

Efficacy Results:
The primary efficacy analysis demonstrated that taliglucerase alfa treatment significantly reduced spleen volume from screening to the Month 9 timepoint (taliglucerase alfa 30 units/kg, 26.91%; taliglucerase alfa 60 units/kg, 38.01%; $p<0.0001$) and at the Month 6 timepoint (taliglucerase alfa 30 units/kg, 22.21%; taliglucerase alfa 60 units/kg, 29.94%; $p<0.0001$) in patients with Gaucher disease. These results are statistically robust and consistent for both ITT and PP analysis populations regardless of whether the average combined imputation or individual imputation model (1 to 100), or independent reader (1 and 2) or using LOCF method is used.

The secondary efficacy analysis demonstrated that taliglucerase alfa treatment significantly increased hemoglobin level from the baseline at Month 9 timepoint (taliglucerase alfa 30 units/kg, 1.6 g/dL; taliglucerase alfa 60 units/kg, 2.2 g/dL; $p<0.0001$). A significant reduction in liver volume from screening was also observed in both taliglucerase alfa dose groups at the end of the study (taliglucerase alfa 30 units/kg, 10.48%, $P=0.0041$; taliglucerase alfa 60 units/kg, 11.11%, $p<0.0001$). In addition, a significant increase in platelet count from baseline was observed in the 60 units/kg dose group at Month 9 (41,494/mm^3, $p=0.0031$) and a clinically relevant improvement in platelet count at Month 9 was also observed for the taliglucerase alfa 30 units/kg dose group (11,427/mm^3, $P=0.0460$). Improvements were also observed at the 6 month visit. At the end of study, all taliglucerase alfa treated patients had at least a 10% reduction in spleen volume.

Taliglucerase alfa treatment also decreased Gaucher disease severity as evidenced by the clinically relevant decrease in biomarker chitotriosidase levels at the end of study reflective of the severity of the disease state.

Overall, taliglucerase alfa 60 units/kg treatment appeared to have slightly more clinical improvement than 30 units/kg treatment in spleen volume reduction, hemoglobin level increase and platelet count increase at the end of study. However, the differences probably have limited clinical relevance.

Quantitative chemical shift imaging results showed a definite increase in fat-fraction in this 9 month study. A significant improvement was observed in the number of patients who were considered "bone at risk" (fat fraction ≤ 0.23), only 25% (2/8) of the patients with fat fraction of > 0.23 at baseline, which increased to 75% (6/8) of the patients after 9 month treatment at the end of study.

Taligucerase alfa 30 and 60 units/kg administered by intravenous infusion for 9 months in 31 patients with moderate to severe Gaucher disease demonstrated efficacy in a clinically relevant and statistically robust manner.

Pharmacokinetic Results:
Mean C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were higher for patients who received taliglucerase alfa 60 units/kg than those receiving taliglucerase alfa 30 units/kg, although there was an overlap in the range of values. Exposure appeared to be linearly related to dose. The mean values of T_{max} ranged from 82.5 to 95.0 min. The mean values of $t_{1/2}$ ranged from 25.0 to 34.8 min. The mean values for CL ranged from 19.9 to 30.7 L/hr, and the mean values for V_z ranged from 11.7 to 17.5 L. There was no apparent dependence on dose or sampling day for either T_{max}, mean $t_{1/2,}$ CL or V_z. The available data from patients excluded from the pharmacokinetic evaluation (interrupted infusions and missing samples) did not alter the conclusions reached with the included patients.

Safety Results:
Twenty three (23) taliglucerase alfa treated patients (30 units/kg, 12; 60 units/kg, 11) experienced 137 AEs (30 units/kg, 65; 60 units/kg, 72). Eight of these patients (30 units/kg, 3; 60 units/kg, 5) experienced 28 events (30 units/kg, 12; 60 units/kg, 16) which were considered treatment related. All AEs were mild or moderate in intensity and the majority of the events spontaneously resolved. The percentage of patients who experienced at least one AE was comparable between two dose groups.

Two patients developed hypersensitivity reactions. One patient developed a reaction after 11 infusions and was withdrawn from the study. [redacted] did not develop a positive IgG antibody response, but did have an increase in tryptase. Another patient developed an immediate hypersensitivity reaction during [redacted] first infusion and had a positive IgE titer at the pre dose sample taken prior to the first infusion. [redacted] was discontinued from the study. This patient had a similar reaction when exposed to [redacted]. Overall, there did not appear to be a relationship between development of positive IgG titer (2 patients) and hypersensitivity responses. There was no development of neutralizing antibodies.

No deaths or SAEs occurred during the study. One patient in each of the taliglucerase alfa dose groups discontinued from the study due to a hypersensitivity reaction.

Conclusion:
This study demonstrated that taliglucerase alfa at 30 units/kg or 60 units/kg dose proved to be a safe and highly effective therapeutic agent for Gaucher disease.

Date of the report: 22Nov2009