

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Translational Sciences
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/ Supporting Document Number: 22-458/0002, 0035, 0036, 0037

Drug Name: ELELYSO™ [taliglucerase alpha – plant cell expressed recombinant human glucocerebrosidase (prGCD)] 60 units/kg (b) (4) delivered by Intravenous (IV) Infusion every Two Weeks

Indication(s): Treatment of Type I Gaucher Disease

Applicant: Protalix Biotherapeutics, Ltd.

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1.0 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

This statistical review provides an in-depth analysis of supportive studies PB-06-002 and PB-06-003 based on additional trial data received in reply to a Complete Response (CR) action. These two studies support the pivotal trial, PB-06-001, already deemed adequate and well-controlled during the first review cycle of this NDA. Although the trials are not closed at this time, the efficacy data have been deemed sufficient for final review by the Division of Gastroenterology and Inborn Error Products (DGIEP).

Due to the orphan nature of Type I Gaucher Disease, and the limitations of the submitted clinical studies, the determination of the clinical effectiveness of ELELYSO[®] will rely more on clinical judgment than on the statistical rigor usually required for larger controlled studies. The results from the PB-06-002 study appear supportive of treatment benefit with regard to the efficacy parameters of interest (spleen volume, hemoglobin concentration, liver volume, and platelet count). This suggests that patients previously receiving CERZYME can retain response when switching over to ELELYSO treatment.

The results from the extension study PB-06-003 indicate that patients treated for at least 24 months continue to show treatment benefit. PB-06-001 patients showed continued positive response, and PB-06-002 patients showed little, if any, deterioration in efficacy parameters. This suggests that longer term treatment-experienced patients can maintain their response.

1.2 Brief Overview of Clinical Studies

ELELYSO[®] has been studied by Protalix Ltd. for the treatment of Type I Gaucher Disease, and its clinical efficacy and safety has been principally evaluated through three studies: a Phase 3, multicenter, randomized, double-blind, and parallel dose-group study (PB-06-001) which serves as the sponsor's only adequate and well controlled study for this clinical development program; a Phase 3, multicenter, open-label, switchover study (PB-06-002); and a Phase 3, multicenter, double-blind, parallel dose-group study (PB-06-003) which is a long term extension study of patients from trials PB-06-001 and PB-06-002.

1.3 Statistical Issues and Findings

As communicated during the original review cycle, the statistical review issues for this application continue to concern overall level of evidence of efficacy and the PB-06-002 study design. These primary statistical review concerns are summarized below.

Level of Evidence

VPRIV was the latest Type 1 Gaucher Disease treatment approved by the FDA on February 26, 2010. The primary basis for efficacy was based on positive results from two principal studies which included a single arm study (similar to PB-06-001) and a non-inferiority study comparing VPRIV and CERZYME.

For the current submission however, Protalix Biotherapeutics, Ltd., did not include a ‘head-to-head’ study between ELELYSO and a previously approved FDA treatment for Type 1 Gaucher Disease (i.e. CEREZYME or VPRIV). The absence of an active control study within the development program of ELELYSO presents a lower level of evidence compared to that previously demonstrated for VPRIV.

However, due to the current product shortage issues for CEREZYME, a request for an additional request for a pre-market, well-controlled study may be deemed burdensome. The evaluation of further long term data (e.g. up to 5 years of total exposure) from the PB-06-003 study would be an important post-marketing requirement.

PB-06-002 Study Design

The efficacy results from study PB-06-002 are marginally supportive at best due to the open-label switchover design utilized by the sponsor. This study could have been designed as a double-blind randomized withdrawal or double-blind randomized add-on study which would have resulted in much more useful and supportive efficacy data. Nonetheless, from a clinical standpoint, the supportive data generated from this study may be sufficient. Please see the clinical review document for details.

2.0 INTRODUCTION

2.1 Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations, Protalix Ltd. previously submitted the New Drug Application (NDA) for ELELYSO® (taliglucerase alfa) on April 26, 2010. The active pharmaceutical ingredient in ELELYSO [delivery by intravenous (IV) infusion every two weeks] is taliglucerase alfa. This is the first prescription product to have taliglucerase alfa as its active pharmaceutical ingredient. ELELYSO has undergone clinical development under IND 69,703 in patients with Type 1 (i.e. non-neurological) Gaucher Disease, and has been developed specifically to establish safety and efficacy in this patient population. Currently, there are effective FDA-approved treatment options for patients with Type 1 Gaucher disease; however, due to product shortages caused primarily by manufacturing issues, this serious and life threatening condition still remains as one with an unmet medical need.

Protalix Ltd. obtained Fast Track designation from the Agency on August 24, 2009, and the final component of their original rolling submission (which officially started the original PDUFA clock) was delivered on April 26, 2010. This original review cycle established by DGIEP was a standard 10 month cycle. (b) (4)

DGIEP ultimately assessed the original NDA submission as insufficient. On February 25, 2011 a CR action letter was sent to Protalix listing all deficiencies encountered by the division within the original review cycle which precluded product approval. Protalix has subsequently resubmitted the NDA on August 1, 2011 with the intent to correct all deficiencies outlined by the Agency. This NDA resubmission is categorized as Class 2 which corresponds to a 6 month review cycle.

2.2 Brief Overview and Summary of Relevant Trials

ELELYSO has been studied by Protalix Ltd. for the treatment of Type I Gaucher Disease, and its clinical efficacy and safety has been principally evaluated through three studies: a Phase 3, multicenter, randomized, double-blind, and parallel dose-group study (PB-06-001) which serves as the lone adequate and well controlled study of this clinical development program as per 21 CFR 314.126 (this study was already reviewed within the previous review cycle); a Phase 3, multicenter, open-label, switchover study (PB-06-002) whose updated data will be reviewed within this review cycle; and a Phase 3, multicenter, double-blind, parallel dose-group study (PB-06-003), which is a long term extension study of patients from trials PB-06-001 and PB-06-002, whose updated data will be reviewed within this review cycle.

Table 1 below presents information on the three relevant trials contained in the submission.

Table 1
Summary Information for Relevant Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety; Phase 3	PB-06-001	To assess the safety and efficacy of taliglucerase alfa in treatment naïve patients	Multicenter, randomized, double-blind, parallel dose-group	taliglucerase alpha 60 units/kg and 30 units/kg; every two weeks; IV infusion	60 units/kg: 17 30 units/kg: 16 Total: 33	Patients with Type I Gaucher Disease	38 weeks	Complete; Full
Efficacy and Safety; Phase 3	PB-06-002	To assess the safety and efficacy of taliglucerase alfa in patients previously treated with Imiglucerase (CEREZYME®)	Multicenter, open-label, switchover	taliglucerase alpha equivalent to Imiglucerase dose; every two weeks; IV infusion	Total: 28 (30 planned)	Patients with Type I Gaucher Disease	38 weeks	Ongoing; Abbreviated
Efficacy and Safety; Phase 3	PB-06-003	To extend the assessment of the safety and efficacy of taliglucerase alpha in PB-06-001 and PB-06-002 patients who completed 9 months of treatment	Multicenter, double-blind, parallel dose-group, extension	taliglucerase alpha 60 units/kg and 30 units/kg (PB-06-001 patients), and dose equivalent to Imiglucerase dose (PB-06-002 patients); every two weeks; IV infusion	60 units/kg: 14 30 units/kg: 12 PB-06-002 dose: 18 Total: 44 (up to 60 planned)	Patients with Type I Gaucher Disease	64 – 128 weeks (15 – 30 months)	Ongoing; Abbreviated

Source: Reviewer's Table.

2.3 Data Sources

This NDA resubmission was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). Its content, including the electronic data sets and labeling information, has been stored in the electronic document room (EDR) at this path location: \\Cdsub1\evsprod\NDA022458.

3.0 STATISTICAL EVALUATION

3.1 Study PB-06-001 – Review completed within prior review cycle (see statistical review, dated February 24, 2011)

3.2 Study PB-06-002 – Reflects new data accumulated since original NDA submission

3.2.1 Background and Analysis Information

The objective of this ongoing multi-center, open-label, switchover trial was to assess the safety and efficacy of ELELYSO in 30 patients, 2 years or older, with Type 1 Gaucher disease who had been receiving CERZYME for at least 2 years at a stable maintenance regimen (i.e. dose unchanged) for at least six months prior to screening. As of May 1, 2011, 28 patients are currently being treated at 10 investigational centers in 8 countries with a total of 25 of these patients having completed this study. As previously stated, up to 30 total patients were planned to be enrolled into the trial, consequently the CSR submitted within this NDA is still an abbreviated one based on interim data.

Eligible patients will enter a 12-week Baseline Stability Evaluation Period in order to establish the stability of their disease. During the Stability Evaluation Period, the patients will continue CERZYME treatment, and if the patient's CERZYME was discontinued due to drug shortage, the patient could start receiving ELELYSO infusions based on historical data pertaining to disease stability. The screening visit is conducted more than 5 days after the last stability period CERZYME infusion in order to ensure an accurate baseline evaluation. Hemoglobin concentration and platelet count are measured by the local laboratory every two weeks for a total of up to 6 measurements during this stability period. Patients with stable disease are then switched from CERZYME to receive IV infusions of ELELYSO. Infusions are performed every two weeks for a total of 20 infusions. The starting dose of ELELYSO is equivalent to each patient's CERZYME dose in the past 6 months or to the dose prior to the shortage of CERZYME. The infusions are administered at the selected medical center, infusion center, or at the patient's home. The total duration of treatment is nine months (i.e. 38 weeks), and at the end of the 9-month treatment period (spanning 20 protocol defined visits) eligible patients are subsequently offered enrollment in the PB-06-003 extension study.

Efficacy is determined by evaluation of the following parameters for clinical deterioration. It is to be noted that this evaluation is based on clinical determination/judgment which is reflected in the criteria presented below and not on inference derived from formal statistical methodology.

- Spleen Volume
- Hemoglobin Concentration
- Liver Volume
- Platelet Count

Two interim analyses were planned. The first interim analysis, which was the basis of the submitted abbreviated CSR from the previous review cycle, was performed on monitored data as of April 30, 2010. The second interim analysis, which is the basis of the current submitted abbreviated CSR, is performed on monitored data as of May 1, 2011. The study population used for the results presented within the abbreviated CSR is defined as all enrolled subjects who received treatment with ELELYSO. The data used for the summary tables will be the records collected on or before the date of May 1, 2011.

The main effectiveness criteria are based on whether the clinical status of the patient was maintained over the treatment period with ELELYSO after switching from CERZYME. Clinical disease deterioration was defined in a pre-specified manner as follows:

- 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. The image evaluation plan for determining spleen volume is the same as what was instituted in the PB-06-001 study (please see previous review checked into DARRTS for details).
- Hemoglobin – a decrease of >20% from the arithmetic mean of the up to six hemoglobin concentration values measured during the Stability Evaluation Period was considered a clinically relevant deterioration. If less than six values are available during the Stability Evaluation Period, the available values are used to estimate the mean. If the patient's treatment with CERZYME was temporarily discontinued due to shortage of the drug at the time of enrollment, historical data on hemoglobin concentration is used to determine clinical 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 image evaluation plan for determining spleen volume is the same as what was instituted in the PB-06-001 study (please see previous review checked into DARRTS for details).
- Platelet counts – a decrease of >20% from the arithmetic mean of the up to six platelet count values measured during the Stability Evaluation Period of $\leq 120,000$ or a decrease of >40% from the arithmetic mean of the six platelet count values measured during the Stability Evaluation Period of $>120,000$ were considered a clinically relevant deterioration. If less than six values are available during the Stability Evaluation Period, the available values are used to estimate the mean. If the patient's treatment with CERZYME was temporarily discontinued due to shortage of the drug at the time of enrollment, historical data on platelet count is used to determine clinical deterioration.

Below, tables which present clinically relevant deterioration by pivotal study weeks are presented for each of the aforementioned efficacy parameters (i.e. spleen volume, hemoglobin concentration, liver volume, and platelet count). In addition, accompanying figures are also presented for hemoglobin concentration and platelet count. Due to sparse organ volume data (i.e. image volumes were determined/captured only at the baseline and month 9 visits), spleen and liver volume figures were not produced.

The specification for the two figures created by the statistical review team pertaining to hemoglobin concentration and platelet count is as follows. In this study, the screening assessment was conducted at Week -12. Then, as previously described, a Stability Evaluation Period commenced prior to the baseline visit where multiple assessments were made for each lab parameter of which hemoglobin concentration and platelet count are of interest here. Since there was not much variability observed in the hemoglobin concentration and platelet count values within each patient during this pre-baseline evaluation period, the median stability evaluation period value of each of these two lab parameters was obtained per patient. This calculation was made in order to obtain one stability evaluation value for each of these two parameters per patient. Ideally it would have been best to keep the stability evaluation period values separated, but the potential problem was that no corresponding exact time point was captured in the datasets with these measurements relative to screening/Week -12. Hence the statistical review team did not want to risk mixing values from differing time points. For example, one patient's first stability evaluation visit may have occurred much earlier or much later, relative to screening, than another patient's first stability evaluation visit. This resulting one stability evaluation value was ultimately assigned to Week -6 within the figures. The statistical review team ultimately utilized descriptive statistics within the two figures, specifically median, min and max as opposed to means (which are descriptive as well) and confidence limits (which are inferential and parametric). These statistics chosen to be reflected within the figures are, at the same time, descriptive and non-parametric which is most optimal in this exploratory small sample setting.

3.2.2 Disposition and Demographics/Baseline Information

The disposition information for all enrolled patients is presented in Table 2 below.

Table 2
Disposition
(All Enrolled)

	Total (N = 28)
Completed the Study?	
Yes	25 (87.9%)
No	3 (12.1%)
Rolled over into the PB-06-003 Study?	
Yes	18 (64.3%)
No	10 (35.7%)

Source: Reviewer's Table.

Note: Denominators for percentages are N, the number of patients overall.

The demographics and baseline characteristics of all enrolled patients are presented in Table 3 below.

Table 3
Demographics and Baseline Characteristics
(All Enrolled)

	Total (N = 28)
Age (years) at Informed Consent	
n	28
Mean (SD)	44.7 (15.10)
Median	46.5
Min, Max	13, 66
Gender – n (%)	
Female	15 (53.6%)
Male	13 (46.4%)
Religion – n (%)	
Jewish - Ashkenazi	14 (50.0%)
Jewish – Non-Ashkenazi	0
Non-Jewish	12 (42.9%)
Not Reported	2 (7.1%)
Race – n (%)	
Caucasian	28 (100.0%)
African American	0
Native American	0
Asian/Pacific Islander	0
Other	0
Weight (kg)	
n	28
Mean (SD)	76.5 (17.23)
Median	74.5
Min, Max	45, 112
Average of All Dose Infusions (units/kg)	
n	28
Mean (SD)	29.2 (15.90)
Median	25.5
Min, Max	11, 60

Source: Reviewer along with Tables 3 and 4 from pgs. 26-27 of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are N, the number of patients overall.

3.2.3 Analysis Tables and Figures for Efficacy Parameters

3.2.3.1 Spleen Volume

Among the 25 patients completing 9 months of treatment, three patients had no spleen volume readings due to splenectomy and two patients were evaluated by ultrasound and are not included in the analysis. Table 4 below presents the specifics.

Table 4
Spleen Volume with Clinically Relevant Deterioration at Month 9
(All Enrolled)

		Total (N = 28)
Spleen Volumes (mL) at Visit 1 (Day 1)		
n		20
Mean (SD)		822.4 (603.70)
Median		814.2
Min, Max		14, 2151
Spleen Volumes (mL) at Visit 20 (Month 9)		
n		20
Mean (SD)		749.3 (559.70)
Median		697.3
Min, Max		15, 2141
Percentage (%) Change from Baseline in Spleen Volume		
n		20
Mean (SD)		-7.6 (13.30)
Median		-7.4
Min, Max		-33, 22
Clinically Relevant Deterioration at Visit 20 (Month 9)	n	20
	Yes	1 (5.0%)
	No	19 (95.0%)

Source: Table 6, 7.2 and 7.3 from pgs. 31, 60, and 61, respectively, of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

3.2.3.2 Hemoglobin Concentration

Hemoglobin concentration was measured at the local laboratory for 9 visits (i.e. 0, 1, 3, 5, 7, 10, 14, 17 and 20) or for additional visits at the discretion of the Investigator as clinically indicated. Table 5 and Figure 1 below present the specifics.

Table 5
Hemoglobin Concentration with Clinically Relevant Deterioration at Month 9
(All Enrolled)

		Total (N = 28)
Hemoglobin Concentration (g/dL) at Baseline[1]		
n		28
Mean (SD)		13.6 (1.50)
Median		13.7
Min, Max		11, 16
Hemoglobin Concentration (g/dL) at Visit 20 (Month 9)		
n		26
Mean (SD)		13.4 (1.60)
Median		13.7
Min, Max		10, 16
Change from Baseline in Hemoglobin Concentration (g/dL)		
n		26
Mean (SD)		-0.2 (0.70)
Median		-0.2
Min, Max		-1, 1
Clinically Relevant Deterioration at Visit 20 (Month 9)	n	26
	Yes	0 (5.0%)
	No	26 (95.0%)

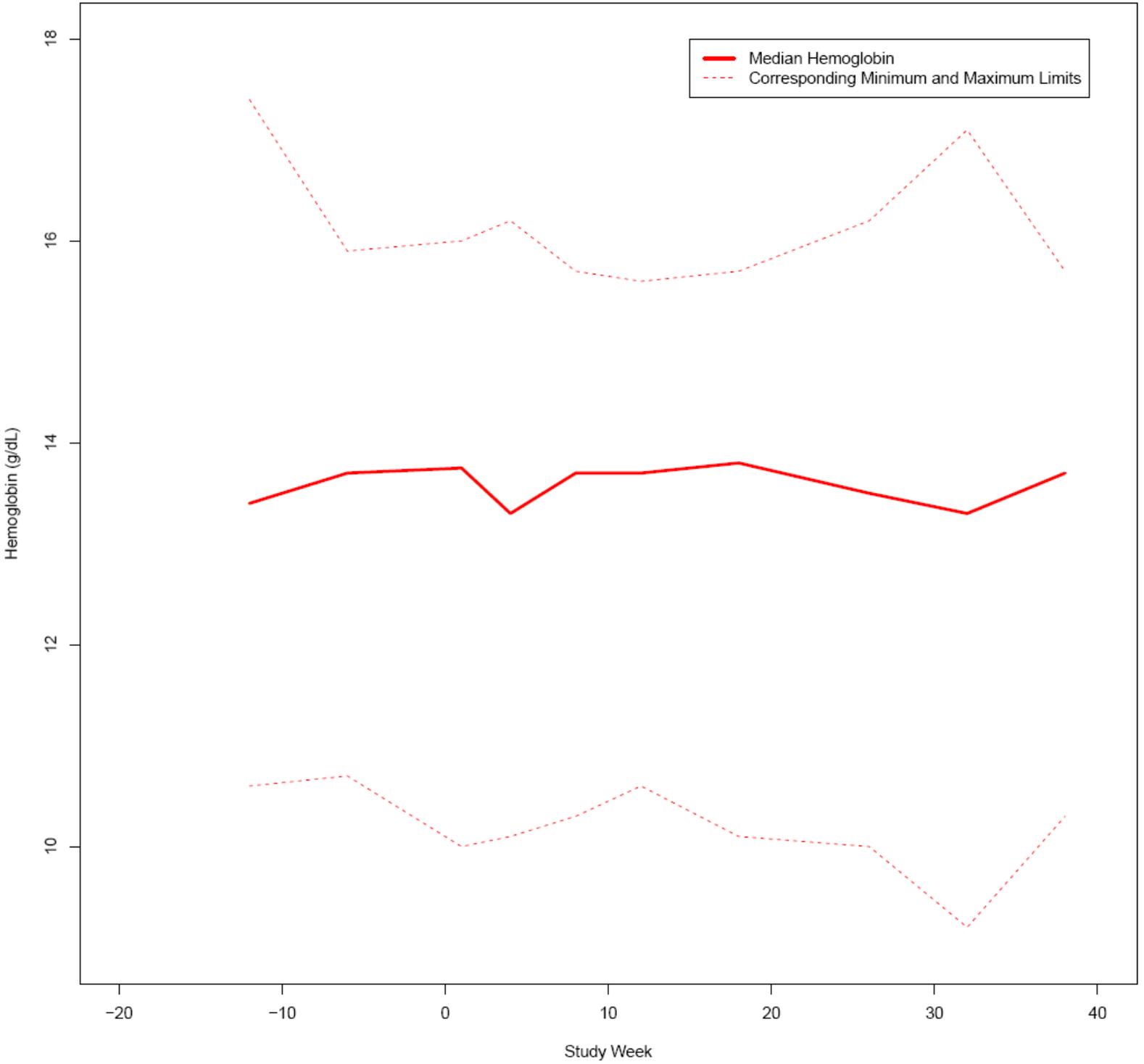
Source: Table 8, 9.2 and 9.3 from pgs. 32 and 66-76 of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

[1]: Baseline = Mean of the up to six evaluations during the Stability Evaluation Period along with the Screening evaluation.

Figure 1
(All Enrolled)

Median Hemoglobin By Study Week



Source: Reviewer's Figure.

3.2.3.3 Liver Volume

Among the 25 patients completing 9 months of treatment, two patients were evaluated by ultrasound and are not included in the analysis. Table 6 below presents the specifics.

Table 6
Liver Volume Specifics and Clinically Relevant Deterioration at Month 9
(All Enrolled)

		Total (N = 28)
Liver Volumes (mL) at Visit 1 (Day 1)		
n		23
Mean (SD)		1857.4 (440.00)
Median		1816.5
Min, Max		1167, 2659
Liver Volumes (mL) at Visit 20 (Month 9)		
n		23
Mean (SD)		1785.8 (423.70)
Median		1800.6
Min, Max		1276, 2604
Percentage (%) Change from Baseline in Liver Volume		
N		23
Mean (SD)		-3.5 (8.10)
Median		-4.1
Min, Max		-16, 22
Clinically Relevant Deterioration at Visit 20 (Month 9)		
n		23
Yes		1 (4.3%)
No		22 (95.7%)

Source: Table 7, 8.2 and 8.3 from pgs. 31, 63, and 64, respectively, of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

3.2.3.4 Platelet Count

Platelet count was measured at the local laboratory for 9 visits (i.e. 0, 1, 3, 5, 7, 10, 14, 17 and 20) or for additional visits at the discretion of the Investigator as clinically indicated. Table 7 and Figure 2 below present the specifics.

Table 7
Platelet Count with Clinically Relevant Deterioration at Month 9
(All Enrolled)

		Total (N = 28)
Platelet Count (/mm ³) at Baseline[1]		
n		28
Mean (SD)		169427.4 (81204.19)
Median		177583.3
Min, Max		37833, 322200
Platelet Count (/mm ³) at Visit 20 (Month 9)		
n		26
Mean (SD)		165653.8 (94037.80)
Median		164500.0
Min, Max		37000, 361000
Change from Baseline in Platelet Count (/mm ³)		
n		26
Mean (SD)		-1014.1 (30266.80)
Median		-1833.3
Min, Max		-88500, 56000
Percentage Change (%) from Baseline in Platelet Count		
n		26
Mean (SD)		-1.0 (21.30)
Median		-1.7
Min, Max		-36, 69
Clinically Relevant Deterioration at Visit 20 (Month 9)		
n		26
Yes		2 (7.7%)
No		24 (92.3%)

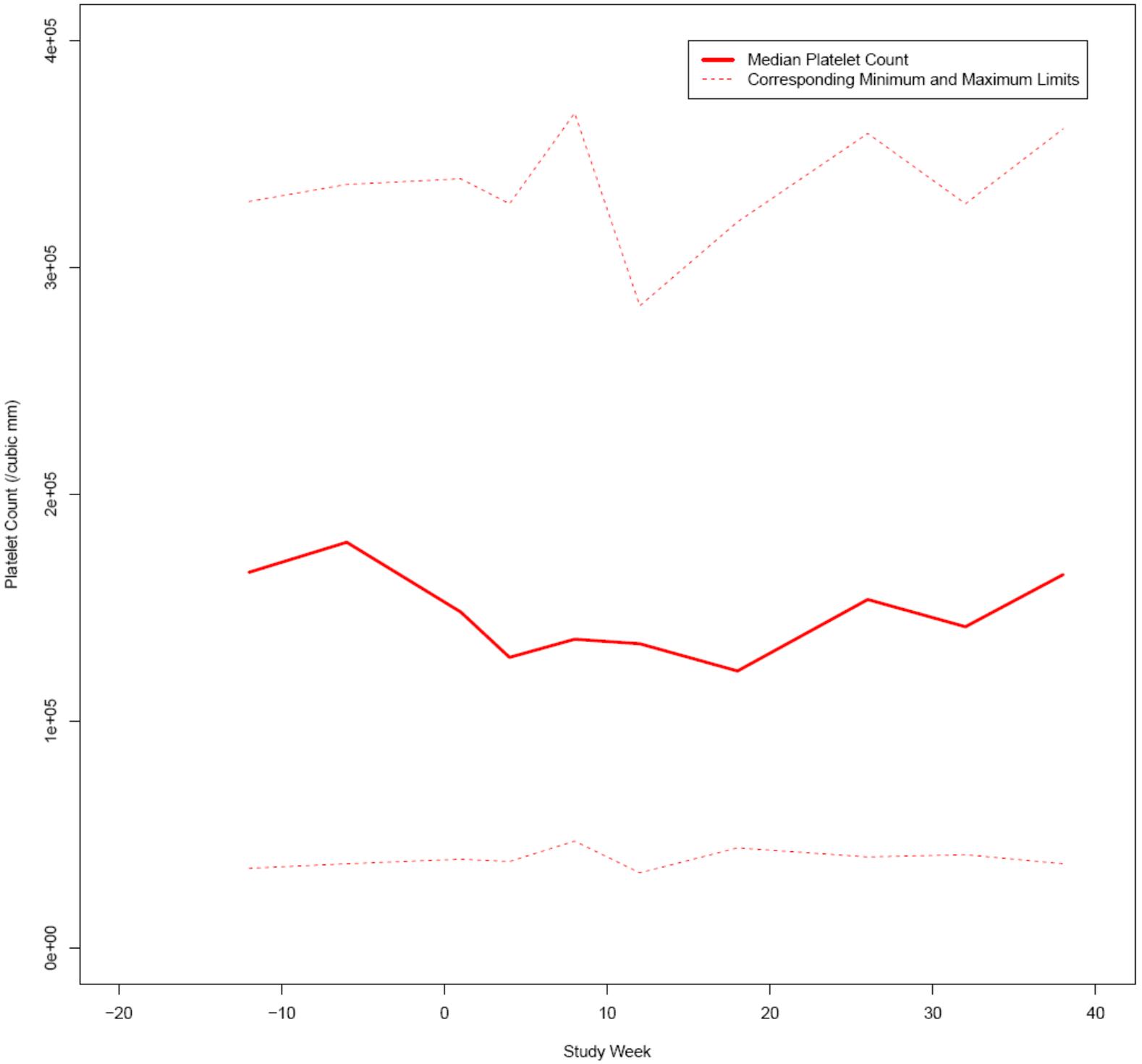
Source: Table 9, 10.2, 10.3 and 10.4 from pgs. 34 and 77-94 of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

[1]: Baseline = Mean of the up to six evaluations during the Stability Evaluation Period along with the Screening evaluation.

Figure 2
(All Enrolled)

Median Platelet Count By Study Week



Source: Reviewer's Figure.

Reviewer Comments:

The interim results from the PB-06-002 study appear to show stability over the efficacy parameters of interest (i.e. spleen volume, hemoglobin concentration, liver volume, and platelet count) for the enrolled cohort. This suggests that patients who had previously been receiving CERZYME can retain/maintain their desired clinically effective response when switching over to ELELYSO treatment; however this judgment should be based on the clinical review. From a statistical standpoint, the data are descriptive in nature and, although exploratory, appear to be supportive of efficacy based on the open-label switchover design utilized by the sponsor. However, this study could have been designed as a double-blind randomized withdrawal or double-blind randomized add-on study which would have resulted in much more useful and supportive efficacy data. Please see the clinical review for details.

3.3 Study PB-06-003 - Reflects new data accumulated since original NDA submission

3.3.1 Background and Analysis Information

The objective of this multi-center, double-blind, parallel dose-group extension trial is to extend the assessment of the safety and efficacy of ELELYSO in patients with Type 1 Gaucher disease who completed 9 months of treatment in studies PB-06-001 or PB-06-002. In this extension trial, patients receive IV infusion of ELELYSO every two weeks and have the option to receive their infusions at the selected medical center, infusion center, or at home. The total duration of treatment will be at least 15 months (64 weeks) and no more than 30 months (128 weeks). Day 1 of this study is the final visit of Study PB-06-001 or the final visit of PB-06-002.

There are three treatment groups in this study, with patients continuing to receive the allocated dose from PB-06-001 in a blinded fashion or the same dose received at the completion of PB-06-002 in an open-label fashion.

Treatment Group 1: 30 units/kg from study PB-06-001

Treatment Group 2: 60 units/kg from study PB-06-001

Treatment Group 3: the same ELELYSO dose received at the completion of PB-06-002

Up to 60 patients from 15 study sites in 12 countries are planned to be enrolled into this study. When the last datacut was made on May 1, 2011, 44 patients from 15 study sites were enrolled with 26 patients (12 from the 30 units/kg dose group and 14 from the 60 units/kg dose group) from the pivotal dose-comparison study, PB-06-001, and 18 patients from the switch-over study, PB-06-002. Consequently the CSR submitted within this NDA is still an abbreviated one based on interim data from this ongoing study.

Efficacy is determined through clinical judgment by evaluation of the following parameters.

- Percentage change from Baseline in Spleen Volume at all timepoints
- Change from Baseline in Hemoglobin Concentration at all timepoints
- Percentage change from Baseline in Liver Volume at all timepoints
- Change from Baseline in Platelet Count at all timepoints

Descriptive statistics are subsequently utilized with no inferences made from formal statistical methodology. In this analysis, for patients rolling over from the PB-06-001 study, the screening visit value from PB-06-001 represents the baseline measure for their spleen and liver volumes while the study day 1 visit value from PB-06-001 represents the baseline measure for their hemoglobin concentration and platelet count. For patients rolling over from the PB-06-002 study, the study day 1 visit value from PB-06-002 represents the baseline measure for their spleen and liver volumes while the mean of the up to six evaluations during the Stability Evaluation Period along with the Screening evaluation from PB-06-002 represents the baseline measure for their hemoglobin concentration and platelet count.

This interim analysis, which is the basis of the submitted abbreviated CSR, is performed on cleaned data as of May 1, 2011. The study population used for the results of interest presented within the abbreviated CSR (i.e. “Interim Population”) is defined as all enrolled subjects who received treatment with ELELYSO on or before May 1, 2011. The data used for the summary tables will be the records collected on or before the date of May 1, 2011. The image evaluation plan for determining spleen and liver volumes is the same as what was described in section 3.1.4 within the statistical review document from the previous review cycle.

The individual analysis of the said parameters is primarily driven by descriptive statistics and a relevant corresponding figure. Specifically for each parameter, two separate tables of descriptive statistics will be presented along with a corresponding figure which presents two separate data plots. The first table displays descriptive statistics for the measured value of the parameter of interest (i.e. spleen volume, hemoglobin concentration, liver volume, or platelet count) at pivotal study weeks starting from Week 1 of study PB-06-001/PB-06-002. The second table displays descriptive statistics for the percentage change (or change) from baseline in the parameter of interest at pivotal PB-06-001/PB-06-002 post-baseline study weeks which lead into the PB-06-003 study weeks. The following figure corresponding to these two tables first presents the sample median of the measured value for the parameter of interest by dose/study group across all treatment experienced study weeks starting from Week 1 of PB-06-001/PB-06-002 along with corresponding minimum and maximum limits. This figure then presents the sample median for the percentage change (or change) from baseline in the parameter of interest by dose/study group across all PB-06-001/PB-06-002 post-baseline study weeks which lead into the PB-06-003 study weeks along with corresponding minimum and maximum limits. These descriptive and non-parametric statistics were chosen to be reflected within the figures because they are most optimal in this exploratory small sample setting. Each

figure will have a vertical line at Week 38 separating the PB-06-001/PB-06-002 and PB-06-003 data.

It is to be noted that the spleen and liver volume data was presented only up to 24 months/104 weeks of exposure (which is Month 15 of the PB-06-003 study) due to sparse exposure after Month 24 in that there were only 2 patients who had more than 24 months of exposure (i.e. 36 months) at the time of last datacut. In addition, the hemoglobin concentration and platelet count data was presented only up to 27 months/116 weeks of exposure (which is Month 18 of the PB-06-003 trial) due to sparse exposure after Month 27 in that there were only 9 patients, all originally from the PB-06-001 study, who had more than 27 months of exposure at the time of last datacut (4 30 units/kg patients and 5 60 units/kg patients).

Note also that no spleen volume data existed for patients 15-223 (screening number 15S203), 15-225 (screening number 15S205), and 22-226 (screening number 22S201), and no liver volume data existed for patients 15-225 (screening number 15S205) and 22-226 (screening number 22S201). It was also assumed that patient 23-204's (screening number 23S201) post-baseline spleen and liver volume assessment was indeed taken at Month 3 (i.e. at Month 12 overall).

3.3.2 Disposition and Demographics/Baseline Information

The disposition information for all study patients in the interim population is presented in Table 8 below.

Table 8
Disposition
(Interim Population)

	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Still Ongoing	11 (91.7%)	10 (71.4%)	16 (88.9%)	37 (84.1%)
Discontinued the Study	0	2 (14.3%)	2 (11.1%)	4 (9.1%)
Completed the Study	1 (8.3%)	2 (14.3%)	0	3 (6.8%)

Source: Reviewer's Table.

Note: Denominators for percentages are N, the number of patients in each treatment group or overall.

The demographics and baseline characteristics for all study patients in the interim population are presented in Table 9 below.

Table 9
Demographics and Baseline Characteristics
(Interim Population)

	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Age (years) at Informed Consent				
n	12	14	18	44
Mean (SD)	38.9 (12.10)	35.6 (12.00)	45.4 (13.50)	40.5 (13.10)
Median	35.0	33.0	46.5	39.5
Min, Max	24, 74	19, 58	18, 66	18, 74
Gender – n (%)				
Female	5 (41.7%)	6 (42.9%)	9 (50.0%)	20 (45.5%)
Male	7 (58.3%)	8 (57.1%)	9 (50.0%)	24 (54.5%)
Religion – n (%)				
Jewish - Ashkenazi	4 (33.3%)	2 (14.3%)	11 (61.1%)	17 (38.6%)
Jewish – Non-Ashkenazi	0	0	0	0
Non-Jewish	8 (66.7%)	12 (85.7%)	7 (38.9%)	27 (61.4%)
Race – n (%)				
Caucasian	12 (100.0%)	13 (92.9%)	18 (100.0%)	43 (97.7%)
African American	0	0	0	0
Native American	0	0	0	0
Asian/Pacific Islander	0	0	0	0
Other	0	1 (7.1%)	0	1 (2.3%)
Weight (kg)				
n	12	14	18	44
Mean (SD)	73.4 (12.95)	72.4 (9.00)	75.7 (14.33)	74.0 (12.27)
Median	76.0	71.4	73.4	75.0
Min, Max	53, 99	60, 88	53, 109	53, 109
Average of All Dose Infusions (units/kg)				
n	12	14	18	44
Mean (SD)	34.1 (2.70)	64.9 (3.30)	31.9 (17.40)	43.0 (18.80)
Median	33.7	63.6	28.7	36.6
Min, Max	31, 40	61, 70	12, 60	12, 70

Source: Reviewer along with Tables A and B from pgs. 71-72 of the PB-06-003 Abbreviated CSR.

Note: Denominators for percentages are N, the number of patients in each treatment group or overall.

3.3.3 Analysis Tables and Figures for Efficacy Parameters

3.3.3.1 Spleen Volume

Table 10
Spleen Volume by Pivotal Study Week
(Interim Population)

Spleen Volume (mL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	15	41
Mean (SD)	2324.0 (1208.97)	2120.1 (1426.5)	778.0 (666.3)	1688.8 (1309.92)
Median	1656.9	1699.5	548.7	1481.5
Min, Max	1026, 4901	914, 5418	14, 2151	14, 5418
Study Week 38/9-Month[2]				
n	12	14	15	41
Mean (SD)	1690.7 (956.43)	1352.0 (1096.81)	706.7 (608.85)	1215.1 (971.40)
Median	1226.1	1044.6	518.6	989.5
Min, Max	754, 3894	483, 4220	15, 2141	15, 4220
Study Week 52/12-Month				
n	12	14	8	34
Mean (SD)	1707.7 (1069.53)	1267.9 (1114.05)	807.3 (736.1)	1314.8 (1051.02)
Median	1135.2	937.1	685.6	947.3
Min, Max	693, 4332	442, 4339	14, 2178	14, 4339
Study Week 104/24-Month				
n	12	14	1	27
Mean (SD)	1420.4 (852.33)	946.7 (699.6)	2037.5 (0)	1197.7 (797.5)
Median	1054.9	721.4	2037.5	926.0
Min, Max	503, 3317	368, 3013	2037.5, 2037.5	368, 3317

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.

[2]: This is Study Day 1 of the PB-06-003 study.

Table 11
Percentage Change from Screening/Baseline in Spleen Volume by Pivotal Study
Week

(Interim Population)

Percentage Change (%)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
n	12	14	15	41
Mean (SD)	-27.9 (7.79)	-39.3 (8.75)	-7.5 (13.09)	-24.3 (17.02)
Median	-27.9	-38.2	-8.2	-27.9
Min, Max	-43, -16	-56, -20	-28, 22	-56, 22
Baseline[1] to Study Week 52/12-Month				
n	12	14	8	34
Mean (SD)	-28.9 (8.17)	-43.5 (11.39)	-11.1 (11.56)	-30.7 (16.31)
Median	-28.7	-43.4	-9.6	-31.3
Min, Max	-44, -12	-64, -17	-28, 4	-64, 4
Baseline[1] to Study Week 104/24-Month				
n	12	14	1[3]	27
Mean (SD)	-40.5 (9.61)	-54.9 (12.79)	. (.)	-46.7 (15.51)
Median	-37.5	-56.3	.	-46.8
Min, Max	-58, -28	-75, -30	., .	-75, -5

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.

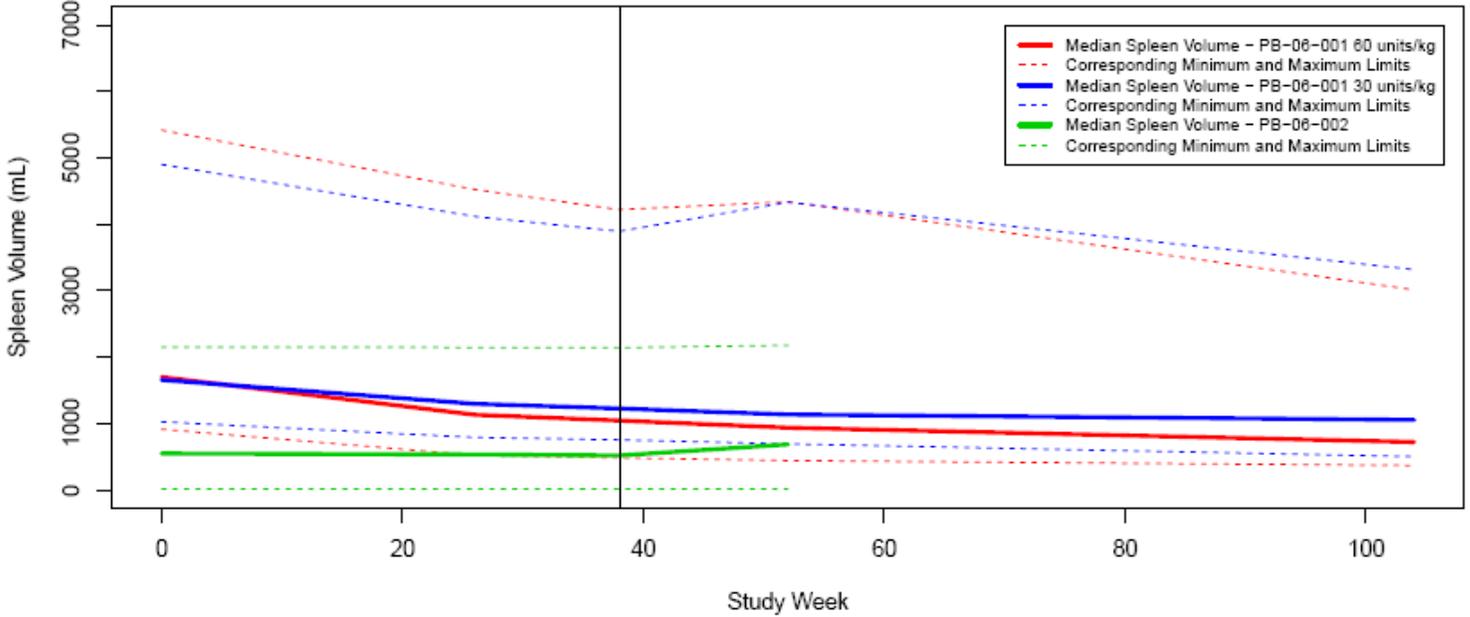
[2]: This is Study Day 1 of the PB-06-003 study.

[3]: No statistics were displayed due to there being only one patient with exposure at 24 months.

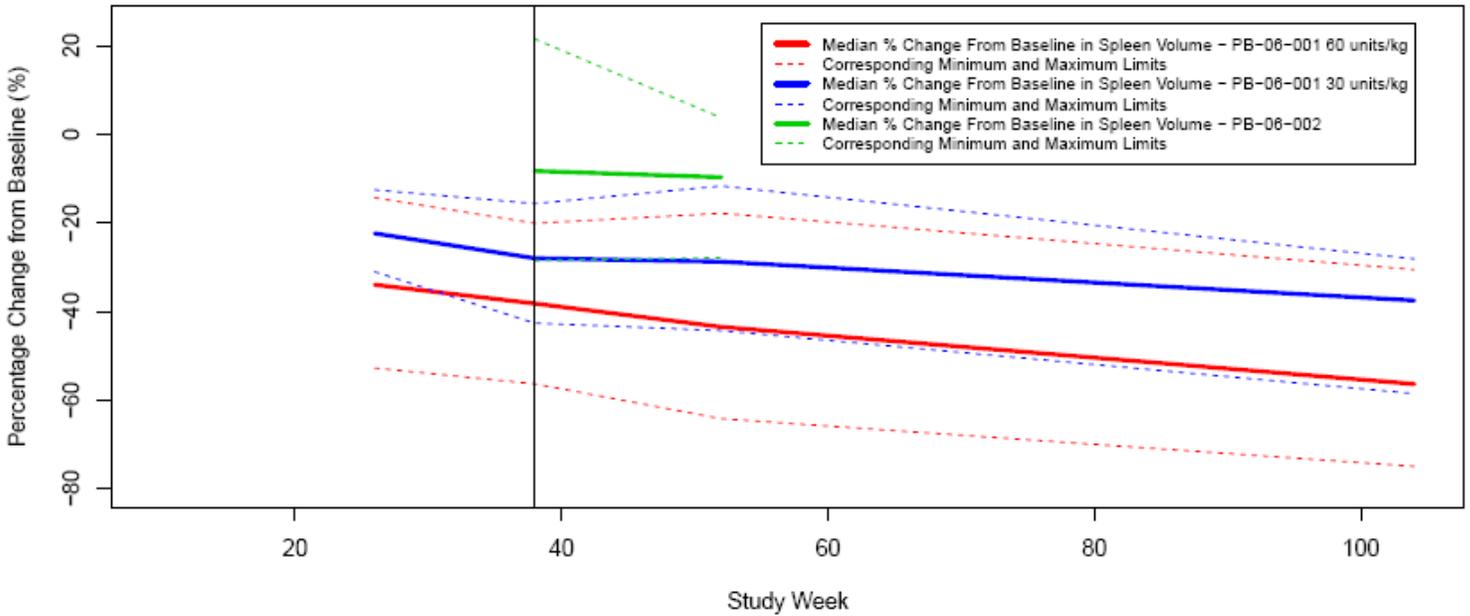
**Figure 3
(Interim Population)**

PB-06-003: SPLEEN VOLUME - Vertical Line at Week 38 Separating PB-06-001/PB-06-002 and PB-06-003 Data

Spleen Volume By Study Week



Percentage Change from Baseline in Spleen Volume By Study Week



Source: Reviewer's Figure.

3.3.3.2 Hemoglobin Concentration

Table 12
Hemoglobin Concentration by Pivotal Study Week
(Interim Population)

Hemoglobin Concentration (g/dL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	18	44
Mean (SD)	12.49 (1.822)	11.39 (2.746)	13.64 (1.600)	12.61 (2.252)
Median	12.95	10.60	13.67	13.10
Min, Max	7.9, 14.6	5.5, 16.0	10.7, 16.1	5.5, 16.1
Study Week 38/9-Month[2]				
n	12	14	18	44
Mean (SD)	14.22 (1.408)	13.63 (2.057)	13.42 (1.674)	13.70 (1.733)
Median	13.80	14.25	13.75	13.90
Min, Max	12.2, 16.9	8.6, 16.5	10.3, 15.7	8.6, 16.9
Study Week 52/12-Month				
n	12	14	12	38
Mean (SD)	14.21 (1.687)	13.63 (2.560)	13.63 (1.705)	13.81 (2.022)
Median	14.00	13.80	13.50	13.70
Min, Max	11.3, 17.4	7.3, 17.1	10.0, 16.6	7.3, 17.4
Study Week 104/24-Month				
n	11	14	0	25
Mean (SD)	13.75 (1.595)	13.78 (1.840)	. (.)	13.77 (1.701)
Median	14.00	13.70	.	13.90
Min, Max	10.9, 17.2	11.3, 17.6	..	10.9, 17.6

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.

[2]: This is Study Day 1 of the PB-06-003 study.

Table 13
Change from Baseline in Hemoglobin Concentration by Pivotal Study Week
(Interim Population)

Hemoglobin Concentration (g/dL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
N	12	14	18	44
Mean (SD)	1.73 (1.494)	2.24 (1.474)	-0.23 (0.613)	-1.09 (1.63)
Median	1.60	1.75	-0.13	0.71
Min, Max	-0.1, 5.8	0.5, 5.1	-1.3, 0.7	-1.3, 5.8
Baseline[1] to Study Week 52/12-Month				
N	12	14	12	38
Mean (SD)	1.72 (1.135)	2.24 (1.472)	0.01 (0.733)	1.37 (1.493)
Median	1.60	1.85	-0.05	1.15
Min, Max	0.0, 4.1	0.9, 6.2	-1.2, 1.3	-1.2, 6.2
Baseline[1] to Study Week 104/24-Month				
N	11	14	0	25
Mean (SD)	1.30 (1.723)	2.39 (2.312)	. (.)	1.91 (2.106)
Median	1.20	1.60	.	1.30
Min, Max	-1.2, 5.0	-1.5, 7.3	., .	-1.5, 7.3

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

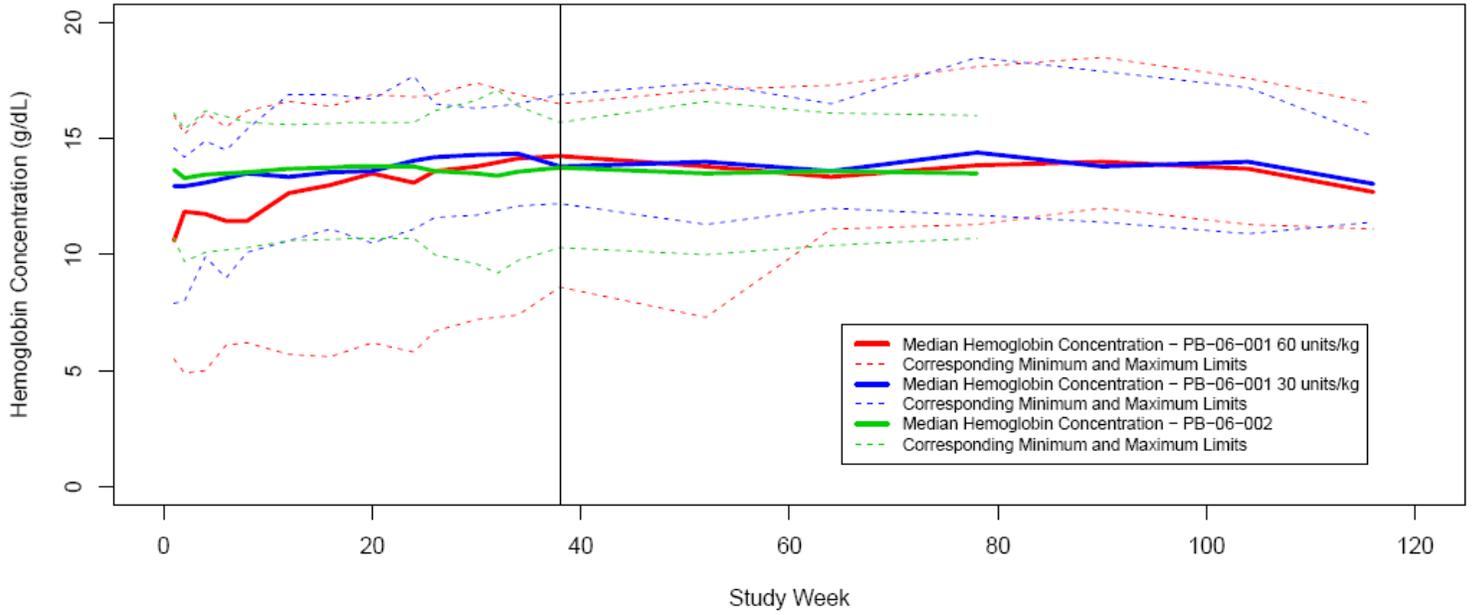
[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.

[2]: This is Study Day 1 of the PB-06-003 study.

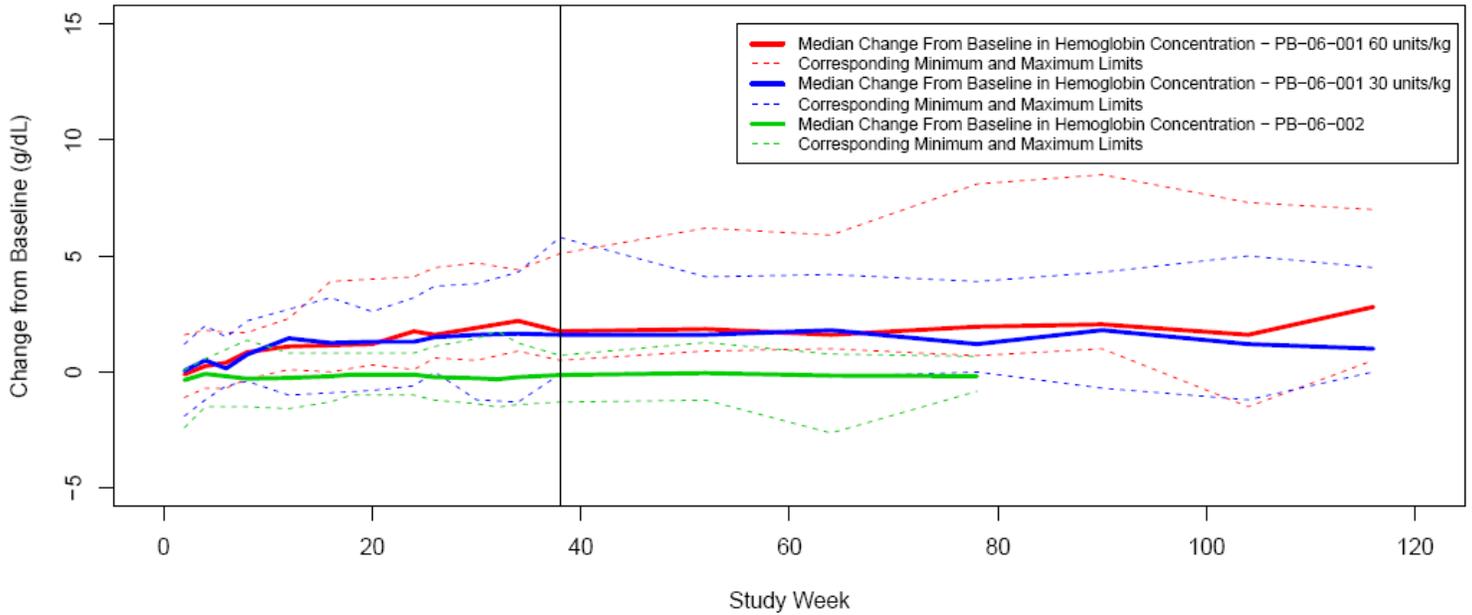
**Figure 4
(Interim Population)**

PB-06-003: HEMOGLOBIN CONCENTRATION - Verticle Line at Week 38 Separating PB-06-001/PB-06-002 and PB-06-003 Data

Hemoglobin Concentration By Study Week



Change from Baseline in Hemoglobin Concentration By Study Week



Source: Reviewer's Figure.

3.3.3.3 Liver Volume

Table 14
Liver Volume by Pivotal Study Week
(Interim Population)

Liver Volume (mL)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	16	42
Mean (SD)	2999.7 (779.45)	2470.5 (484.9)	1775.7 (434.39)	2357.0 (750.83)
Median	2794.3	2440.1	1625.0	2327.7
Min, Max	2282, 5096	1758, 3297	1167, 2643	1167, 5096
Study Week 38/9-Month[2]				
n	12	14	16	42
Mean (SD)	2584.5 (577.8)	2189.5 (390.87)	1737.3 (440.13)	2130.1 (575.11)
Median	2473.2	2094.7	1575.3	2094.7
Min, Max	2000, 4122	1654, 2894	1276, 2604	1276, 4122
Study Week 52/12-Month				
n	12	14	9	35
Mean (SD)	2515.6 (642.08)	2118.7 (318.09)	1718.7 (411.56)	2151.9 (555.62)
Median	2461.7	2157.1	1582.7	2097.0
Min, Max	1944, 4255	1678, 2600	1157, 2544	1157, 4255
Study Week 104/24-Month				
n	12	14	1	27
Mean (SD)	2362.8 (518.68)	1998.2 (291.88)	1532.3 (0)	2143.0 (452.03)
Median	2321.8	2040.6	1532.3	2119.4
Min, Max	1729, 3558	1522, 2430	1532.3, 1532.3	1522, 3558

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.

[2]: This is Study Day 1 of the PB-06-003 study.

Table 15
Percentage Change from Screening/Baseline in Liver Volume by Pivotal Study
Week
(Interim Population)

Percentage Change (%)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
n	12	14	16	42
Mean (SD)	-13.2 (4.96)	-10.8 (6.84)	-1.9 (8.56)	-8.1 (8.56)
Median	-14.1	-12.2	-3.8	-10.0
Min, Max	-19, -3	-22, 2	-11, 22	-22, 22
Baseline[1] to Study Week 52/12-Month				
n	12	14	9	35
Mean (SD)	-15.9 (5.20)	-13.2 (8.89)	-3.8 (5.54)	-11.7 (8.36)
Median	-16.4	-11.3	-2.1	-12.8
Min, Max	-26, -5	-33, -2	-13, 2	-33, 2
Baseline[1] to Study Week 104/24-Month				
n	12	14	1[3]	27
Mean (SD)	-20.6 (6.87)	-17.5 (13.29)	. (.)	-18.6 (10.67)
Median	-18.2	-15.8	.	-17.6
Min, Max	-34, -11	-41, 9	., .	-41, -9

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

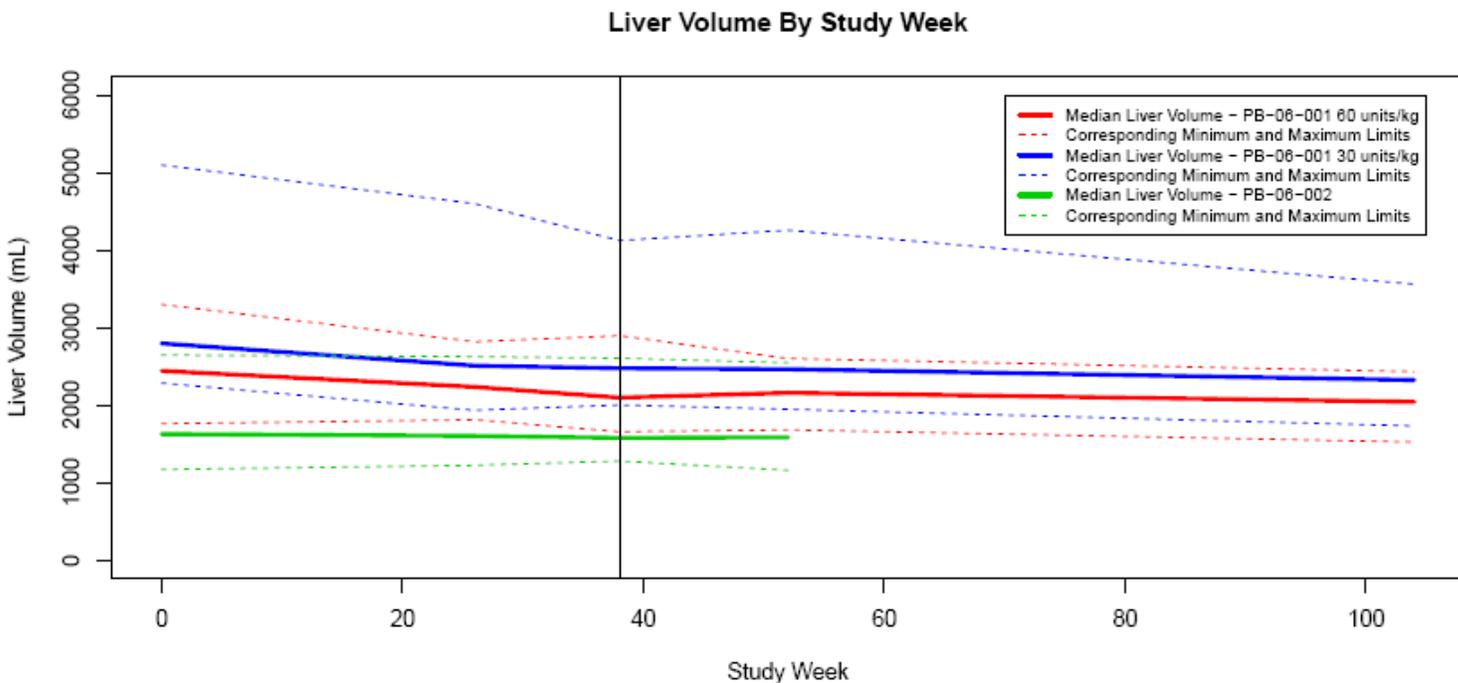
[1]: PB-06-001 patients: Screening visit from PB-06-001 study. PB-06-002 patients: Study Day 1 visit from PB-06-002 study.

[2]: This is Study Day 1 of the PB-06-003 study.

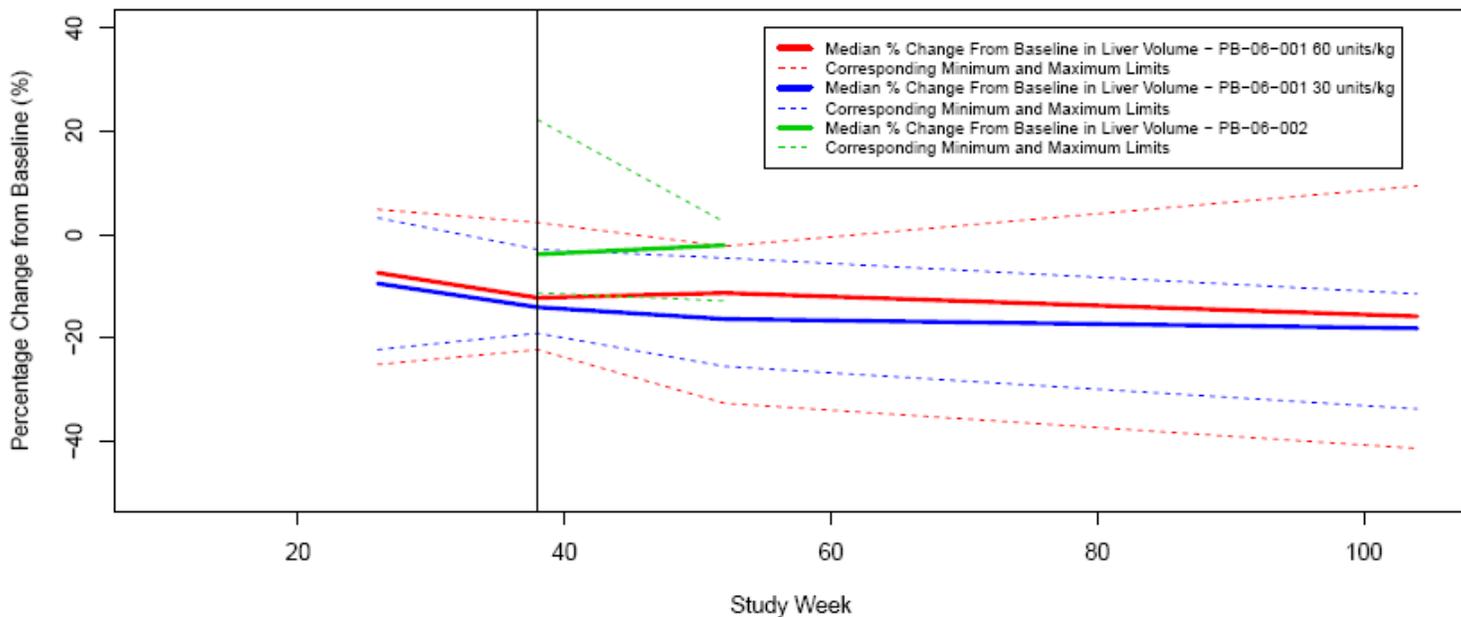
[3]: No statistics were displayed due to there being only one patient with exposure at 24 months.

**Figure 5
(Interim Population)**

PB-06-003: LIVER VOLUME - Verticle Line at Week 38 Separating PB-06-001/PB-06-002 and PB-06-003 Data



Percentage Change from Baseline in Liver Volume By Study Week



Source: Reviewer's Figure.

3.3.3.4 Platelet Count

Table 16
Platelet Count by Pivotal Study Week
(Interim Population)

Platelet Count (/mm ³)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1]				
n	12	14	18	44
Mean (SD)	64900.0 (30132.62)	61471.4 (23257.17)	163722.2 (95953.30)	104236.4 (80896.88)
Median	55000.0	53500.0	138000.0	77000.0
Min, Max	27000, 112000	28000, 103000	39000, 328000	27000, 328000
Study Week 38/9-Month[2]				
n	12	14	18	44
Mean (SD)	75350.0 (45283.52)	112892.9 (53329.23)	165555.6 (97770.57)	124197.7 (81160.76)
Median	66500.0	110500.0	165000.0	108500.0
Min, Max	20000, 166000	25000, 241000	37000, 361000	20000, 361000
Study Week 52/12-Month				
n	12	14	12	38
Mean (SD)	80325.0 (41805.98)	122857.1 (53857.16)	145250.0 (97426.08)	116497.4 (71192.77)
Median	70000.0	137500.0	121500.0	110500.0
Min, Max	23000, 153000	25000, 228000	47000, 352000	23000, 352000
Study Week 104/24-Month				
n	12	14	0	26
Mean (SD)	93333.3 (53327.60)	141071.4 (73896.46)	. (.)	119038.5 (68409.49)
Median	79000.0	141500.0	.	1100500.0
Min, Max	31000, 180000	29000, 271000	..	29000, 271000

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.

[2]: This is Study Day 1 of the PB-06-003 study.

Table 17
Change from Baseline in Platelet Count by Pivotal Study Week
(Interim Population)

Platelet Count (/mm ³)	PB-06-001 30 units/kg (N = 12)	PB-06-001 60 units/kg (N = 14)	PB-06-002 Total (N=18)	Grand Total (N = 44)
Baseline[1] to Study Week 38/9-Month[2]				
n	12	14	18	44
Mean (SD)	10450.0 (22341.67)	43850.0 (49818.51)	1722.2 (32739.02)	17506.8 (40569.87)
Median	7100.0	40500.0	-1833.3	8833.3
Min, Max	-25000, 59000	-15000, 186000	-88500, 56000	-88500, 186000
Baseline[1] to Study Week 52/12-Month				
n	12	14	12	38
Mean (SD)	15425.0 (22003.06)	53814.3 (51270.23)	10888.9 (24473.38)	28136.0 (40545.54)
Median	14450.0	53500.0	9250.0	19750.0
Min, Max	-33000, 42000	-15000, 173000	-21667, 58000	-33000, 173000
Baseline[1] to Study Week 104/24-Month				
n	12	14	0	26
Mean (SD)	28433.3 (31996.43)	72028.6 (68156.69)	. (.)	51907.7 (57941.79)
Median	15350.0	49000.0	.	43200.0
Min, Max	-14000, 87000	-10000, 202000	.,.	-14000, 202000

Source: Reviewer's Table.

Note: Study Weeks presented within this table correspond to those from study PB-06-001/PB-06-002.

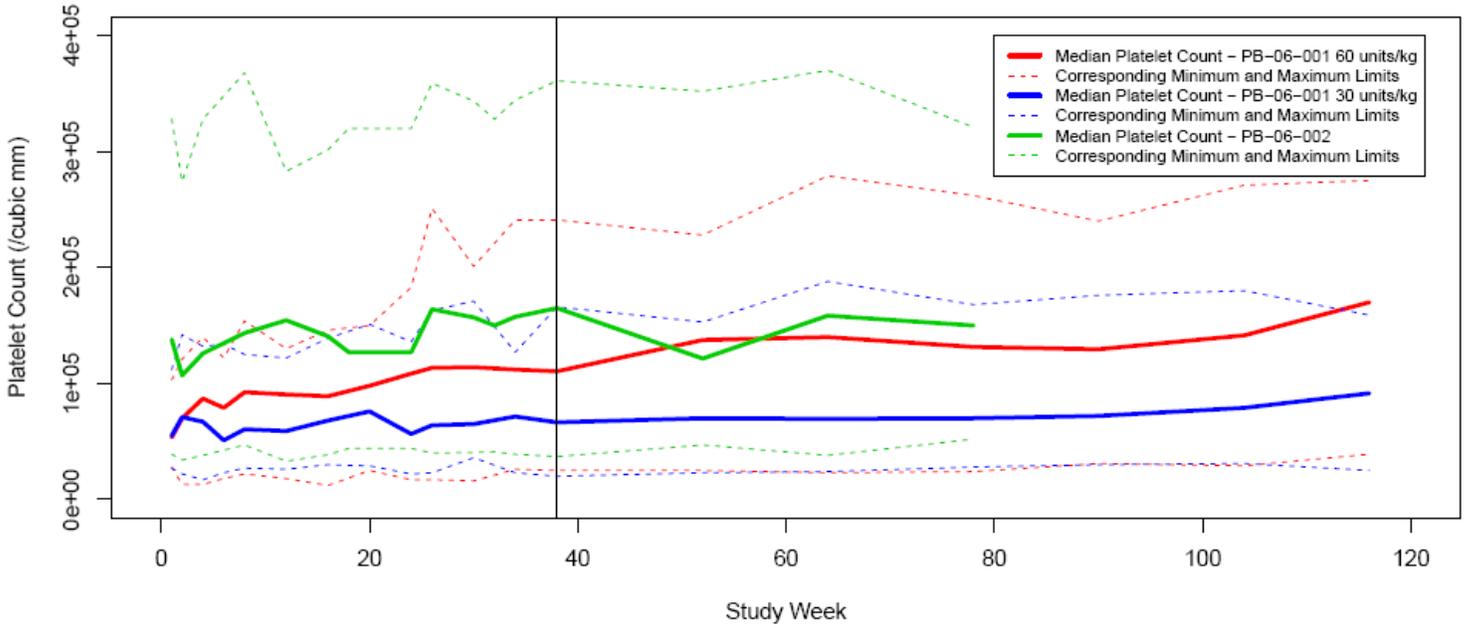
[1]: PB-06-001 patients: Study Day 1 visit from PB-06-001 study. PB-06-002 patients: Mean of up to six stability evaluation visits including the screening day visit from PB-06-002 study.

[2]: This is Study Day 1 of the PB-06-003 study.

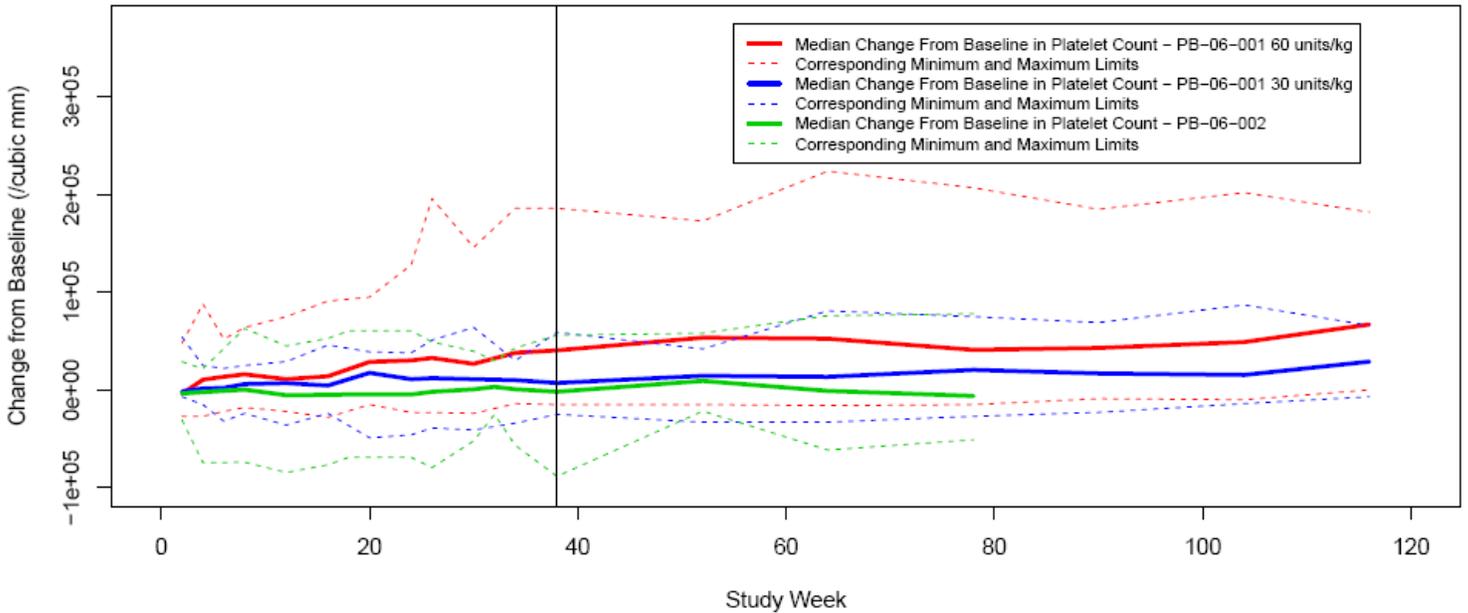
**Figure 6
(Interim Population)**

PB-06-003: PLATELET COUNT – Vertical Line at Week 38 Separating PB-06-001/PB-06-002 and PB-06-003 Data

Platelet Count By Study Week



Change from Baseline in Platelet Count By Study Week



Source: Reviewer's Figure.

Reviewer Comments:

Based on the descriptive statistics and metrics presented in the displayed outputs, it appears that PB-06-001 and PB-06-002 patients treated for at least 24 months/104 weeks continue to do well in this extension study. These results appear to show stability with continued positive response for patients over all of the efficacy parameters of interest (i.e. spleen volume, hemoglobin concentration, liver volume, and platelet count). This suggests that patients with longer term treatment exposure can maintain an effective response. However, longer term follow-up may still be needed (e.g. up to 5 years). Please see the clinical review for further details.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The only subgroup analyses that were administered pertained to the PB-06-001 study which was reviewed during the previous review cycle. See the previous statistical review document.

5.0 SUMMARY AND CONCLUSIONS

The subject of this statistical review pertains to a more in depth analysis of trials PB-06-002 and PB-06-003. These two studies support the lone pivotal trial, PB-06-001, which was reviewed and judged as adequate and well-controlled by the review team during the last review cycle of this NDA. However it was during this last review cycle, where a CR action was ultimately taken by DGP, in which the data submitted for the aforementioned two supportive clinical studies was deemed insufficient by the review team due to lack of adequate patient enrollment at that particular point in time. Although the submitted data for these two studies is still currently at an interim stage, i.e. the studies are still not closed at this time, this data has been deemed sufficient for final review by DGIEP. Consequently this statistical review closes the loop from the last review cycle where the principle component of the overall efficacy assessment was made through the review of trial PB-06-001. This will be the last statistical review of this NDA regardless of division action.

There were no major statistical review issues or deficiencies which could preclude approval encountered throughout the statistical review of this NDA resubmission. Due to the orphan nature of Type I Gaucher Disease, and the limitations of the submitted clinical studies, the determination of the clinical effectiveness of ELELYSO[®] will rely more on clinical judgment than on the statistical rigor usually required for larger controlled studies. The results from the PB-06-002 study appear to show stability in the efficacy parameters of interest (i.e. spleen volume, hemoglobin concentration, liver volume, and platelet count) for the enrolled cohort. This suggests that patients who had previously been receiving CERZYME can retain the response when switching over to ELELYSO treatment. The results from the PB-06-003 study show that PB-06-001 and PB-06-002 patients treated for at least 24 months/104 weeks continue to do well in this extension study. These results appear to show stability with continued positive response for the

PB-06-001 patients and barely, if any, deterioration for the PB-06-002 patients in all of the previously mentioned efficacy parameters of interest. This suggests that these longer term treatment experienced patients can maintain their response.

As communicated during the original review cycle, the statistical review issues for this application continue to concern overall level of evidence and the PB-06-002 study design. These primary statistical review concerns are summarized below. It is to be additionally noted that there are major overall review concerns in regard to manufacturing and immunogenicity which may ultimately preclude application approval.

Level of Evidence

The major statistical issue in this overall NDA review (including the first cycle review) continues to pertain to the level of evidence presented by the sponsor for the effectiveness of ELEYSO.

VPRIV was the latest Type 1 Gaucher Disease treatment approved by the FDA on February 26, 2010, and the main components of its clinical development program, excluding extension studies, consisted of four clinical trials: TKT032 (an analogous study to PB-06-001 with similar results); HGT-GCB-039 (a ‘head-to-head’ non-inferiority study between VPRIV and CERESYME); TKT034 (an analogous study to PB-06-002 with similar results); and TKT025 (a dose escalation Phase 1 study). The primary basis for the efficacy claim ultimately reflected in the approved product label for VPRIV was the joint positive results from the TKT032 and HGT-GCB-039 studies respectively. Protalix Biotherapeutics, Ltd., however, did not include a ‘head-to-head’ study between ELEYSO and the previously approved FDA treatments for Type 1 Gaucher Disease (i.e. CERESYME or VPRIV). The absence of an active control study within the development program of ELEYSO lowers the level of evidence compared to that previously demonstrated for VPRIV. However, due to the current product shortage issues which persist with CERESYME, a request for an additional request for a pre-market adequate and well-controlled study is deemed burdensome. Further long term data (e.g. up to 5 years of total exposure) from the PB-06-003 study could suffice and be obtained by DGIEP via a post-marketing requirement.

PB-06-002 Study Design

The efficacy results from study PB-06-002 are marginally supportive at best due to the open-label switchover design utilized by the sponsor. This study could have been designed as a double-blind randomized withdrawal or double-blind randomized add-on study which would have resulted in much more useful and supportive efficacy data. Nonetheless, from a clinical standpoint, the supportive data generated from this study may be sufficient. Please see the clinical review document for details.

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/s/

BEHRANG VALI
03/02/2012

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03/05/2012
concur with review



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/ Supporting Document Number: 22-458/0002, 0003, 0010, 0011, 0012

Drug Name: ELELYSO™ [taliglucerase alpha – plant cell expressed recombinant human glucocerebrosidase (prGCD)] 60 units/kg (b) (4) delivered by Intravenous (IV) Infusion every Two Weeks

Indication(s): Treatment of Type I Gaucher Disease

Applicant: Protalix Biotherapeutics, Ltd.

Date(s): Stamp Date: April 26, 2010
PDUFA Goal date: February 25, 2011

Submission Type: Type 1 NDA; 505(b)(1)

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1.0 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Due to the orphan nature of Type I Gaucher Disease, and the limitations of the submitted clinical studies, the determination of the clinical effectiveness of ELELYSO[®] will rely more on clinical judgment than on statistical rigor usually required for larger studies. The efficacy results from all three clinical studies within the ELELYSO development program were positive in that they each showed a clinically meaningful change from baseline, based primarily on clinical judgment with supportive statistical methodology, in the endpoints of interest (i.e. spleen volume, hemoglobin concentration, liver volume, and platelet count). This was principally established in study PB-06-001 with additional marginal support from studies PB-06-002 and PB-06-003. Although Type 1 Gaucher Disease is a rare and potentially serious and life threatening condition, the application deficiencies described below motivate a statistical recommendation that the sponsor conduct at least one additional adequate and well-controlled study in order to obtain regulatory approval.

This additional trial should be a randomized, controlled, and properly powered ‘head-to-head’ study which compares ELELYSO with at least one of the currently marketed treatments for Type 1 Gaucher Disease (i.e. CEREZYME[®] or VPRIV[®] or both individually in a three arm trial). This study should recruit patients which are representative of the true Type 1 Gaucher Disease patient population and be of high quality with subsequent compelling and positive results pertaining to the risk/benefit profile of this original biologic. In addition, final CSRs for studies PB-06-002 and PB-06-003 should be submitted with proper identification of ELELYSO dose for patients who participated in the PB-06-002 study. Finalized clinical datasets along with corresponding analysis datasets (with appropriate metadata for each) should also be submitted for both the PB-06-002 and PB-06-003 studies.

1.2 Brief Overview of Clinical Studies

ELELYSO[®] has been studied by Protalix Ltd. for the treatment of Type I Gaucher Disease, and its clinical efficacy and safety has been principally evaluated through three studies: a Phase 3, multicenter, randomized, double-blind, and parallel dose-group study (PB-06-001) which serves as the sponsor’s only adequate and well controlled study for this clinical development program; a Phase 3, multicenter, open-label, switchover study (PB-06-002); and a Phase 3, multicenter, double-blind, parallel dose-group study (PB-06-003) which is a long term extension study of patients from trials PB-06-001 and PB-06-002.

1.3 Statistical Issues and Findings

There were a few, yet significant, deficiencies encountered throughout the statistical review of NDA 22-458. The principal review concerns are summarized below.

Manufacturing

Overall, the primary issue in this NDA review pertained to manufacturing. There were a number of major issues regarding comparability and overall manufacturing quality as determined by the review team from the Division of Therapeutic Proteins (DTP). The consequence of these deficiencies is that the trials presented previously in Section 1.2 can not support the safety and efficacy profile of this biologic product. These specific issues are beyond the scope of this review hence refer to the review document provided by DTP for details.

Level of Evidence

The major statistical issue in this NDA review pertained to the level of evidence presented by the sponsor for the effectiveness of ELEYSO. The development program for this original biologic was ultimately determined by the statistical reviewer as being incomplete.

VPRIV was the latest Type 1 Gaucher Disease treatment approved by the FDA on February 26, 2010, and the main components of its clinical development program, excluding extension studies, consisted of four clinical trials: TKT032 (an analogous study to PB-06-001 with similar results); HGT-GCB-039 (a ‘head-to-head’ non-inferiority study between VPRIV and CERESYME); TKT034 (an analogous study to PB-06-002 with similar results); and TKT025 (a dose escalation Phase 1 study). The primary basis for the efficacy claim ultimately reflected in the approved product label for VPRIV was the joint positive results from the TKT032 and HGT-GCB-039 studies respectively. Protalix Biotherapeutics, Ltd., however, did not include a ‘head-to-head’ study between ELEYSO and the previously approved FDA treatments for Type 1 Gaucher Disease (i.e. CERESYME or VPRIV). The absence an active control study within the development program of ELELYSO lowers the level of evidence compared to that previously demonstrated for VPRIV.

In addition, both PB-06-002 and PB-06-003 were unfinished studies at the time of this NDA submission (April 26, 2010) hence the sponsor only presented interim results within abbreviated CSRs for each study and did not identifying the specific ELELYSO doses for patients who participated in the PB-06-002 trial. The clinical datasets for both the PB-06-002 and PB-06-003 studies were also not submitted by the sponsor (only the analysis datasets were submitted).

PB-06-001 Study Design

This study design is more observational in nature. The use of a within-dose comparison (formally assessed by a one sample *t*-test) is not traditionally an acceptable approach for establishing efficacy. Inferential results (e.g. *p*-values) from this within-group comparison are not statistically valid, therefore have no basis regarding any efficacy claim and thus should not be emphasized. Nonetheless, the change from baseline in each endpoint was determined, by clinical judgment, to be clinically meaningful.

PB-06-001 Patient Population

It was determined by the clinical review team that the patient population studied within the PB-06-001 trial was a relative healthy one which ultimately compromises the interpretability of the study results pertaining to safety. This specific issue is beyond the scope of this review hence refer to the review document provided by the clinical review team for details.

PB-06-002 Study Design

The efficacy results from study PB-06-002 are marginally supportive at best due to the open-label switchover design utilized by the sponsor. This study could have been designed as a double-blind randomized withdrawal or double-blind randomized add-on study which would have resulted in much more useful and supportive efficacy data.

2.0 INTRODUCTION

2.1 Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations, Protalix Ltd. has submitted this New Drug Application (NDA) for ELELYSO™ [taliglucerase alfa - plant cell expressed recombinant human glucocerebrosidase (prGCD)]. The active ingredient in ELELYSO (delivery by intravenous (IV) infusion every two weeks) is taliglucerase alfa. This is the first prescription product to have taliglucerase alfa as its active ingredient. ELELYSO has undergone clinical development under IND 69,703 in patients with Type 1 (i.e. non-neurological) Gaucher Disease, and has been developed specifically to establish safety and efficacy in this patient population. Currently, there are effective FDA-approved treatment options for patients with Type 1 Gaucher disease (i.e. CERZYME® and VPRIV®); however, due to product shortages caused by manufacturing issues, this serious and life threatening condition still remains as one with an unmet medical need.

Protalix Ltd. obtained Fast Track designation from the Agency on August 24, 2009, and the final component of their rolling submission (which officially starts the PDUFA clock) was delivered on April 26, 2010. The review timeline established by the Division of Gastroenterology Products (DGP) was a standard 10 month cycle. The application also qualified for Orphan Exception under section 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act. Protalix Ltd. ultimately obtained *Orphan Designation* from the Office of Orphan Products Development (OOPD) on September 3, 2010.

2.2 Brief Overview and Summary of Relevant Trials

ELELYSO® has been studied by Protalix Ltd. for the treatment of Type I Gaucher Disease, and its clinical efficacy and safety has been principally evaluated through three studies: a Phase 3, multicenter, randomized, double-blind, and parallel dose-group study (PB-06-001) which serves as the sponsor's only adequate and well controlled study for

this clinical development program; a Phase 3, multicenter, open-label, switchover study (PB-06-002); and a Phase 3, multicenter, double-blind, parallel dose-group study (PB-06-003) which is a long term extension study of patients from trials PB-06-001 and PB-06-002.

Table 1 below presents information on the three relevant trials contained in the submission.

Table 1
Summary Information for Relevant Trials

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety; Phase 3	PB-06-001	To assess the safety and efficacy of taliglucerase alfa in treatment naive patients	Multicenter, randomized, double-blind, parallel dose-group	taliglucerase alpha 60 units/kg and 30 units/kg; every two weeks; IV infusion	60 units/kg: 16 30 units/kg: 16 Total: 32	Patients with Type I Gaucher Disease	38 weeks	Complete; Full
Efficacy and Safety; Phase 3	PB-06-002	To assess the safety and efficacy of taliglucerase alfa in patients previously treated with Imiglucerase (CEREZYME®)	Multicenter, open-label, switchover	taliglucerase alpha equivalent to Imiglucerase dose; every two weeks; IV infusion	Total: 24	Patients with Type I Gaucher Disease	38 weeks	Ongoing; Abbreviated
Efficacy and Safety; Phase 3	PB-06-003	To extend the assessment of the safety and efficacy of taliglucerase alpha in PB-06-001 and PB-06-002 patients who completed 9 months of treatment	Multicenter, double-blind, parallel dose-group, extension	taliglucerase alpha 60 units/kg and 30 units/kg (PB-06-001 patients), and dose equivalent to Imiglucerase dose (PB-06-002 patients); every two weeks; IV infusion	60 units/kg: 14 30 units/kg: 12 PB-06-002 dose: 3 Total: 29	Patients with Type I Gaucher Disease	64 weeks	Ongoing; Abbreviated

Source: Reviewer's Table.

2.3 Data Sources

This NDA was submitted electronically in eCTD format. The submission was sent via the FDA Electronic Submissions Gateway (ESG) and its content along with the electronic data sets and labeling information have been stored in the electronic document room (EDR) at this path location: <\\Cdsesub1\evsprod\NDA022458>. The submission can consequently be accessed directly at the previous path specified.

3.0 STATISTICAL EVALUATION

3.1 PB-06-001

3.1.1 Background Information

The objective of this study was to assess the safety and efficacy of ELELYSO in treatment naïve patients with significant signs and symptoms of Type 1 Gaucher disease. This was a multi-center, randomized, double-blind, parallel dose-group trial in 33 untreated patients with Type 1 Gaucher disease. Patients received IV infusion of ELELYSO (Treatment Group 1: 30 units/kg; Treatment Group 2: 60 units/kg) every two weeks at selected medical centers. The duration of treatment was nine months, and at the end of the 9-month treatment period (21 visits spanning 38 weeks), eligible patients were offered enrollment in an open-label extension study (PB-06-003). There were 11 participating study centers from 9 countries with date of first enrolled patient on August 5, 2007 and date of last completed patient on September 11, 2009. A simple 1:1 and non-stratified (i.e. centralized) randomization was instituted for this trial utilizing blocks of size four.

3.1.2 Key Study Endpoints

The primary and key secondary endpoints are as follows.

- **Primary Endpoint**
 - Percentage change from baseline in Spleen Volume measured by MRI at 9 months/38 weeks

- **Secondary Endpoints**
 - Change from baseline in Hemoglobin Concentration at 9 months/38 weeks
 - Percentage change from baseline in Liver Volume measured by MRI at 9 months/38 weeks
 - Change from baseline in Platelet Count at 9 months/38 weeks

3.1.3 Sample Size and Power

This orphan indication allows for a small number of patients, given the rarity of the disease and the difficulties in allocating patients for clinical trials. With 12 patients in each ELELYSO treatment group enrolled (i.e. 30 units/kg and 60 units/kg), there is greater than 95% power to detect a percentage change from baseline in spleen volume after nine months of treatment of 20% or more utilizing a one-sample two-sided t-test at $\alpha = 0.025$ (thereby allowing for each treatment group to be tested separately). This calculation is based on the assumption that the standard deviation for the percent change from baseline in spleen volume is 12%. For this analysis the null hypothesis is that the percent change from baseline in spleen volume is 0 versus the alternative hypothesis that the percent change from baseline in spleen volume is not 0. Based on previous research,

a normal spleen volume is expected to be approximately 0.12 L, and thus the patients in this protocol are expected to have spleen volumes that are 8 times this size (i.e. approximately 0.96 L). Consequently, a 20% reduction in spleen volume is anticipated to be equivalent to a 0.192 L reduction. Since it is anticipated that some patients may not be available for any follow-up assessments (i.e., drop out from the study prior to the 9-month study visit), 15 patients will be enrolled for each treatment group in order to ensure that at least 12 patients will have measurements made from all protocol defined assessments at 9 months.

3.1.4 Image Evaluation Plan

The following MRI parameters will be evaluated during this trial:

- Spleen Volume in cm³ (which is equivalent to mL)
- Liver Volume in cm³ (which is equivalent to mL)

Each patient enrolled in this trial will have 3 MRI timepoints during the course of the study (with no contrast agent used when taking any image):

- Screening (which also serves as the baseline MRI evaluation)
- Month 6
- Month 9

All image management activities will be centralized and conducted by an independent imaging Contract Research Organization (imaging CRO) with operational capabilities in Europe and the United States in compliance with all regulatory requirements. The image acquisition procedure will be standardized by the imaging CRO among all participating sites. The same image acquisition and management procedure will be used by all sites. This procedure will be defined by the imaging CRO and approved by the Sponsor. The sites will be trained and qualified by the imaging CRO prior to start of patient enrolment. Each site will provide test MRI scan(s) during the initial site qualification phase. The source of the test scan(s) will be (in order of preference) a patient volunteer, a healthy volunteer, or the screening image from the first patient tested at the site. All images will be anonymized by the sites (in order to remove any patient-related nominative information) and provided in digital format (DICOM). Only digital images will be centrally processed by the imaging CRO.

The image data will be collected and quality controlled by the imaging CRO for checking the technical adequacy, the compliance of data acquisition with the study imaging protocol, the anonymization of the images, and the diagnostic quality of the images (their appropriateness for centralized evaluations). If any quality-related issue is detected by the imaging CRO, specific queries will be sent to the sites to implement appropriate corrective (such as potential repeat scans whenever possible) and preventive actions.

The MRI data will be centrally evaluated in a fully blinded manner by independent readers. The reading sessions will be organized at the imaging CRO site. The same image evaluation procedure will be used by all readers and for all patients' MRI scans in this trial. The readers will be Senior Radiologists with a significant experience in liver

and spleen imaging and MRI. The readers will be fully blinded with regard to treatment group, patient ID, site number and time sequence. The image review sessions will include:

- **Eligibility Image Review:** One reader (out of a pool of readers) will evaluate spleen volumes with all Screening timepoints. Eligibility review results will be reported to the Sponsor and the corresponding site within eight business days after receipt of the data by the imaging CRO. Only Screening timepoints will be displayed during the Eligibility Image Review sessions (separate evaluations).
- **Efficacy Image Review:** Each MRI timepoint (including all screening timepoints already evaluated for Eligibility Image Review which will subsequently serve as the MRI evaluation at baseline) will be evaluated by two readers for the determination of the liver and spleen volumes. All timepoints of a given patient will be centrally evaluated by the same two readers. All timepoints will be fully randomized and displayed separately. All evaluations will be performed after collection of Baseline (which, as noted previously, is the same image as Screening), Month 6 and Month 9 timepoints of a predefined number of patients. In order to leave the readers blinded with respect to the time sequence, the readers will not be aware of the order of the MRI timepoints which will be fully randomized by the imaging CRO.
- **Adjudication Image Review:** In the event that the two readers disagree by 5% or more on the assessment of a given patient, an Adjudication Image Review will be conducted. During the adjudication, a third Radiologist (reading alone) will perform an independent over-read of the concerned liver and spleen volumes. The variable areas will be displayed in color to facilitate the adjudication process. The adjudicator will have access to the evaluation results of the two main readers, be able to select any of the two evaluation results, edit liver and spleen contours for additional corrections if need be, add personal comments on the causes of variabilities among the readers and save the final results. It should be noted that at no point during the PB-06-001 study did the two main readers disagree by 5% or more on an image assessment hence the adjudication image review was not needed during this trial.

All evaluation results, including spleen and liver contours and the imaging CRO electronic Case Report Forms (eCRFs), will be saved in the trial database. In compliance with regulatory requirements (including 21 CFR Part 11), audit trails will be generated for all image manipulation and evaluation steps and the readers will use an electronic signature system to authenticate themselves for the evaluation of each MRI timepoint. The trial specific Image Review Software will be developed, validated and documented by the imaging CRO in compliance with regulatory requirements. Spleen and liver volumes will be directly computed from organ masks validated by the blinded readers. The result of this quantification will be stored in the database. The file containing final results will be automatically generated from the values of the database, thus avoiding any result to be modified after the review sessions. The final dataset provided for statistical

analysis will include both individual reader results (2 lines per patient), and the final result (1 line per patient, either as the computed mean using individual reader results, or as the adjudicator results if adjudication was necessary which was not the case at any point during the PB-06-001 study).

If an adequate patient image cannot be obtained (i.e. an unevaluable MRI) for a given time point in the study, then the problem with the image will be documented within the database by the imaging CRO. In addition, the imaging CRO will document all attempted corrective actions with the investigative site imaging center. It should be noted that no MRI was deemed unevaluable during the PB-06-001 study.

3.1.5 Statistical Analysis Information

3.1.5.1 ANALYSIS SETS

The two efficacy analysis sets pre-specified by the sponsor in their Statistical Analysis Plan (SAP) are as follows:

1. **Intent-to-Treat (ITT)** defined as randomized patients who received at least one dose of study medication and have at least the Screening/Baseline MRI evaluation. This analysis set serves as the basis for all efficacy analyses conducted by the sponsor.
2. **Per Protocol (PP)** defined as randomized patients who complete the study to 9 months with no major protocol violations.

There were 44 patients who signed the Informed Consent form and were ultimately screened for entry into the PB-06-001 study. Of these screened patients, 33 of them were deemed eligible for the trial and were subsequently randomized with ultimately 16 into the 30 units/kg dose group and 17 into the 60 units/kg dose group. Their disposition is as follows:

- Patient 30-023 was randomized to the 60 units/kg dose group, but voluntarily withdrew from the study for personal reasons and did not receive study treatment and hence was excluded by Protalix from their ITT Analysis Set defined above. Consequently, there were 32 total patients (16 in each dose arm) who received treatment in this trial.
- Of these 32 patients, there were 29 (14 from the 30 units/kg dose group and 15 from the 60 units/kg dose group) who completed all 20 study visits (i.e. all 9 months of the study). The three patients who discontinued the study are as follows:
 - Patient 10-002 in the 60 units/kg arm experienced an adverse event
 - Patient 10-003 in the 30 units/kg arm experienced an adverse event and received only a partial dose of study medication (4.5 mL or 3.3% of the dose) during the first infusion and was subsequently excluded by Protalix from their ITT Analysis Set defined previously defined.
 - Patient 10-012 in the 30 units/kg arm had a major protocol violation of pregnancy.

The Intention-to-Treat (ITT) Principle from E9 [1] states that “the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment.” E9 continues and subsequently defines the FAS as “the set of subjects that is as close as possible to the ideal implied by the Intention-to-Treat principle. It is derived from the set of all randomized subjects by minimal and justified elimination of subjects.” The FAS is consequently the basis for all primary (i.e. non-sensitivity) efficacy analyses (potential exception: *non-inferiority* and/or *equivalence* trials which the PB-06-001 study is not). It should be noted that the Agency may have a more stringent requirement based on the ITT principle which disallows any elimination of patients whatsoever from the all-randomized patient set (regardless of whether the elimination is minimal and justified). This resulting all-randomized analysis set truly preserves the ITT principle and, consequently, guards against overly optimistic estimates of efficacy corresponding to the treatment arm of interest.

Due to the principles and subsequent practices previously described and condoned by regulators, the sponsor’s pre-specified definition of their ITT analysis set was determined to be insufficient especially in a rare disease setting where any elimination of patients is unjustifiable. In order to be technically consistent with the ITT principle, the statistical review team constructed a corrected ITT analysis set to serve as the basis for all primary (i.e. non-sensitivity) efficacy analyses. All necessary efficacy analyses for regulatory review (presented below) were subsequently re-conducted utilizing this corrected ITT analysis set which consisted of the 33 total randomized patients of whom 16 were randomized to receive 30 units/kg of ELELYSO while 17 were randomized to receive 60 units/kg of ELELYSO. Consequently, patients 10-003 (30 units/kg) and 30-023 (60 units/kg) were re-introduced in order to construct this more appropriate full analysis set. The sponsor’s PP definition was deemed appropriate by the statistical review team and ultimately consisted of 29 patients of whom 14 were randomized to receive 30 units/kg of ELELYSO while 15 were randomized to receive 60 units/kg of ELELYSO.

3.1.5.2 ANALYSIS METHODOLOGY

The primary analysis for each of the four study endpoints previously presented in Section 3.1.2 above will be two separate one-sample *t*-tests (one for each dose group) to determine if the sample mean percent change from baseline (in spleen and liver volume) at 9 months/38 weeks or the sample mean change from baseline (in hemoglobin concentration and platelet count) at 9 months/38 weeks is significantly different than zero. The null and alternative hypotheses are as follows where μ represents the population mean percent change from baseline (in spleen and liver volume) at 9 months/38 weeks or population mean change from baseline (in hemoglobin concentration and platelet count) at 9 months/38 weeks:

$$\begin{aligned}H_0: \mu &= 0 \\H_A: \mu &\neq 0\end{aligned}$$

In addition, a corresponding 95% Confidence Interval (C.I.) for the population mean percentage change (or change) from baseline at 9 months/38 weeks utilizing an assumed *t*-distribution will be presented.

A two independent sample *t*-test will be administered as an additional exploratory analysis of each endpoint for dose comparison purposes. This two independent sample *t*-test will compare the mean difference in the endpoints of interest between the two dosing arms. The null and alternative hypotheses are as follows where μ_x represents the population mean of each endpoint, as previously specified in the one sample case above, at dose *x*:

$$\begin{aligned} H_0: \mu_{60 \text{ units/kg}} - \mu_{30 \text{ units/kg}} &= 0 \\ H_A: \mu_{60 \text{ units/kg}} - \mu_{30 \text{ units/kg}} &\neq 0 \end{aligned}$$

A corresponding 95% C.I. for this difference in population means between dosing arms utilizing an assumed *t*-distribution will also be presented for each endpoint.

To further support the analysis, descriptive statistics and relevant corresponding figures will be presented for each of the four endpoints previously described. Specifically for each endpoint, two separate tables of descriptive statistics will be presented along with a corresponding figure for each which presents two separate data plots. The first table displays descriptive statistics for the measured value of the parameter of interest (i.e. spleen volume, hemoglobin concentration, liver volume, or platelet count) at pivotal study weeks. Its corresponding figure first presents the sample mean of the measured value for the parameter of interest by dose group across all study weeks along with corresponding 95% confidence limits utilizing the *t*-distribution. This figure then presents the difference in sample means of the measured value for the parameter of interest between dose groups (i.e. 60 units/kg - 30 units/kg) across all study weeks along with corresponding 95% confidence limits utilizing the *t*-distribution.

The second table displays descriptive statistics for the percentage change (or change) from baseline in the parameter of interest at pivotal post-baseline study weeks along with the results from the primary analysis previously described. Its corresponding figure first presents the sample mean for the percentage change (or change) from baseline in the parameter of interest by dose group across all post-baseline study weeks along with corresponding 95% confidence limits utilizing the *t*-distribution. It is to be noted that the data presented at Week 38 directly corresponds to the results from the primary analysis previously described and presented within the second table for each dose group. This figure then presents the difference in sample means for the percentage change (or change) from baseline in the parameter of interest between dose groups (i.e. 60 units/kg - 30 units/kg) across all post-baseline study weeks along with corresponding 95% confidence limits utilizing the *t*-distribution. It is to be noted that the data presented at Week 38 directly corresponds to the results from the exploratory analysis previously described.

3.1.5.3 MISSING DATA

Based on Corrected ITT analysis, there were only 4 patients (2 from each dose group) in the PB-06-001 trial with missing post-baseline data: patients 10-003 and 10-012 from the 30 units/kg dose group and patients 30-023 and 10-002 from the 60 units/kg dose group. Consequently, missing data did not influence the study results in any way.

The handling of this limited missing data in the analysis of each parameter is as follows:

1. Spleen Volume – For patients 10-012 and 10-002, Multiple Imputation (MI) was conducted utilizing 100 imputations, and, thus, 100 imputed Month 9 spleen volume values were separately generated for each of these 2 patients. The average of these 100 imputations was ultimately employed as the final imputed Month 9 spleen volume for each of these 2 patients. For patients 10-003 and 30-023, a no-change-from-baseline approach was utilized at all post-baseline timepoints. The baseline data for each of these 2 patients was obtained from their screening visit found within the clinical datasets (these 2 patients were not included in the analysis datasets by the sponsor).
2. Liver Volume – For patients 10-012 and 10-002, Last Observation Carried Forward (LOCF) was utilized. For patients 10-003 and 30-023, a no-change-from-baseline approach was utilized at all post-baseline timepoints. Since these patients had screening liver volumes which were not found within the clinical datasets, the mean screening liver volume from the other 31 randomized patients was obtained and subsequently used as the screening liver volume for both of these patients. This value was thus carried forward through all post-baseline timepoints.
3. Hemoglobin Concentration and Platelet Count – For all patients, LOCF was utilized for any intermittent missing data. For patients 10-012 and 10-002, LOCF was also utilized for all post-dropout timepoints. For patients 10-003 and 30-023, a no-change-from-baseline approach was utilized at all post-baseline timepoints. The baseline data for each of these 2 patients was obtained from their baseline visit found within the clinical datasets (as previously stated, these 2 patients were not included in the analysis datasets by the sponsor).

3.1.5.4 MULTIPLICITY

In order to examine the three key secondary endpoints, a sequential (step-down) approach was pre-specified by the sponsor and is described in their SAP as such: First, the primary efficacy analysis is performed at each dose level using an α level of 0.025 to allow each dose to be tested independently. If spleen volume as the primary endpoint is shown to be significant for either one or both doses, then the mean change in hemoglobin concentration will be tested for that dose (or doses) using an α level of 0.025 to allow each dose to be tested independently. Next, if the change in hemoglobin is shown to be significant for either one or both doses, then the percent change in liver volume will be tested for that dose (or doses) using an α level of 0.025 to allow each dose to be tested independently. Finally, if the percent change in liver volume is shown to be significant

for either one or both doses, then the mean change in platelet count will be tested for that dose (or doses) using an α level of 0.025 to allow each dose to be tested independently.

3.1.5.5 ADDITIONAL SENSITIVITY ANALYSES

As previously mentioned, the primary (i.e. non-sensitivity) analyses for all study endpoints will utilize the corrected ITT. For further sensitivity analysis purposes, all efficacy analyses will be repeated using the sponsor's ITT and PP analysis sets. In addition, all analyses for spleen and liver volume under all three analysis sets will be further conducted by Reader in order to identify whether the overall results varied by Radiologist.

3.1.6 Statistical Analysis Results

All analyses presented below utilize the sponsor's full Case Report Tabulation (CRT) whose final component was submitted on June 4, 2010.

3.1.6.1 Disposition and Baseline Information

The disposition of all patients within the Corrected ITT is presented in Table 2 below.

Table 2
Disposition
(Corrected ITT)

	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Completed the Study?			
Yes	14 (87.5%)	15 (88.2%)	29 (87.9%)
No	2 (12.5%)	2 (11.8%)	4 (12.1%)
Reason for Discontinuation			
Adverse Event	1 (6.3%)	1 (5.9%)	2 (6.1%)
Protocol Violation	1 (6.3%)	0	1 (3.0%)
Voluntary Withdrawal	0	1 (5.9%)	1 (3.0%)
Investigator Recommendation	0	0	0
Lost to Follow-up	0	0	0
Other	0	0	0

Source: Reviewer's Table.

Note: Denominators for percentages are N, the number of patients within each dose group or overall.

The demographics and baseline characteristics of all patients within the Corrected ITT are presented in Table 3 below, and it can be seen that no important differences exist between the dose arms.

Table 3
Demographics and Baseline Characteristics
(Corrected ITT)

	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Age (years) at Informed Consent			
n	16	17	33
Mean (SD)	36.3 (11.82)	37.0 (12.50)	36.7 (11.99)
Median	35.0	33.0	35.0
Min, Max	19, 74	19, 58	19, 74
Gender – n (%)			
Female	8 (50.0%)	8 (47.1%)	16 (48.5%)
Male	8 (50.0%)	9 (52.9%)	17 (51.5%)
Religion – n (%)			
Jewish - Ashkenazi	6 (37.5%)	4 (23.5%)	10 (30.3%)
Jewish – Non-Ashkenazi	0	0	0
Non-Jewish	10 (62.5%)	13 (76.5%)	23 (69.7%)
Race – n (%)			
Caucasian	16 (100.0%)	16 (94.1%)	32 (97.0%)
African American	0	0	0
Native American	0	0	0
Asian/Pacific Islander	0	0	0
Other	0	1 (5.9%)	1 (3.0%)
Weight (kg)			
n	16	17	33
Mean (SD)	68.2 (12.82)	68.4 (9.83)	68.3 (11.12)
Median	68.0	70.5	69.0
Min, Max	52, 96	51, 86	51, 96

Source: Reviewer's Table.

Note: Denominators for percentages are N, the number of patients within each dose group or overall.

3.1.6.2 Primary Efficacy Analysis – Spleen Volume

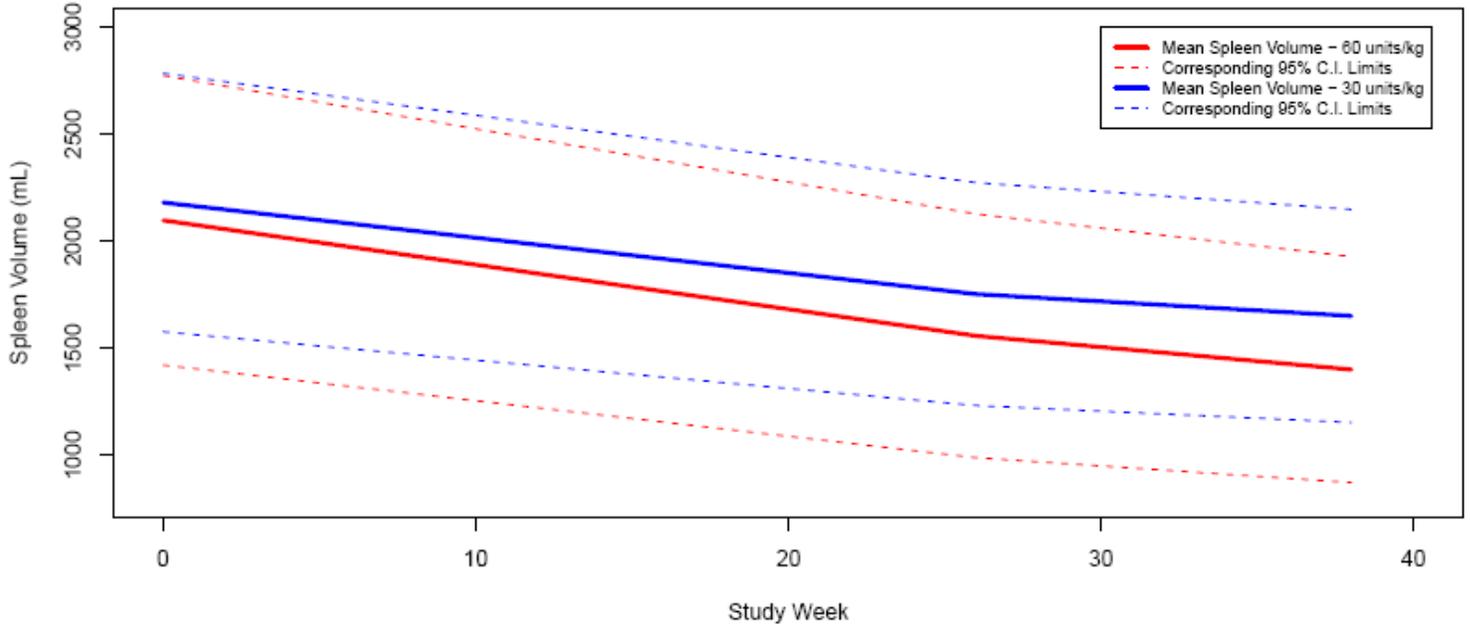
Table 4
Spleen Volume by Pivotal Study Week
(Corrected ITT)

Spleen Volume (mL)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 0 / Screening			
n	16	17	33
Mean (SD)	2180.7 (1133.21)	2097.6 (1315.64)	2137.9 (1212.10)
Median	1656.9	1758.0	1671.7
Min, Max	886, 4901	914, 5418	886, 5418
Study Week 26 / 6-Month			
n	16	17	33
Mean (SD)	1753.2 (977.54)	1558.0 (1107.35)	1652.6 (1034.83)
Median	1296.2	1146.6	1250.4
Min, Max	630, 4117	523, 4524	523, 4524
Study Week 38 / 9-Month			
n	16	17	33
Mean (SD)	1651.2 (933.89)	1400.6 (1026.97)	1522.1 (975.87)
Median	1226.1	1065.2	1137.9
Min, Max	606, 3894	483, 4220	483, 4220

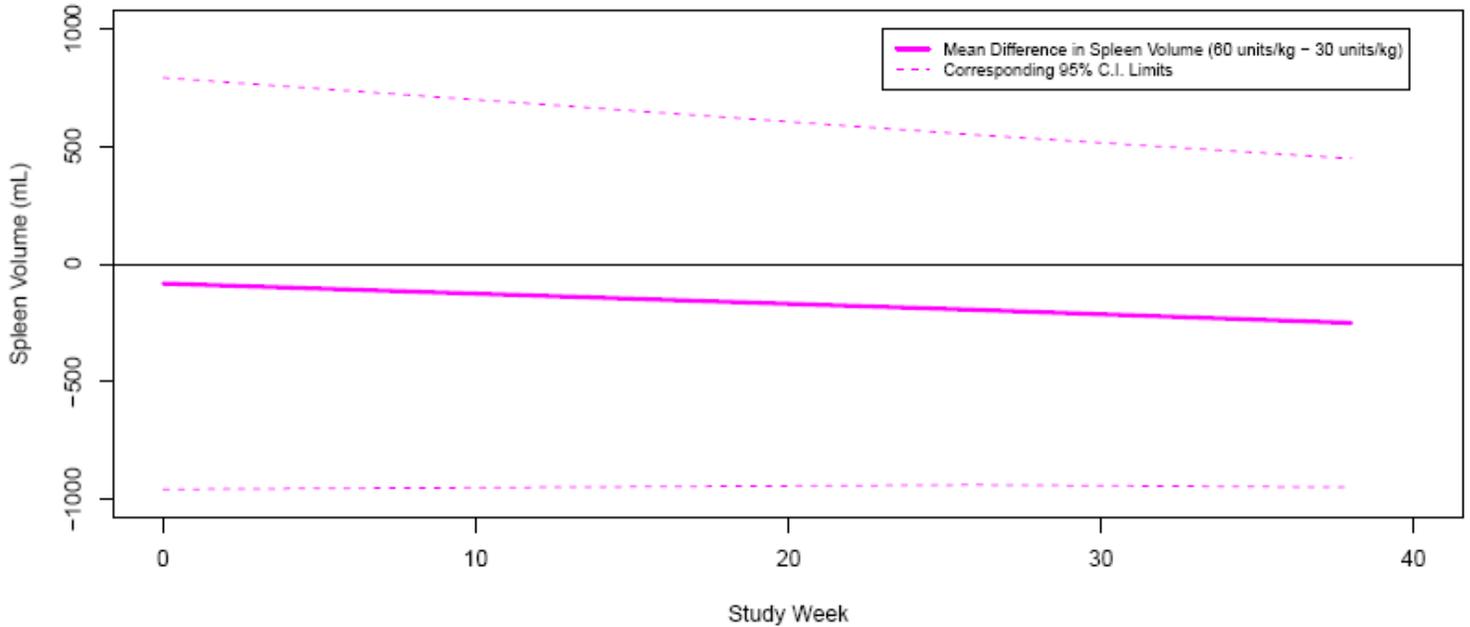
Source: Reviewer's Table.

Figure 1
(Corrected ITT)
PB-06-001: SPLEEN VOLUME

By Study Week



Dose Difference by Study Week



Source: Reviewer's Figure.

Table 5
Percentage Change from Screening/Baseline in Spleen Volume by Pivotal Study
Week
(Corrected ITT)

Percentage Change (%)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 0 to Study Week 26 / Screening to 6-Month			
n	16	17	33
Mean (SD)	-20.8 (7.13)	-28.2 (14.24)	-24.6 (11.80)
Median	-22.3	-30.3	-23.1
Min, Max	-31, 0	-53, 3	-53, 3
Study Week 0 to Study Week 38 / Screening to 9-Month			
n	16	17	33
Mean (SD)	-25.2 (10.09)	-35.8 (12.94)	-30.7 (12.65)
Median	-27.2	-37.6	-31.6
Min, Max	-43, 0	-56, 0	-56, 0
p-value from one sample <i>t</i>-test	<0.0001	<0.0001	
95 % C.I.	(-30.61, -19.85)	(-42.43, -29.12)	

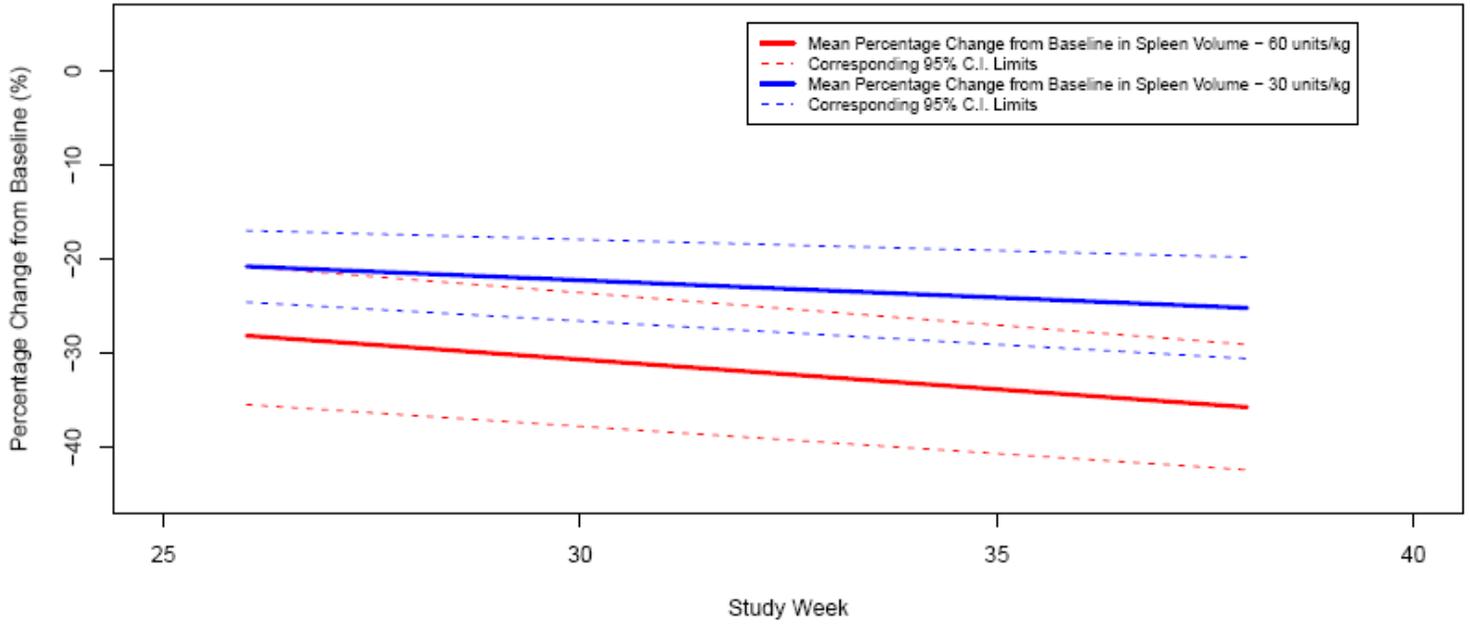
Source: Reviewer's Table.

It can be seen that the percentage change from baseline in spleen volume was highly significant within both individual dose arms. When these dose arms are compared utilizing a two independent sample *t*-test, a significant difference between the arms is also recognized. The p-value from this two independent sample *t*-test, which assumes equal variance between the two arms, equals 0.0142. The mean difference between these dosing arms (60 units/kg – 30 units/kg) in percentage change from baseline in spleen volume is -10.6 with corresponding 95% C.I. (-18.82, -2.27). Although the result from this dose comparison is exploratory in nature, it does suggest the greater effectiveness of the 60 units/kg dose.

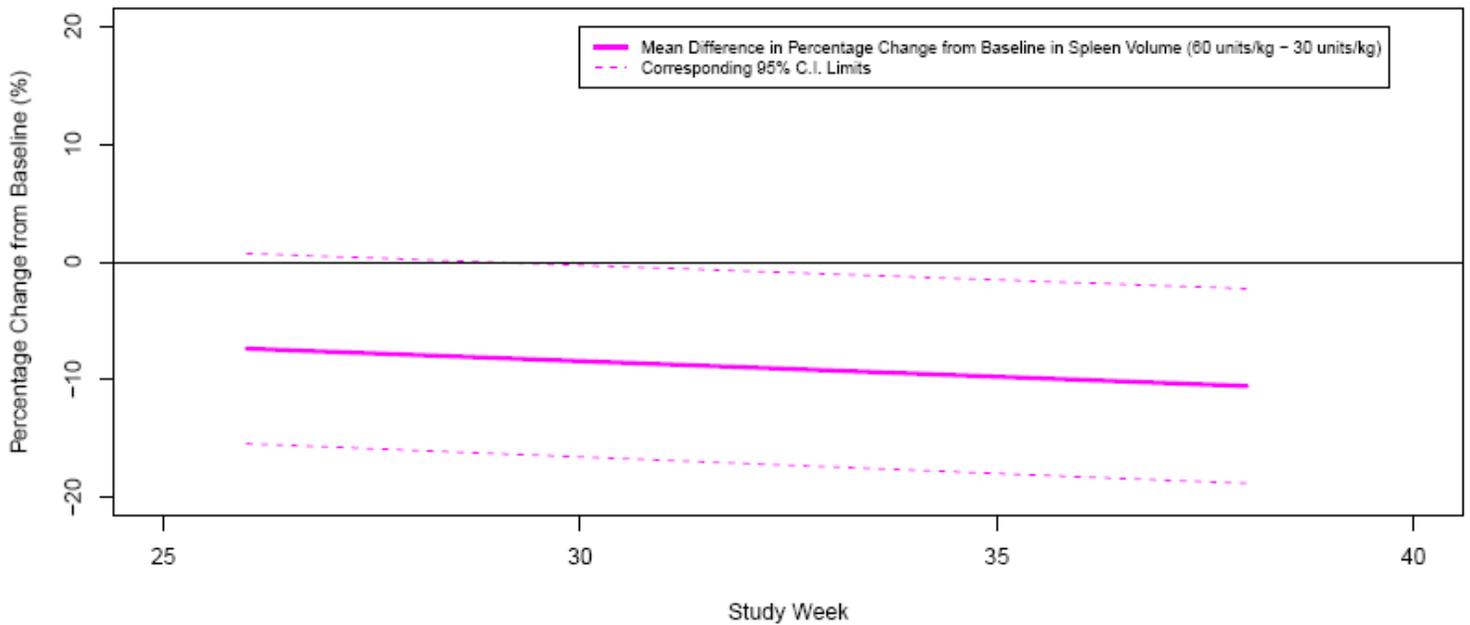
Figure 2
(Corrected ITT)

PB-06-001: PERCENTAGE CHANGE FROM BASELINE IN SPLEEN VOLUME

By Study Week



Dose Difference by Study Week



Source: Reviewer's Figure.

3.1.6.3 Key Secondary Efficacy Analysis – Hemoglobin Concentration

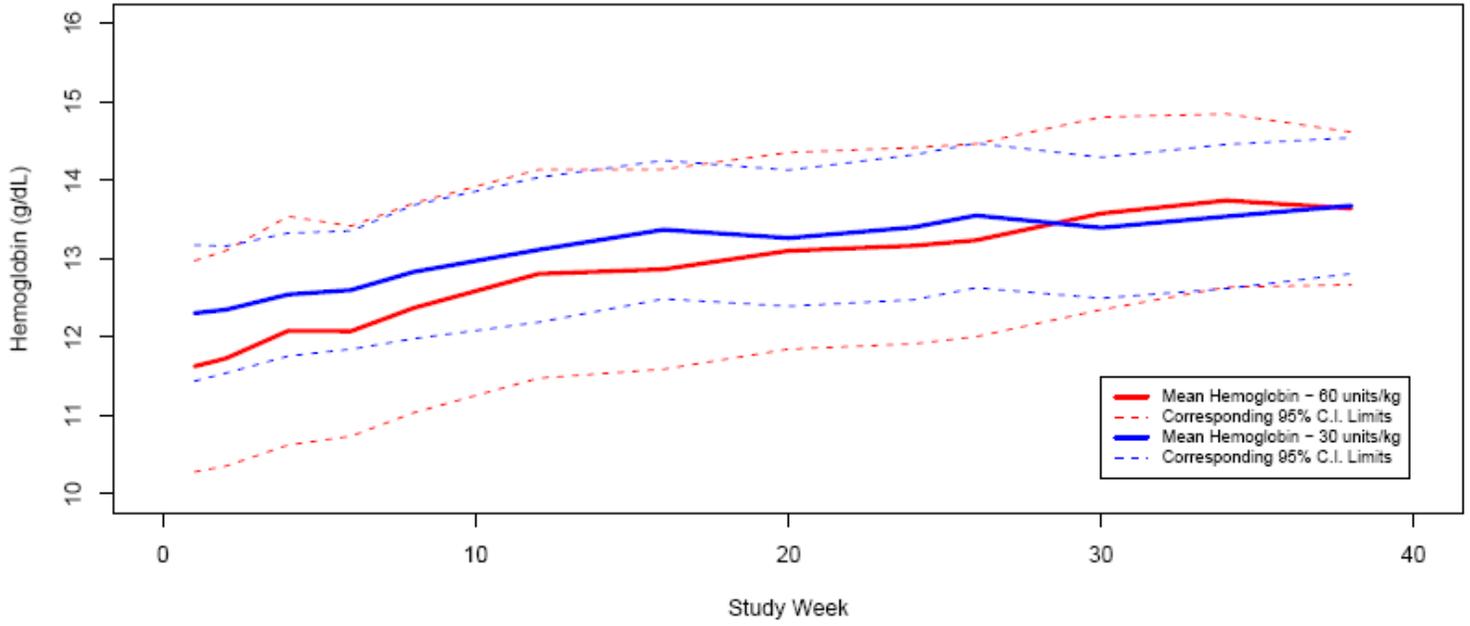
Table 6
Hemoglobin Concentration by Pivotal Study Week
(Corrected ITT)

Hemoglobin Concentration (g/dL)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 1 / Baseline			
n	16	17	33
Mean (SD)	12.31 (1.625)	11.62 (2.616)	11.96 (2.186)
Median	12.55	11.60	12.00
Min, Max	7.9, 14.6	5.5, 16.0	5.5, 16.0
Study Week 26 / 6-Month			
n	16	17	33
Mean (SD)	13.55 (1.729)	13.24 (2.391)	13.39 (2.070)
Median	13.95	13.50	13.70
Min, Max	10.4, 16.5	6.7, 16.9	6.7, 16.9
Study Week 38 / 9-Month			
n	16	17	33
Mean (SD)	13.68 (1.627)	13.64 (1.892)	13.66 (1.741)
Median	13.70	14.20	13.70
Min, Max	10.4, 16.9	8.6, 16.5	8.6, 16.9

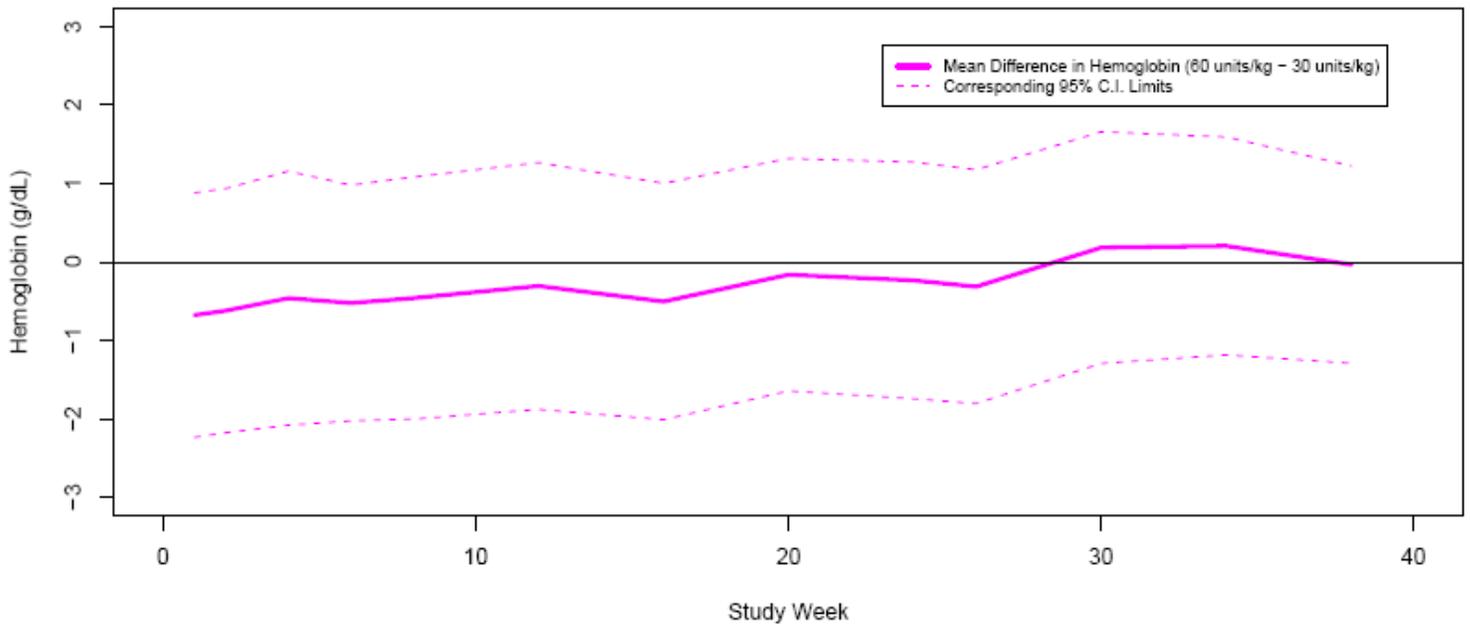
Source: Reviewer's Table.

Figure 3
(Corrected ITT)
PB-06-001: HEMOGLOBIN

By Study Week



Dose Difference by Study Week



Source: Reviewer's Figure.

Table 7
Change from Baseline in Hemoglobin Concentration by Pivotal Study Week
(Corrected ITT)

Hemoglobin Concentration (g/dL)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 1 to Study Week 26 / Baseline to 6-Month			
n	16	17	33
Mean (SD)	1.24 (1.172)	1.61 (1.170)	1.43 (1.167)
Median	1.20	1.50	1.40
Min, Max	-0.5, 3.7	-0.2, 4.5	-0.5, 4.5
Study Week 1 to Study Week 38 / Baseline to 9-Month			
n	16	17	33
Mean (SD)	1.37 (1.463)	2.01 (1.453)	1.70 (1.471)
Median	1.15	1.60	1.30
Min, Max	-0.5, 5.8	0.0, 5.1	-0.5, 5.8
p-value from one sample <i>t</i>-test	0.0020	<0.0001	
95 % C.I.	(0.589, 2.15)	(1.26, 2.76)	

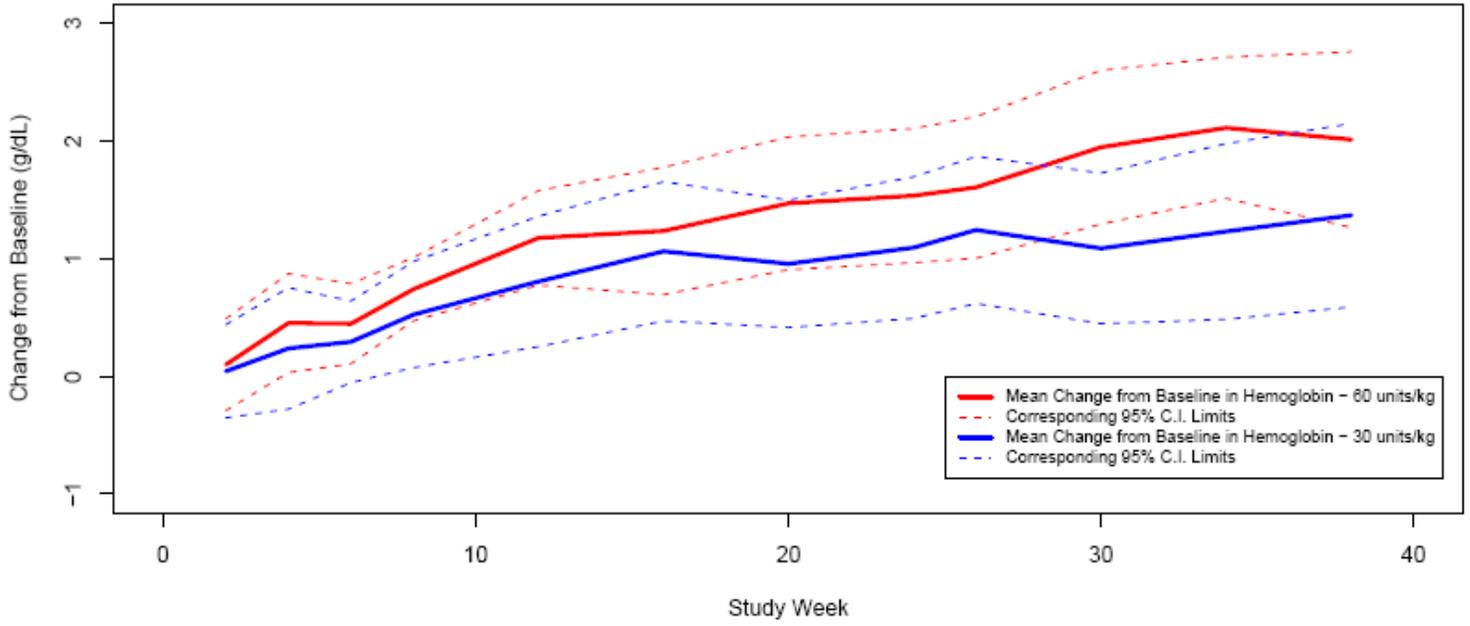
Source: Reviewer's Table.

It can be seen that the change from baseline in hemoglobin concentration was highly significant within both individual dose arms. However, when these dose arms are compared utilizing a two independent sample *t*-test, a non-significant difference between the doses is observed. The p-value from this two independent sample *t*-test, which assumes equal variance between the two arms, equals 0.2147. The mean difference between these dosing arms (60 units/kg – 30 units/kg) in change from baseline in hemoglobin concentration is 0.64 with corresponding 95% C.I. (-0.392, 1.678).

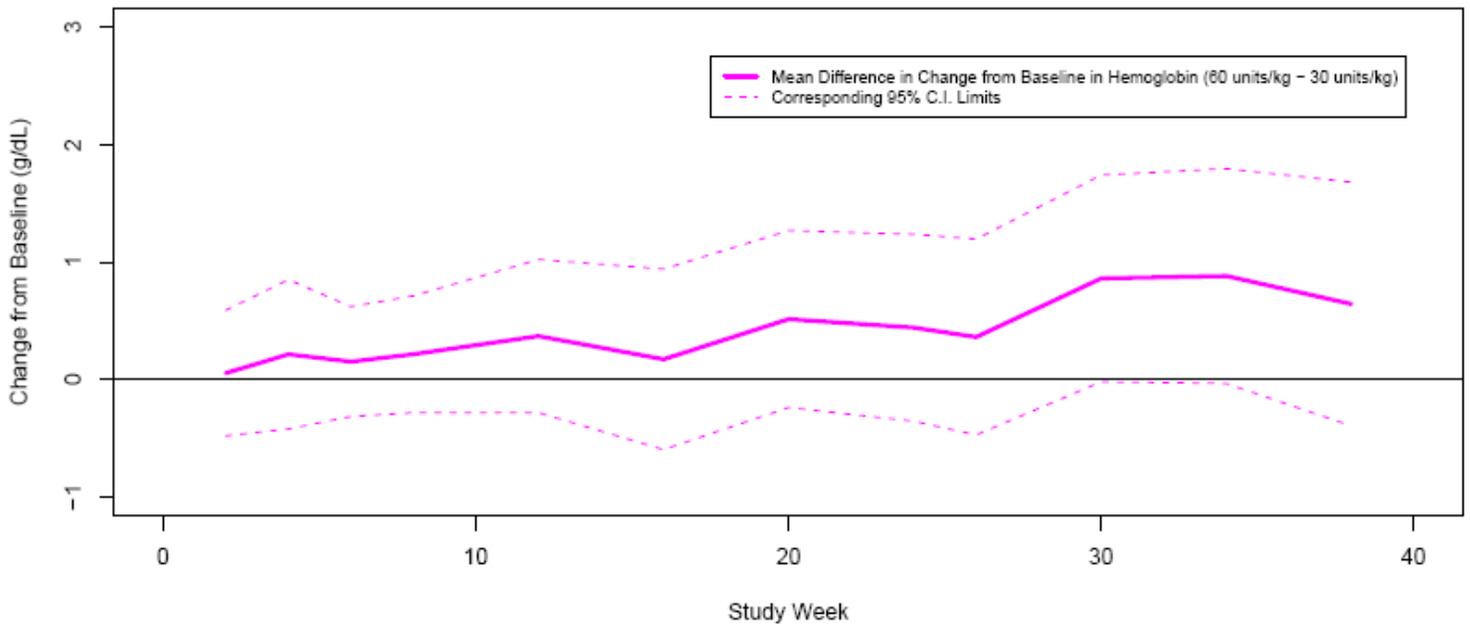
Figure 4
(Corrected ITT)

PB-06-001: CHANGE FROM BASELINE IN HEMOGLOBIN

By Study Week



Dose Difference by Study Week



Source: Reviewer's Figure.

3.1.6.4 Key Secondary Efficacy Analysis – Liver Volume

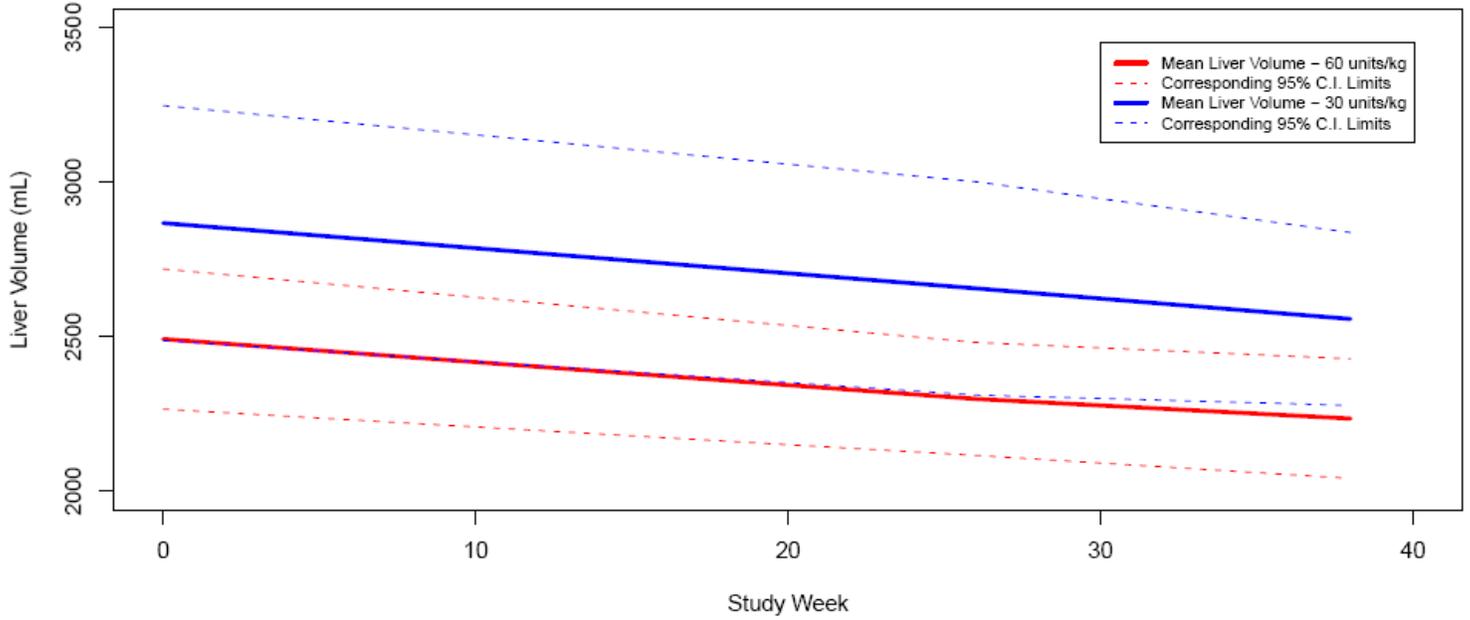
Table 8
Liver Volume by Pivotal Study Week
(Corrected ITT)

Liver Volume (mL)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 0 / Screening			
n	16	17	33
Mean (SD)	2867.7 (713.03)	2492.7 (440.86)	2674.5 (609.69)
Median	2642.2	2508.2	2597.0
Min, Max	2282, 5096	1758, 3297	1758, 5096
Study Week 26 / 6-Month			
n	16	17	33
Mean (SD)	2656.7 (647.45)	2299.3 (355.15)	2472.6 (540.79)
Median	2479.9	2279.7	2406.8
Min, Max	1930, 4598	1809, 2815	1809, 4598
Study Week 38 / 9-Month			
n	16	17	33
Mean (SD)	2557.8 (524.50)	2235.7 (376.06)	2391.9 (475.81)
Median	2473.2	2211.5	2353.5
Min, Max	2000, 4122	1654, 2894	1654, 4122

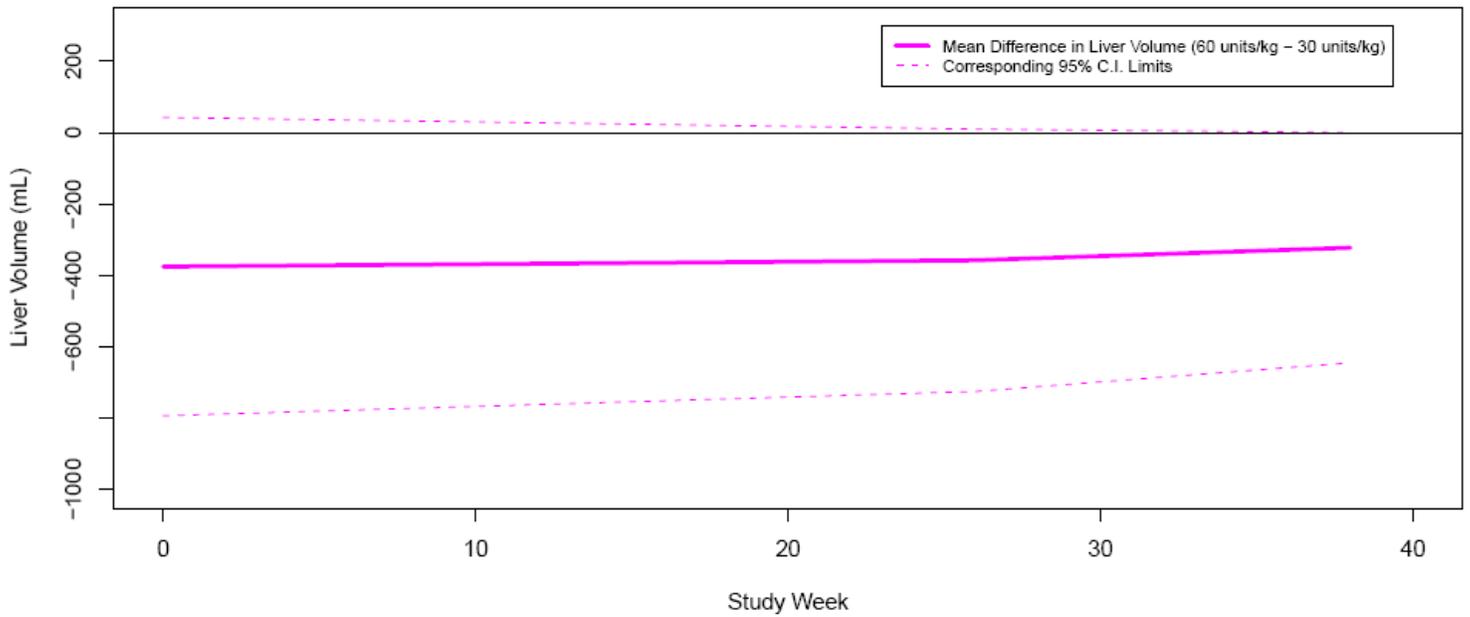
Source: Reviewer's Table.

Figure 5
(Corrected ITT)
PB-06-001: LIVER VOLUME

By Study Week



Dose Difference by Study Week



Source: Reviewer's Figure.

Table 9
Percentage Change from Screening/Baseline in Liver Volume by Pivotal Study
Week
(Corrected ITT)

Percentage Change (%)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 0 to Study Week 26 / Screening to 6-Month			
n	16	17	33
Mean (SD)	-7.1 (7.71)	-7.1 (8.11)	-7.1 (7.80)
Median	-9.1	-6.5	-7.5
Min, Max	-22, 11	-25, 5	-25, 11
Study Week 0 to Study Week 38 / Screening to 9-Month			
n	16	17	33
Mean (SD)	-9.7 (10.81)	-9.9 (7.13)	-9.8 (8.96)
Median	-13.0	-12.2	-12.3
Min, Max	-19, 25	-22, 2	-22, 25
p-value from one sample <i>t</i>-test	0.0026	<0.0001	
95 % C.I.	(-15.49, -3.97)	(-13.57, -6.23)	

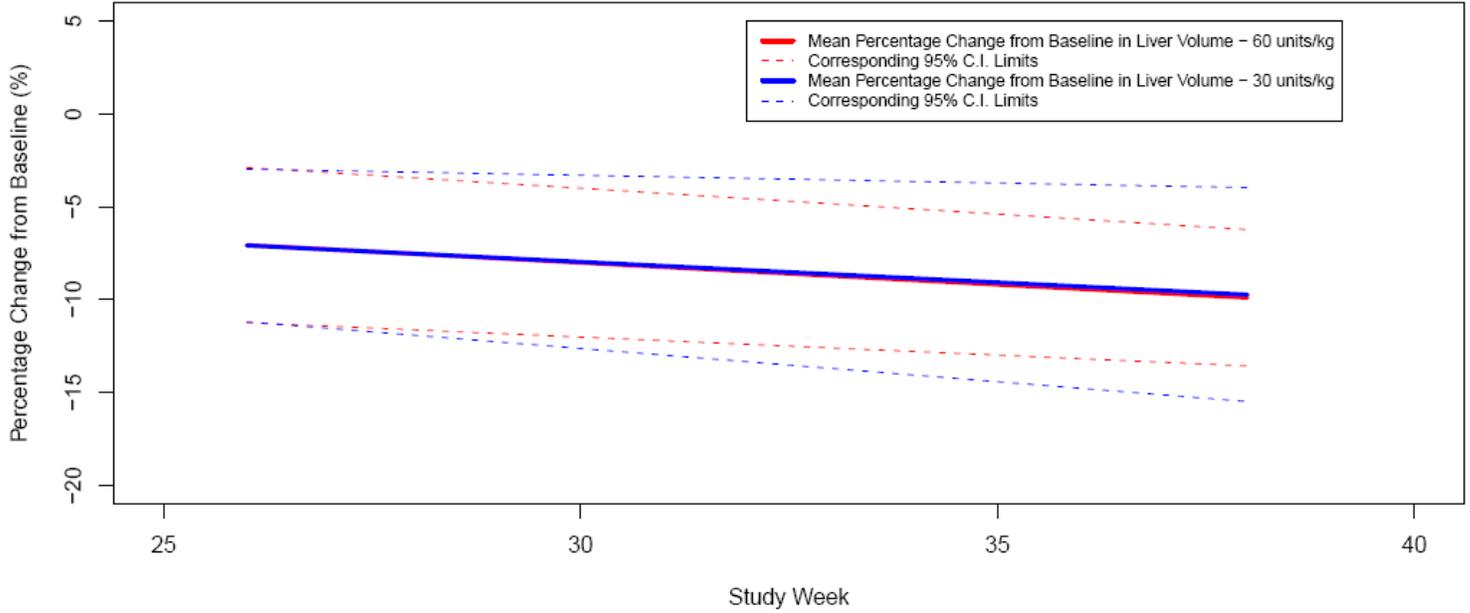
Source: Reviewer's Table.

It can be seen that the percentage change from baseline in liver volume was highly significant within both individual dose arms. However, when these dose arms are compared utilizing a two independent sample *t*-test, a non-significant difference between the doses is observed. The p-value from this two independent sample *t*-test, which assumes equal variance between the two arms, equals 0.9587. The mean difference between these dosing arms (60 units/kg – 30 units/kg) in percentage change from baseline in liver volume is -0.2 with corresponding 95% C.I. (-6.63, 6.30).

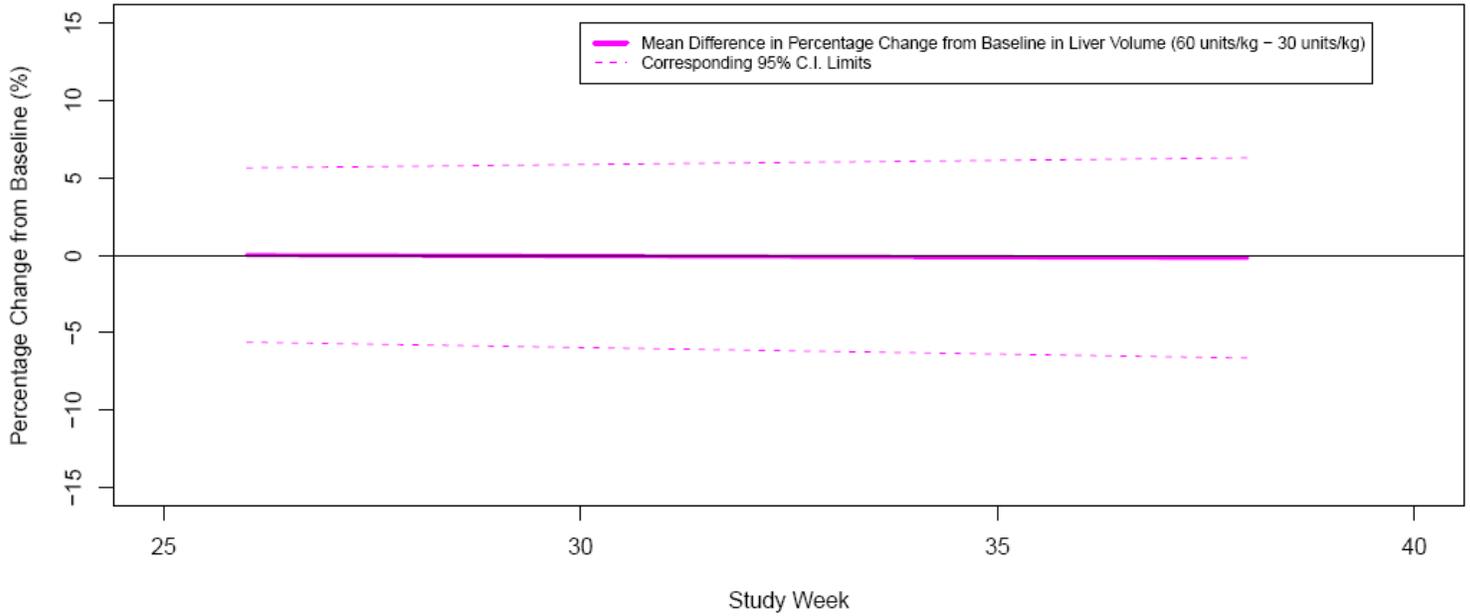
Figure 6
(Corrected ITT)

PB-06-001: PERCENTAGE CHANGE FROM BASELINE IN LIVER VOLUME

By Study Week



Dose Difference by Study Week



Source: Reviewer's Figure.

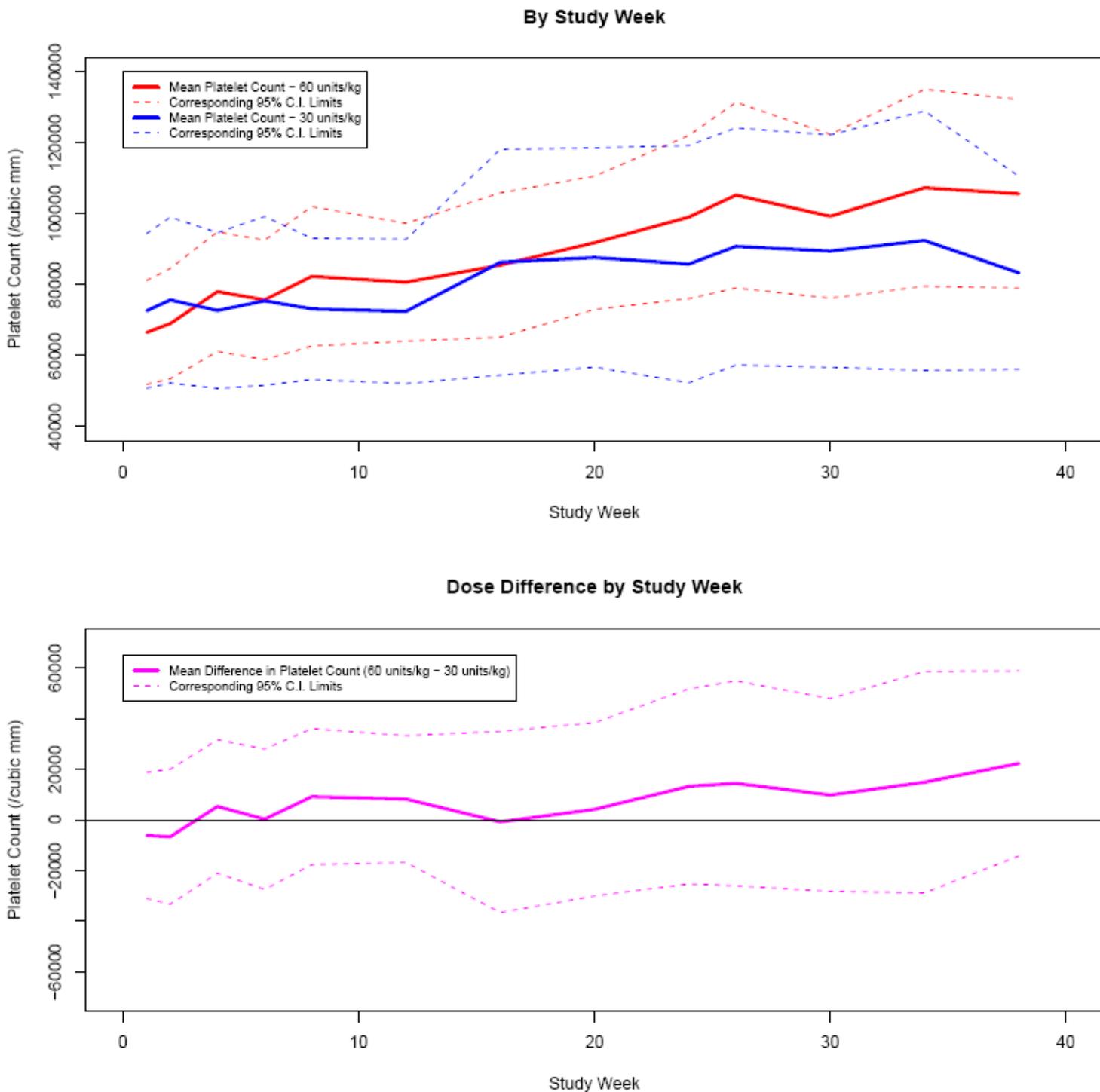
3.1.6.5 Key Secondary Efficacy Analysis – Platelet Count

Table 10
Platelet Count by Pivotal Study Week
(Corrected ITT)

Platelet Count (/mm ³)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 1 / Baseline			
n	16	17	33
Mean (SD)	72654.2 (40890.00)	66564.7 (28463.07)	69517.2 (34617.49)
Median	55000.0	55000.0	55000.0
Min, Max	27000, 163000	28000, 134000	27000, 163000
Study Week 26 / 6-Month			
n	16	17	33
Mean (SD)	90779.2 (62703.20)	105235.3 (50901.29)	98226.3 (56500.26)
Median	65000.0	97000.0	90000.0
Min, Max	23000, 246000	17000, 251000	17000, 251000
Study Week 38 / 9-Month			
n	16	17	33
Mean (SD)	83366.7 (51081.70)	105617.7 (51659.80)	94829.3 (51817.21)
Median	71000.0	108000.0	91000.0
Min, Max	20000, 168000	25000, 241000	20000, 241000

Source: Reviewer's Table.

Figure 7
(Corrected ITT)
PB-06-001: PLATELET COUNT



Source: Reviewer's Figure.

Table 11
Change from Baseline in Platelet Count by Pivotal Study Week
(Corrected ITT)

Platelet Count (/mm ³)	30 units/kg (N = 16)	60 units/kg (N = 17)	Total (N = 33)
Study Week 1 to Study Week 26 / Baseline to 6-Month			
n	16	17	33
Mean (SD)	18125.0 (31997.89)	38670.0 (48789.55)	28709.1 (42176.71)
Median	7550.0	38000.0	17000.0
Min, Max	-39000, 109000	-23000, 196000	-39000, 196000
Study Week 1 to Study Week 38 / Baseline to 9-Month			
n	16	17	33
Mean (SD)	10712.5 (19736.53)	39052.9 (46666.88)	25312.1 (38449.59)
Median	7500.0	38000.0	18000.0
Min, Max	-25000, 59000	-15000, 186000	-25000, 186000
p-value from one sample t-test	0.0464	0.0033	
95 % C.I.	(196, 21229)	(15059, 63047)	

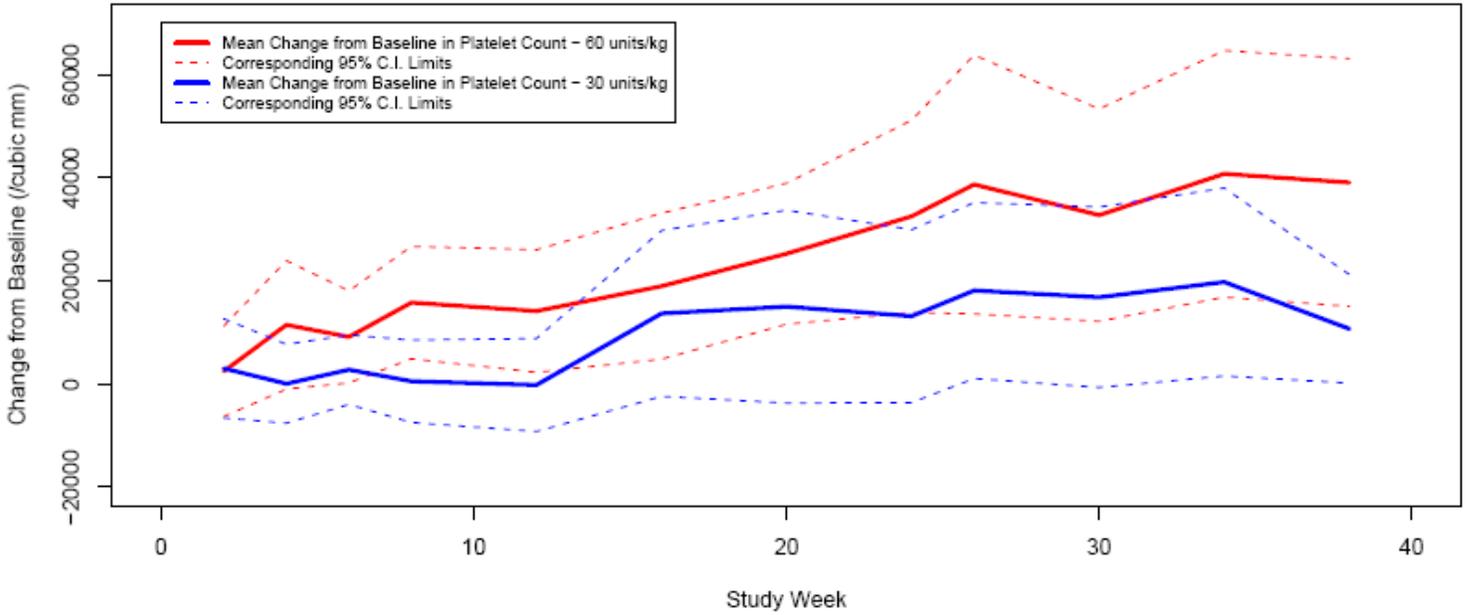
Source: Reviewer's Table.

It can be seen that the change from baseline in platelet count was highly significant within only the 60 units/kg arm. Based on the step-down approach pre-specified by the sponsor for handling multiplicity, the change from baseline in platelet count experienced by patients in the 30 units/kg dose group was not significant when compared to $\alpha=0.025$. When these dose arms are compared utilizing a two independent sample *t*-test, a significant difference between the arms is indeed recognized. The p-value from this two independent sample *t*-test, which assumes non-equal variance between the two arms, equals 0.0317. The mean difference between these dosing arms (60 units/kg – 30 units/kg) in change from baseline in platelet count is 28340 with corresponding 95% C.I. (2604, 54077). Although the result from this dose comparison is exploratory in nature, it does suggest the greater effectiveness of the 60 units/kg dose.

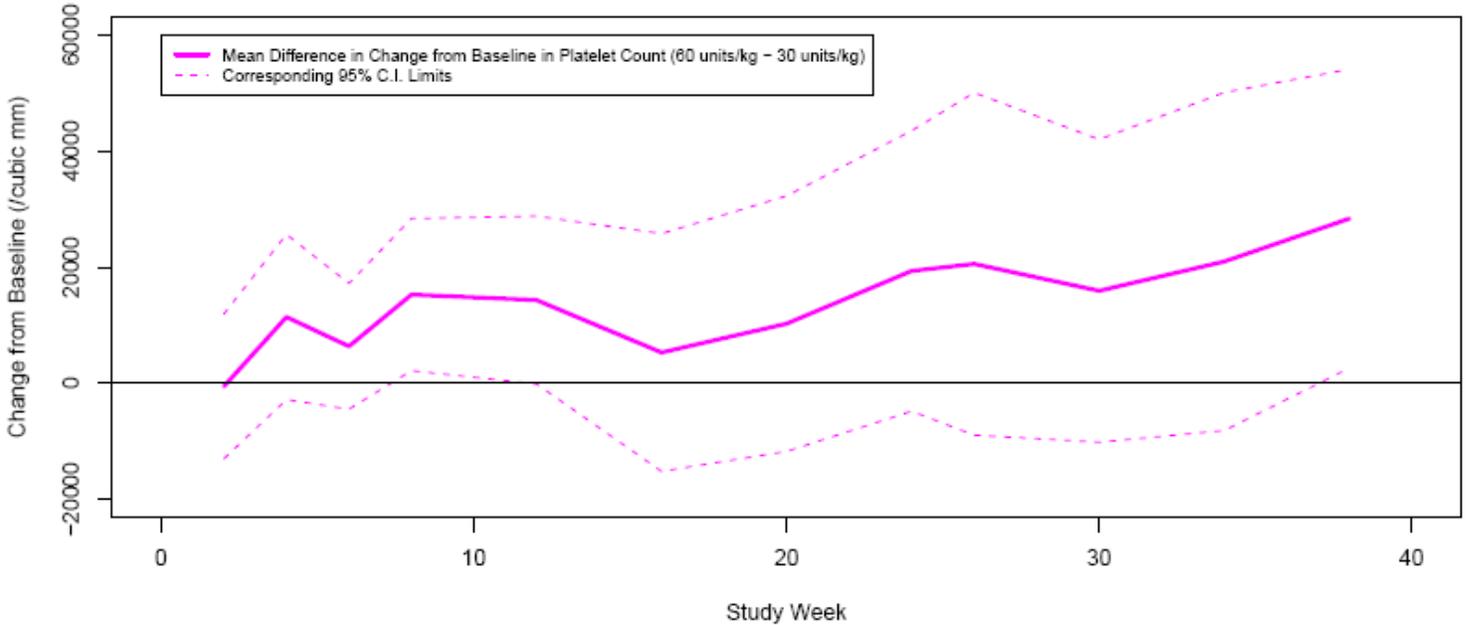
Figure 8
(Corrected ITT)

PB-06-001: CHANGE FROM BASELINE IN PLATELET COUNT

By Study Week



Dose Difference by Study Week



Source: Reviewer's Figure.

3.1.6.6 Additional Sensitivity Analyses

All previous analyses were repeated employing the sponsor's ITT and PP analysis sets, and the results were subsequently shown to be consistent with those previously presented under the Corrected ITT analysis set. The efficacy results for spleen and liver volume under all three analysis sets were also found to be robust when analyzed separately by Reader. Consequently, the results from these sensitivity analyses are not additionally presented herein.

3.1.6.7 Subgroup Analyses

Subgroup analyses of the primary endpoint (i.e. percentage change from baseline in spleen volume) corresponding to gender were administered (see Table 12 below) with no differences in inferential results when compared to the overall analysis of this endpoint (previously presented above in Table 5). No other special subpopulations were identified. The number of non-Caucasian patients in this study was too small (only one patient) to adequately assess any difference in effects by race. In addition, there were no Pediatric patients (i.e. age < 18) and there was only one Geriatric patient (i.e. age > 65) participating in this trial. Consequently, an adequate assessment of any difference in effects by age group could not be made either. As a result, only valid generalizations to Caucasian adults can be made.

Table 12
Percentage Change from Screening/Baseline in Spleen Volume at Study Week 38/9-
Month by Gender
(Corrected ITT)

Percentage Change (%)	30 units/kg (N = 16)	60 units/kg (N = 17)
Female		
p-value from one sample t-test	0.0001	<0.0001
95 % C.I.	(-33.97, -17.88)	(-49.34, -27.94)
Male		
p-value from one sample t-test	0.0004	<0.0001
95 % C.I.	(-33.87, -15.2)	(-43.43, -23.02)

Source: Reviewer's Table.

3.2 PB-06-002

3.2.1 Background and Analysis Information

The objective of this ongoing multi-center, open-label, switchover trial was to assess the safety and efficacy of ELELYSO in 30 patients, 2 years or older, with Type 1 Gaucher disease who had been receiving CERZYME for at least 2 years at a stable maintenance regimen (i.e. dose unchanged) for at least six months prior to screening. As of April 30, 2010, 24 patients are currently being treated at 9 investigational centers in 7 countries with a total of 4 of these patients having completed this study. Up to 30 total patients are planned to be enrolled into the trial, consequently the CSR submitted within this NDA is an abbreviated one based on interim data.

Eligible patients will enter a 12-week Baseline Stability Evaluation Period in order to establish the stability of their disease. During the Stability Evaluation Period, the patients will continue CERZYME treatment, and if the patient's CERZYME was discontinued due to drug shortage, the patient could start receiving ELELYSO infusions based on historical data pertaining to disease stability. The screening visit is conducted more than 5 days after the last stability period CERZYME infusion in order to ensure an accurate baseline evaluation. Hemoglobin concentration and platelet count are measured by the local laboratory every two weeks for a total of 6 measurements during this stability period. Patients with stable disease are then switched from CERZYME to receive IV infusions of ELELYSO. Infusions are performed every two weeks for a total of 20 infusions. The starting dose of ELELYSO is equivalent to each patient's CERZYME dose in the past 6 months or to the dose prior to the shortage of CERZYME. The infusions are administered at the selected medical center, infusion center, or at the patient's home. The total duration of treatment is nine months (i.e. 38 weeks), and at the end of the 9-month treatment period (spanning 20 protocol defined visits) eligible patients are subsequently offered enrollment in the PB-06-003 extension study.

Efficacy is determined by evaluation of the following parameters for clinical deterioration. It is to be noted that this evaluation is based on clinical determination/judgment which is reflected in the criteria presented below and not on inference derived from formal statistical methodology.

- Spleen Volume
- Hemoglobin Concentration
- Liver Volume
- Platelet Count

Two interim analyses were planned. The first interim analysis, which is the basis of the submitted abbreviated CSR, is performed on monitored data as of April 30, 2010. The second interim analysis will eventually be performed based on the monitored data when the first 15 patients complete or prematurely withdraw from the study. The study population used for the results presented within the abbreviated CSR (i.e. "Interim Population #1") is defined as all enrolled subjects who received treatment with ELELYSO on or before April 30, 2010. The data used for the summary tables will be the records collected on or before the date of April 30, 2010.

The main effectiveness criteria are based on whether the clinical status of the patient was maintained over the treatment period with ELELYSO after switching from CEREZYME. Clinical disease deterioration was defined in a pre-specified manner as follows:

- 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. The image evaluation plan for determining spleen volume is the same as what was previously presented in section 3.1.4.
- Hemoglobin – a decrease of >20% from the arithmetic mean of the six hemoglobin concentration values measured during the Stability Evaluation Period was considered a clinically relevant deterioration. If less than six values are available during the Stability Evaluation Period, the available values are used to estimate the mean. If the patient's treatment with CEREZYME was temporarily discontinued due to shortage of the drug at the time of enrollment, historical data on hemoglobin concentration is used to determine clinical 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 image evaluation plan for determining spleen volume is the same as what was previously presented in section 3.1.4.
- Platelet counts – a decrease of >20% from the arithmetic mean of the six platelet count values measured during the Stability Evaluation Period of $\leq 120,000$ or a decrease of >40% from the arithmetic mean of the six platelet count values measured during the Stability Evaluation Period of $> 120,000$ were considered a clinically relevant deterioration. If less than six values are available during the Stability Evaluation Period, the available values are used to estimate the mean. If the patient's treatment with CEREZYME was temporarily discontinued due to shortage of the drug at the time of enrollment, historical data on platelet count is used to determine clinical deterioration.

Below, tables which present clinically relevant deterioration by pivotal study weeks are presented for each of the aforementioned efficacy parameters (i.e. spleen volume, hemoglobin concentration, liver volume, and platelet count). In addition, accompanying figures are also presented for hemoglobin concentration and platelet count. Due to sparse organ volume data (i.e. only 4 patients finished the study by April 30, 2010 and thus were the only patients who obtained the Month-9 MRI assessment), spleen and liver volume figures were not produced.

The specification for the two figures created by the statistical review team pertaining to hemoglobin concentration and platelet count is as follows. In this study, the screening assessment was conducted at Week -12. Then, as previously described, a Stability Evaluation Period commenced prior to the baseline visit where multiple assessments were made for each lab parameter of which hemoglobin concentration and platelet count are of interest here. Since there was not much variability observed in the hemoglobin concentration and platelet count values within each patient during this pre-baseline evaluation period, the median stability evaluation period value of each of these two lab parameters was obtained per patient. This calculation was made in order to obtain one

stability evaluation value for each of these two parameters per patient. Ideally it would have been best to keep the stability evaluation period values separated, but the potential problem was that no corresponding exact time point was captured in the datasets with these measurements relative to screening/Week -12. Hence the statistical review team did not want to risk mixing values from differing time points. For example, one patient's first stability evaluation visit may have occurred much earlier or much later, relative to screening, than another patient's first stability evaluation visit. This resulting one stability evaluation value was ultimately assigned to Week -6 within the figures. The statistical review team ultimately utilized descriptive statistics within the two figures, specifically median, min and max as opposed to means (which are descriptive as well) and confidence limits (which are inferential and parametric). These statistics chosen to be reflected within the figures are, at the same time, descriptive and non-parametric which is most optimal in this exploratory small sample setting.

3.2.2 Analysis Tables and Figures for Efficacy Parameters

Table 13
Spleen Volume – Clinically Relevant Deterioration at Month 9
(Interim Population #1)

Parameter	Visit		prGCD (N=24)
Clinically Relevant Deterioration	Visit 20 (Month 9)	n	4
		Yes	1 (25.0%)
		No	3 (75.0%)

Source: Table 7.3 from pg. 42 of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

Table 14
Hemoglobin Concentration – Clinically Relevant Deterioration at Pivotal Visits
(Interim Population #1)

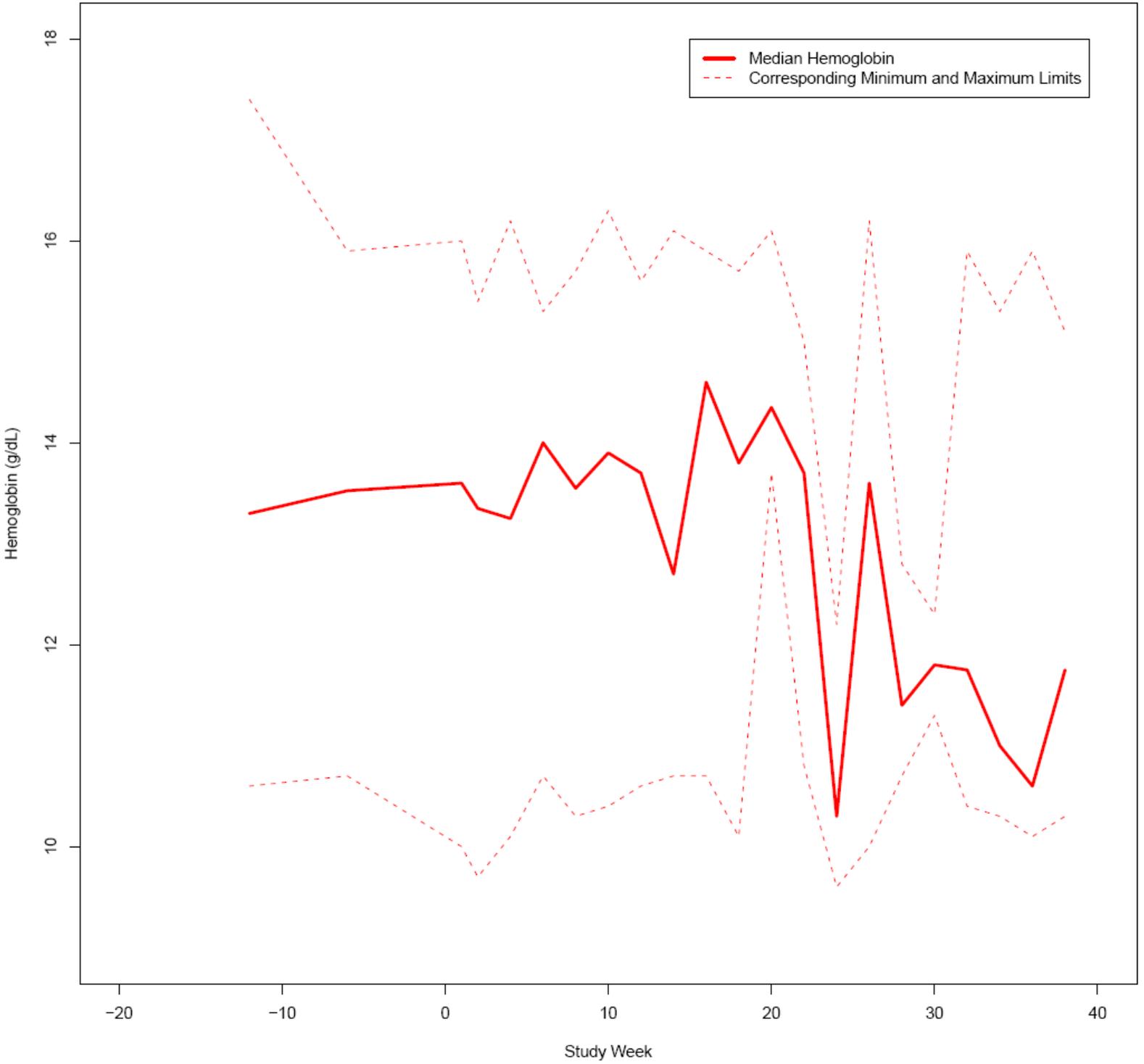
Parameter	Visit		prGCD (N=24)
Clinically Relevant Deterioration	Visit 1 (Day 1)	n	24
		Yes	0
		No	24 (100.0%)
	Visit 3 (Week 4)	n	24
		Yes	0
		No	24 (100.0%)
	Visit 5 (Week 8)	n	24
		Yes	0
		No	24 (100.0%)
	Visit 7 (Month 3)	n	23
		Yes	0
		No	23 (100.0%)
	Visit 14 (Month 6)	n	14
		Yes	0
		No	14 (100.0%)
	Visit 20 (Month 9)	n	4
		Yes	0
		No	4 (100.0%)

Source: Table 9.3 from pgs. 44 - 47 of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

Figure 9
(Interim Population #1)

Median Hemoglobin By Study Week



Source: Reviewer's Figure.

At the time of last data cutoff (i.e. April 30, 2010), the data became very sparse after Study Week 20 as only a few patients had available data after that time point. With the exception of the Month 6 visit (data available for 14 patients), data for only 2-6 patients were available after Study Week 20, and this predictably resulted in more variable hemoglobin concentration fluctuations. There was, however, a fairly stable hemoglobin concentration level (relative to the screening and the stability evaluation periods) through Study Week 20.

Table 15
Liver Volume - Clinically Relevant Deterioration at Month 9
(Interim Population #1)

Parameter	Visit		prGCD (N=24)
Clinically Relevant Deterioration	Visit 20 (Month 9)	n	4
		Yes	0
		No	4 (100.0%)

Source: Table 8.3 from pg. 43 of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

Table 16
Platelet Count – Clinically Relevant Deterioration at Pivotal Visits
(Interim Population #1)

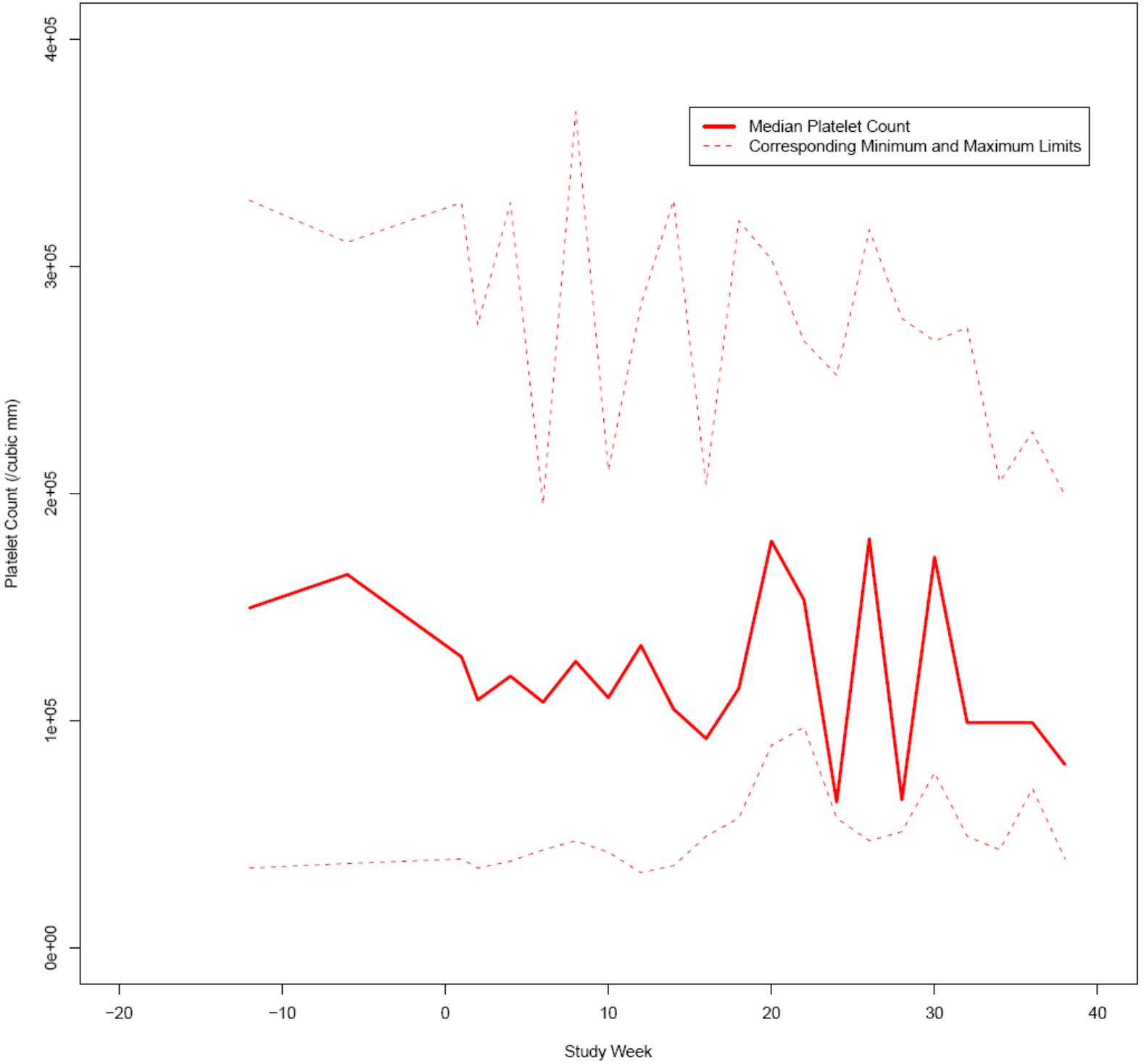
Parameter	Visit		prGCD (N=24)
Clinically Relevant Deterioration	Visit 1 (Day 1)	n	24
		Yes	1 (4.2%)
		No	23 (95.8%)
	Visit 3 (Week 4)	n	24
		Yes	0
		No	24 (100.0%)
	Visit 5 (Week 8)	n	24
		Yes	0
		No	24 (100.0%)
	Visit 7 (Month 3)	n	23
		Yes	1 (4.3%)
		No	22 (95.7%)
	Visit 14 (Month 6)	n	14
		Yes	2 (14.3%)
		No	12 (85.7%)
	Visit 20 (Month 9)	n	4
		Yes	1 (25.0%)
		No	3 (75.0%)

Source: Table 10.3 from pgs. 48 - 51 of the PB-06-002 Abbreviated CSR.

Note: Denominators for percentages are n, the number of overall patients with data at a given protocol defined visit.

Figure 10
(Interim Population #1)

Median Platelet Count By Study Week



Source: Reviewer's Figure.

As previously stated for hemoglobin concentration, at the time of last data cutoff (i.e. April 30, 2010), the data became very sparse after Study Week 20 as only a few patients had available data after that time point. With the exception of the Month 6 visit (data available for 14 patients), data for only 2-6 patients were available after Study Week 20, and this predictably resulted in more variable platelet count fluctuations. There was, however, a fairly stable platelet count level (relative to the screening and the stability evaluation periods) through Study Week 20.

3.3 PB-06-003

3.3.1 Background and Analysis Information

The objective of this multi-center, double-blind, parallel dose-group extension trial is to extend the assessment of the safety and efficacy of ELELYSO in patients with Type 1 Gaucher disease who completed 9 months of treatment in studies PB-06-001 or PB-06-002. In this extension trial, patients receive IV infusion of ELELYSO every two weeks and have the option to receive their infusions at the selected medical center, infusion center, or at home. The total duration of treatment will be at least 15 months (64 weeks) and no more than 30 months (128 weeks). Day 1 of this study is the final visit of Study PB-06-001 or the final visit of PB-06-002.

There are three treatment groups in this study, with patients continuing to receive the allocated dose from PB-06-001 in a blinded fashion or the same dose received at the completion of PB-06-002 in an open-label fashion.

Treatment Group 1: 30 units/kg from study PB-06-001

Treatment Group 2: 60 units/kg from study PB-06-001

Treatment Group 3: the same ELELYSO dose received at the completion of PB-06-002

Up to 60 patients from 15 study sites in 12 countries are planned to be enrolled into this study. At the time of database freeze on Apr 30, 2010, 29 patients from 12 study sites were enrolled with 26 patients (12 from the 30 units/kg dose group and 14 from the 60 units/kg dose group) from the pivotal dose-comparison study, PB-06-001, and 3 patients from the switch-over study, PB-06-002. Consequently the CSR submitted within this NDA is an abbreviated one based on interim data. The three patients from Study PB-06-002 have insufficient data (including no specification of ELELYSO dose) and hence are not included in any of the efficacy analyses.

Efficacy is determined through clinical judgment by evaluation of the following parameters. Descriptive statistics are subsequently utilized with no inferences made from formal statistical methodology. In this analysis, the screening visit value from trial PB-06-001 represents the baseline measure for spleen and liver volumes while the study day 1 value from trial PB-06-001 represents the baseline measure for hemoglobin concentration and platelet count.

- Percentage change from Baseline in Spleen Volume at all timepoints
- Change from Baseline in Hemoglobin Concentration at all timepoints
- Percentage change from Baseline in Liver Volume at all timepoints
- Change from Baseline in Platelet Count at all timepoints

This interim analysis, which is the basis of the submitted abbreviated CSR, is performed on cleaned data as of April 30, 2010. The study population used for the results presented within the abbreviated CSR (i.e. “Interim Population”) is defined as all enrolled subjects who received treatment with ELELYSO on or before April 30, 2010. The data used for the summary tables will be the records collected on or before the date of April 30, 2010. The image evaluation plan for determining spleen and liver volumes is the same as what was previously presented in section 3.1.4.

The individual analysis of the said parameters is primarily driven by descriptive statistics and a relevant corresponding figure. Specifically for each parameter, two separate tables of descriptive statistics will be presented along with a corresponding figure which presents two separate data plots. The first table displays descriptive statistics for the measured value of the parameter of interest (i.e. spleen volume, hemoglobin concentration, liver volume, or platelet count) at pivotal study weeks starting from Week 1 of study PB-06-001. The second table displays descriptive statistics for the percentage change (or change) from baseline in the parameter of interest at pivotal PB-06-001 post-baseline study weeks which lead into PB-06-003 study weeks. The following figure corresponding to these two tables first presents the sample median of the measured value for the parameter of interest by dose group across all treatment experienced study weeks starting from Week 1 of PB-06-001 along with corresponding minimum and maximum limits. This figure then presents the sample median for the percentage change (or change) from baseline in the parameter of interest by dose group across all PB-06-001 post-baseline study weeks which lead into PB-06-003 study weeks along with corresponding minimum and maximum limits. These descriptive and non-parametric statistics were chosen to be reflected within the figures because they are most optimal in this exploratory small sample setting. Each figure will have a vertical line at Week 38 separating the PB-06-001 and PB-06-003 data.

It is to be noted that the spleen and liver volume data was presented only up to Month 3 of the PB-06-003 trial due to their sparseness after Month 3. In addition, the hemoglobin concentration and platelet count data was presented only up to Month 6 of the PB-06-003 trial due to their sparseness after Month 6. One further caveat relates to the PB-06-003 analysis datasets pertaining to hemoglobin concentration and platelet count. These datasets incorrectly reflected the screening value from study PB-06-001 as the baseline measure for these lab parameters. The appropriate adjustment was made by the statistical review team and is reflected in the results presented below i.e. utilizing the study day 1 value from trial PB-06-001 as the baseline measure.

3.3.2 Analysis Tables and Figures for Efficacy Parameters

Table 17
Spleen Volume by Pivotal Study Week
(Interim Population)

Spleen Volume (mL)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
PB-06-001: Study Week 0 / Screening			
n	12	14	26
Mean (SD)	2324.0 (1208.97)	2120.1 (1426.5)	2214.2 (1308.5)
Median	1656.9	1699.5	1656.9
Min, Max	1026, 4901	914, 5418	914, 5418
PB-06-001: Study Week 38 / 9-Month			
PB-06-003: Study Week 1 / Day 1			
n	12	14	26
Mean (SD)	1690.7 (956.42)	1352.0 (1096.81)	1508.3 (1028.44)
Median	1226.1	1044.6	1093.4
Min, Max	754, 3894	483, 4220	483, 4220
PB-06-001: Study Week 50 / 12-Month			
PB-06-003: Study Week 12 / 3-Month			
n	12	14	26
Mean (SD)	1707.7 (1069.53)	1267.9 (1114.05)	1470.9 (1094.84)
Median	1135.2	937.1	974.1
Min, Max	693, 4332	442, 4339	442, 4339

Source: Reviewer's Table.

Table 18
Percentage Change from Screening/Baseline in Spleen Volume by Pivotal Study
Week
(Interim Population)

Percentage Change (%)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
Study Week 0 to Study Week 38 / Screening to 9-Month			
n	12	14	26
Mean (SD)	-27.9 (7.79)	-39.3 (8.75)	-34.0 (10.00)
Median	-27.9	-38.2	-35.1
Min, Max	-43, -16	-56, -20	-56, -16
Study Week 0 to Study Week 50 / Screening to 12-Month			
n	12	14	26
Mean (SD)	-28.9 (8.17)	-43.5 (11.39)	-36.8 (12.32)
Median	-28.7	-43.4	-36.2
Min, Max	-44, -12	-64, -17	-64, -12

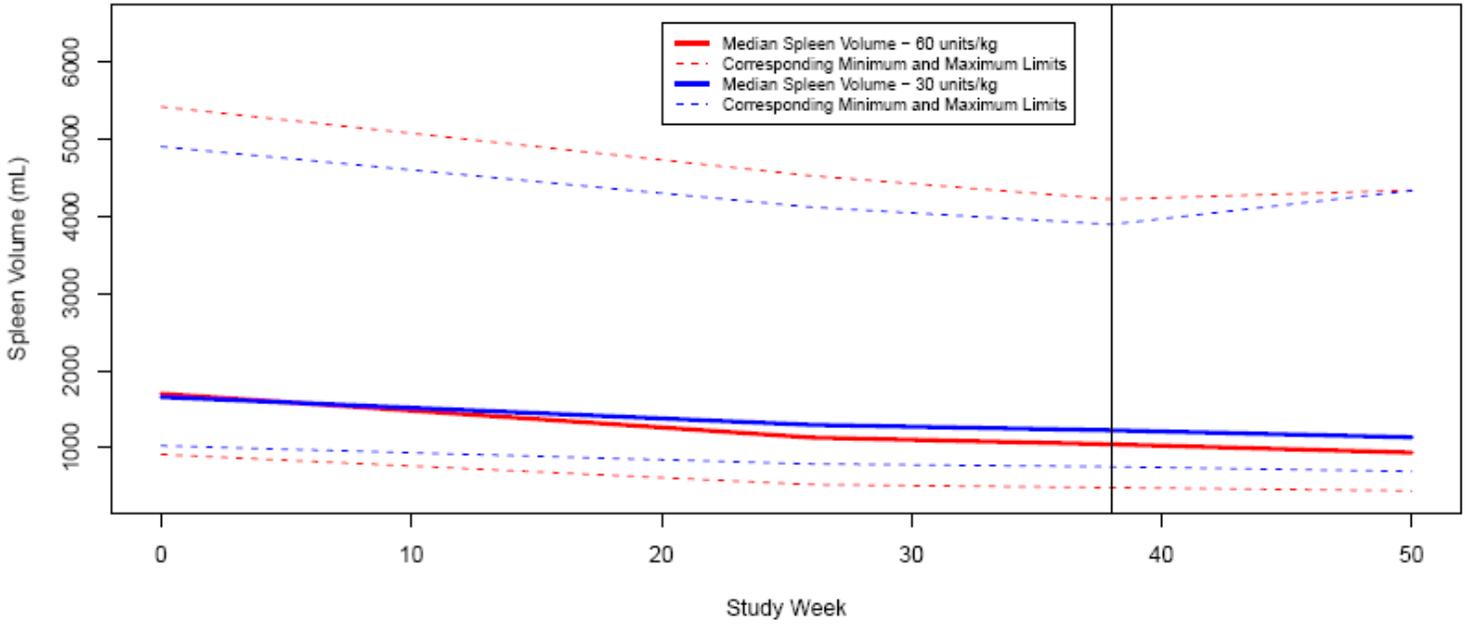
Source: Reviewer's Table.

Note: Study Weeks / Visits presented within this table correspond to those from study PB-06-001. Study Week 38 / 9-Month Visit PB-06-001 = Study Week 1 / Day 1 Visit PB-06-003; Study Week 50 / 12-Month Visit PB-06-001 = Study Week 12 / 3-Month Visit PB-06-003.

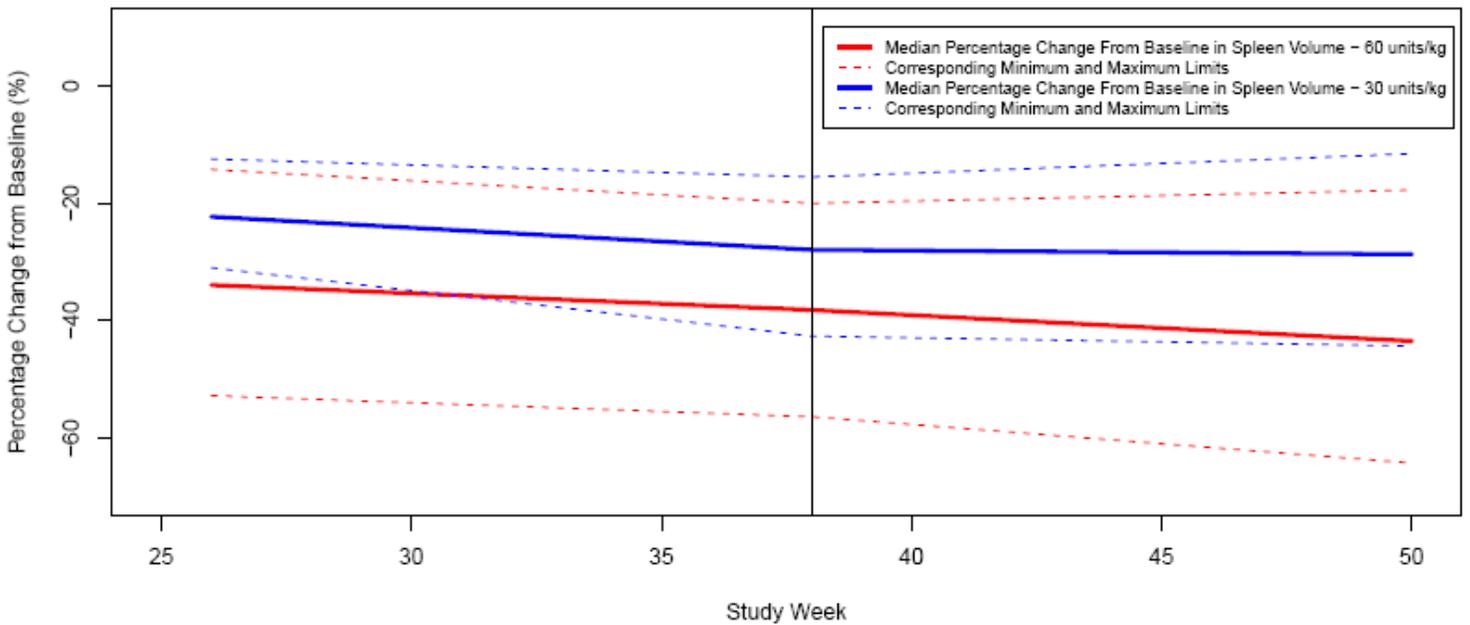
**Figure 11
(Interim Population)**

PB-06-003: SPLEEN VOLUME – Verticle Line at Week 38 Separating PB-06-001 and PB-06-003 Data

Spleen Volume By Study Week



Percentage Change from Baseline in Spleen Volume By Study Week



Source: Reviewer's Figure.

Table 19
Hemoglobin Concentration by Pivotal Study Week
(Interim Population)

Hemoglobin Concentration (g/dL)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
PB-06-001: Study Week 1 / Baseline			
n	12	14	26
Mean (SD)	12.49 (1.822)	11.39 (2.746)	11.90 (2.386)
Median	12.95	10.60	12.25
Min, Max	7.9, 14.6	5.5, 16.0	5.5, 16.0
PB-06-001: Study Week 38 / 9-Month			
PB-06-003: Study Week 1 / Day 1			
n	12	14	26
Mean (SD)	14.22 (1.408)	13.63 (2.057)	13.90 (1.779)
Median	13.80	14.25	14.05
Min, Max	12.2, 16.9	8.6, 16.5	8.6, 16.9
PB-06-001: Study Week 50 / 12-Month			
PB-06-003: Study Week 12 / 3-Month			
n	12	14	26
Mean (SD)	14.21 (1.687)	13.63 (2.560)	13.90 (2.179)
Median	14.00	13.80	14.00
Min, Max	11.3, 17.4	7.3, 17.1	7.3, 17.4
PB-06-001: Study Week 64 / 15-Month			
PB-06-003: Study Week 26 / 6-Month			
n	9	12	21
Mean (SD)	13.87 (1.492)	13.48 (1.811)	13.64 (1.653)
Median	13.60	13.35	13.50
Min, Max	12.0, 16.5	11.1, 17.3	11.1, 17.3

Source: Reviewer's Table.

Table 20
Change from Baseline in Hemoglobin Concentration by Pivotal Study Week
(Interim Population)

Hemoglobin Concentration (g/dL)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
Study Week 1 to Study Week 38 / Baseline to 9-Month			
n	12	14	26
Mean (SD)	1.73 (1.494)	2.24 (1.474)	2.00 (1.476)
Median	1.60	1.75	1.65
Min, Max	-0.1, 5.8	0.5, 5.1	-0.1, 5.8
Study Week 1 to Study Week 50 / Baseline to 12-Month			
n	12	14	26
Mean (SD)	1.72 (1.135)	2.24 (1.472)	2.00 (1.328)
Median	1.60	1.85	1.80
Min, Max	0.0, 4.1	0.9, 6.2	0.0, 6.2
Study Week 1 to Study Week 64 / Baseline to 15-Month			
n	9	12	21
Mean (SD)	1.71 (1.282)	2.31 (1.453)	2.06 (1.383)
Median	1.80	1.60	1.70
Min, Max	-0.2, 4.2	1.0, 5.6	-0.2, 5.6

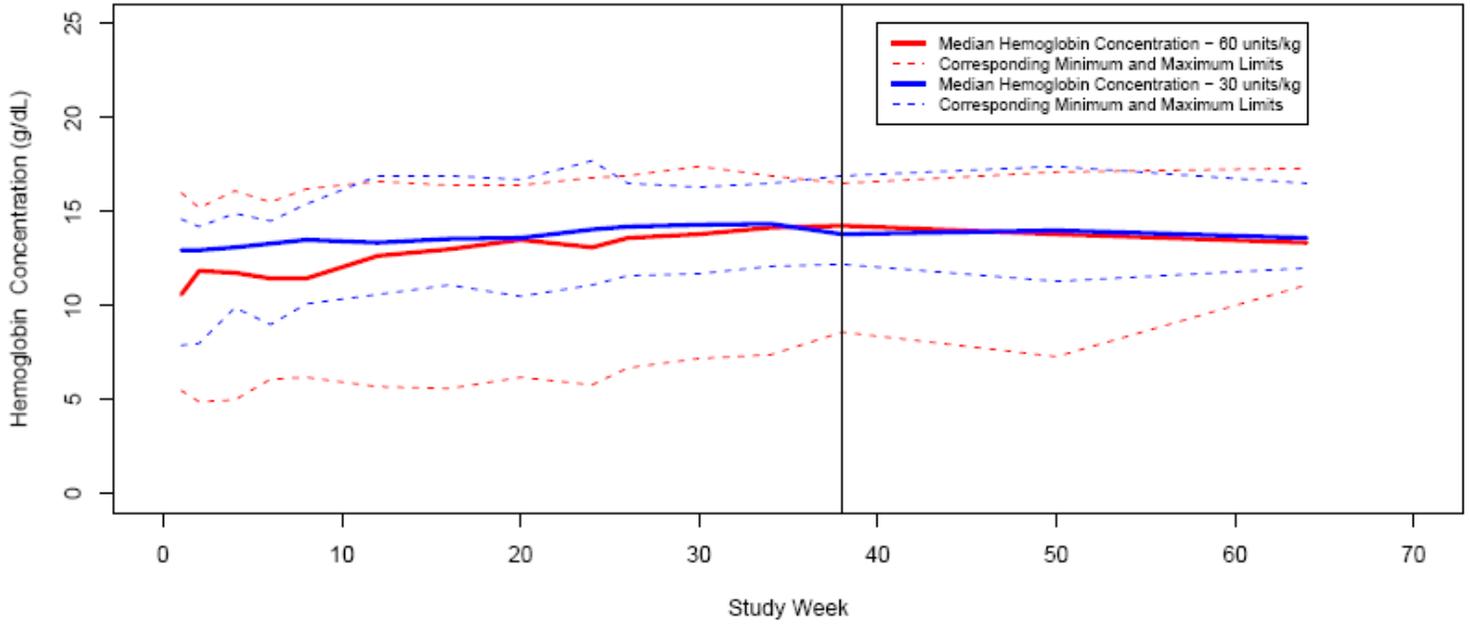
Source: Reviewer's Table.

Note: Study Weeks / Visits presented within this table correspond to those from study PB-06-001. Study Week 38 / 9-Month Visit PB-06-001 = Study Week 1 / Day 1 Visit PB-06-003; Study Week 50 / 12-Month Visit PB-06-001 = Study Week 12 / 3-Month Visit PB-06-003; Study Week 64 / 15-Month Visit PB-06-001 = Study Week 26 / 6-Month Visit PB-06-003.

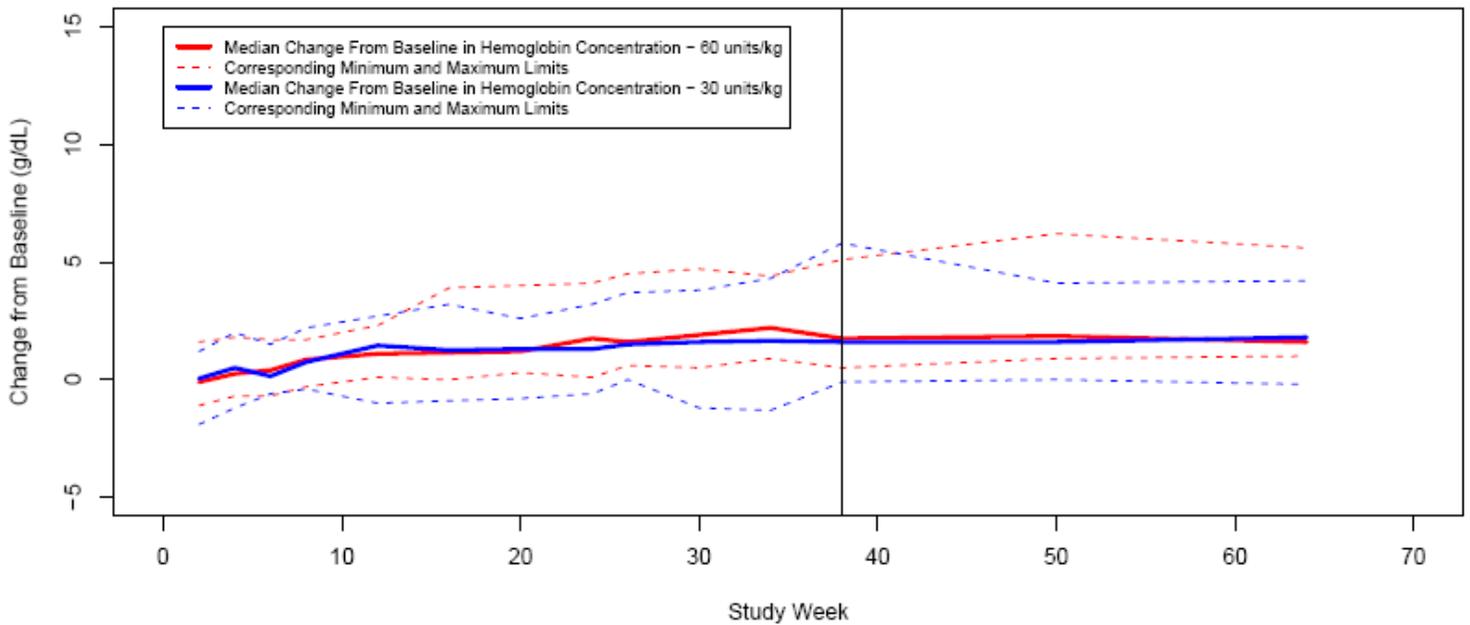
**Figure 12
(Interim Population)**

PB-06-003: HEMOGLOBIN CONCENTRATION – Verticle Line at Week 38 Separating PB-06-001 and PB-06-003 Data

Hemoglobin Concentration By Study Week



Change from Baseline in Hemoglobin Concentration By Study Week



Source: Reviewer's Figure.

Table 21
Liver Volume by Pivotal Study Week
(Interim Population)

Liver Volume (mL)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
PB-06-001: Study Week 0 / Screening			
n	12	14	26
Mean (SD)	2999.7 (779.45)	2470.5 (484.9)	2714.7 (679.7)
Median	2794.3	2440.1	2603.5
Min, Max	2282, 5096	1758, 3297	1758, 5096
PB-06-001: Study Week 38 / 9-Month			
PB-06-003: Study Week 1 / Day 1			
n	12	14	26
Mean (SD)	2584.5 (577.8)	2189.5 (390.87)	2371.8 (516.40)
Median	2473.2	2094.7	2263.8
Min, Max	2000, 4122	1654, 2894	1654, 4122
PB-06-001: Study Week 50 / 12-Month			
PB-06-003: Study Week 12 / 3-Month			
n	12	14	26
Mean (SD)	2515.6 (642.08)	2118.7 (318.09)	2301.9 (524.13)
Median	2461.7	2157.1	2236.9
Min, Max	1944, 4255	1678, 2600	1678, 4255

Source: Reviewer's Table.

Table 22
Percentage Change from Screening/Baseline in Liver Volume by Pivotal Study
Week
(Interim Population)

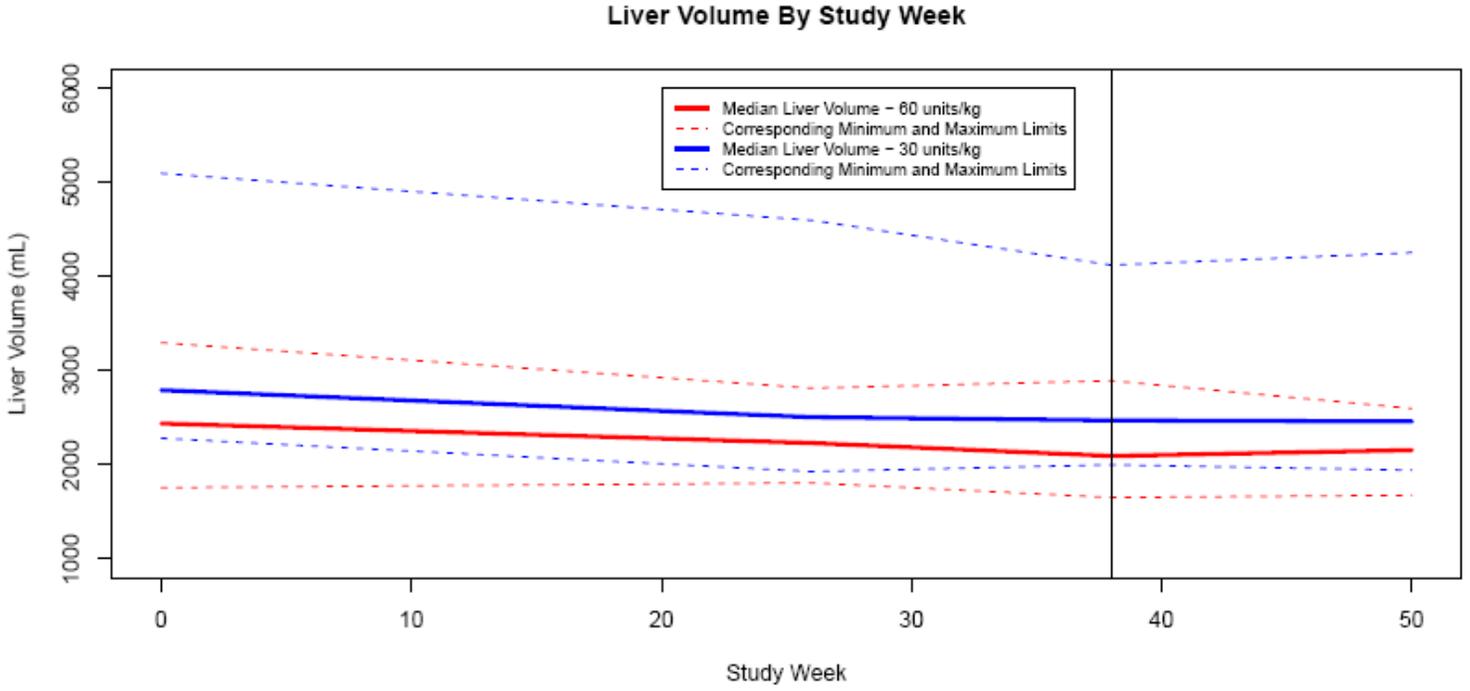
Percentage Change (%)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
Study Week 0 to Study Week 38 / Screening to 9-Month			
n	12	14	26
Mean (SD)	-13.2 (4.96)	-10.8 (6.84)	-11.9 (6.05)
Median	-14.1	-12.2	-13.0
Min, Max	-19, -3	-22, -2	--22, -2
Study Week 0 to Study Week 50 / Screening to 12-Month			
n	12	14	26
Mean (SD)	-15.9 (5.20)	-13.2 (8.89)	-14.4 (7.42)
Median	-16.4	-11.3	-15.2
Min, Max	-26, -5	-33, -2	-33, -2

Source: Reviewer's Table.

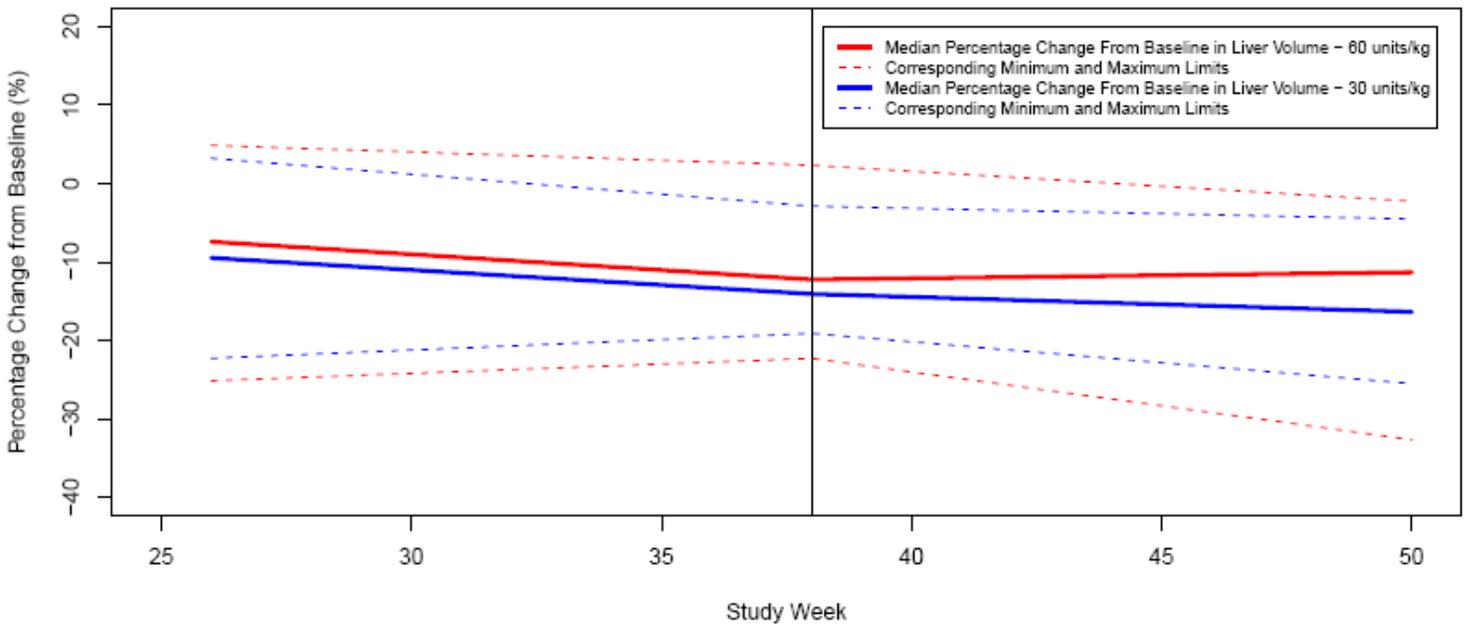
Note: Study Weeks / Visits presented within this table correspond to those from study PB-06-001. Study Week 38 / 9-Month Visit PB-06-001 = Study Week 1 / Day 1 Visit PB-06-003; Study Week 50 / 12-Month Visit PB-06-001 = Study Week 12 / 3-Month Visit PB-06-003.

**Figure 13
(Interim Population)**

PB-06-003: LIVER VOLUME - Verticle Line at Week 38 Separating PB-06-001 and PB-06-003 Data



Percentage Change from Baseline in Liver Volume By Study Week



Source: Reviewer's Figure.

Table 23
Platelet Count by Pivotal Study Week
(Interim Population)

Platelet Count (/mm ³)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
PB-06-001: Study Week 1 / Baseline			
n	12	14	26
Mean (SD)	64900.0 (30132.62)	69042.9 (28242.3)	67130.8 (28613.11)
Median	55000.0	62000.0	55500.0
Min, Max	27000, 112000	39000, 134000	27000, 134000
PB-06-001: Study Week 38 / 9-Month			
PB-06-003: Study Week 1 / Day 1			
n	12	14	26
Mean (SD)	75350.0 (45283.52)	112892.9 (53329.2)	95565.4 (52396.94)
Median	66500.0	110500.0	99750.0
Min, Max	20000, 166000	25000, 241000	20000, 241000
PB-06-001: Study Week 50 / 12-Month			
PB-06-003: Study Week 12 / 3-Month			
n	12	14	26
Mean (SD)	80325.0 (41805.98)	122857.1 (53857.2)	103226.9 (52391.48)
Median	70000.0	137500.0	99000.0
Min, Max	23000, 153000	25000, 228000	23000, 228000
PB-06-001: Study Week 64 / 15-Month			
PB-06-003: Study Week 26 / 6-Month			
n	8	12	20
Mean (SD)	98125.0 (60736.99)	141666.7 (63130.9)	124250.0 (64385.25)
Median	89500.0	155500.0	137500.0
Min, Max	24000, 188000	23000, 279000	23000, 279000

Source: Reviewer's Table.

Table 24
Change from Baseline in Platelet Count by Pivotal Study Week
(Interim Population)

Platelet Count (/mm ³)	30 units/kg (N = 12)	60 units/kg (N = 14)	Total (N = 26)
Study Week 1 to Study Week 38 / Baseline to 9-Month			
n	12	14	26
Mean (SD)	10450.0 (22341.67)	43850.0 (49818.51)	28434.6 (42409.14)
Median	7100.0	40500.0	20500.0
Min, Max	-25000, 59000	-15000, 186000	-25000, 186000
Study Week 1 to Study Week 50 / Baseline to 12-Month			
n	12	14	26
Mean (SD)	15425.0 (22003.06)	53814.3 (51270.23)	36096.2 (44281.09)
Median	14450.0	53500.0	27000.0
Min, Max	-33000, 42000	-15000, 173000	-33000, 173000
Study Week 1 to Study Week 64 / Baseline to 15-Month			
n	8	12	20
Mean (SD)	24125.0 (38524.34)	72250.0 (60981.55)	53000.0 (57313.54)
Median	27500.0	58500.0	47000.0
Min, Max	-33000, 81000	-16000, 224000	-33000, 224000

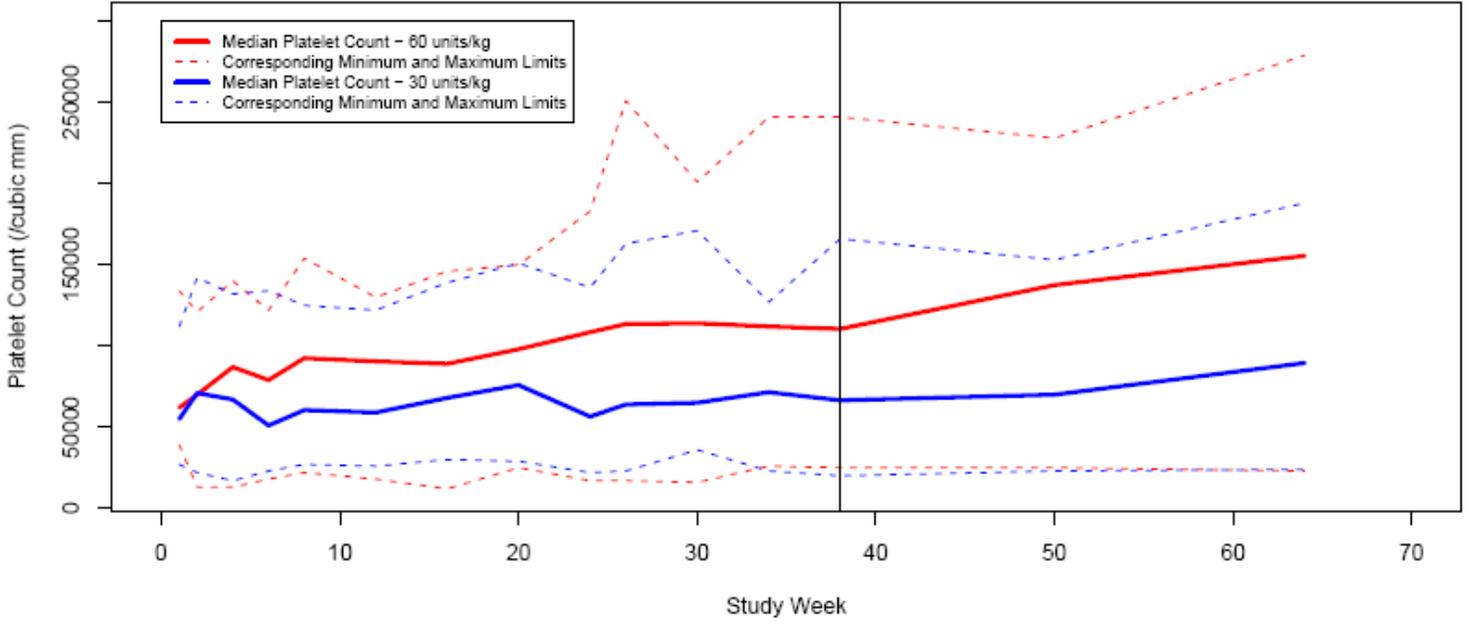
Source: Reviewer's Table.

Note: Study Weeks / Visits presented within this table correspond to those from study PB-06-001. Study Week 38 / 9-Month Visit PB-06-001 = Study Week 1 / Day 1 Visit PB-06-003; Study Week 50 / 12-Month Visit PB-06-001 = Study Week 12 / 3-Month Visit PB-06-003; Study Week 64 / 15-Month Visit PB-06-001 = Study Week 26 / 6-Month Visit PB-06-003.

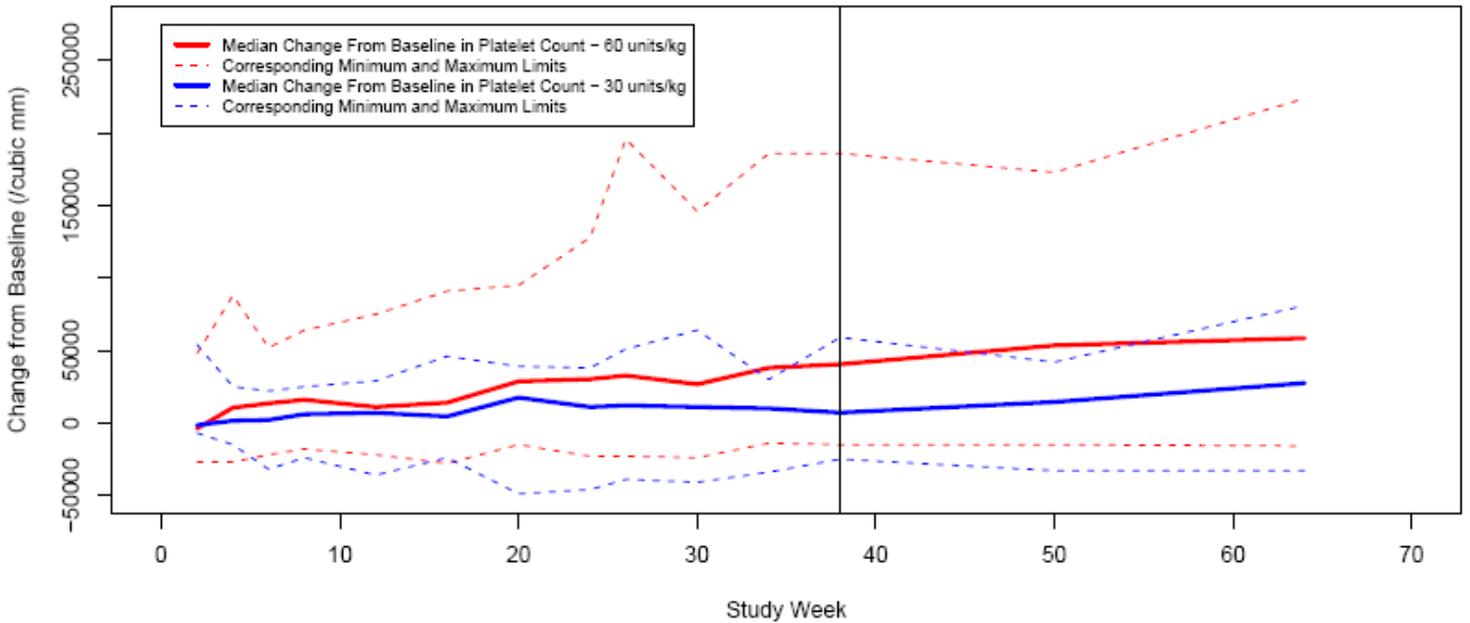
**Figure 14
(Interim Population)**

PB-06-003: PLATELET COUNT – Verticle Line at Week 38 Separating PB-06-001 and PB-06-003 Data

Platelet Count By Study Week



Change from Baseline in Platelet Count By Study Week



Source: Reviewer's Figure.

It can be seen from the presented outputs that patients treated for 9 months in study PB-06-001 continue to do well in extension study PB-06-003.

4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses of the primary endpoint (i.e. percentage change from baseline in spleen volume) in study PB-06-001 corresponding to gender were administered with no differences in inferential results when compared to the overall analysis of this endpoint. No other special subpopulations were identified. The number of non-Caucasian patients in this study was too small (only one patient) to adequately assess any difference in effects by race. In addition, there were no Pediatric patients (i.e. age < 18) and there was only one Geriatric patient (i.e. age > 65) participating in the PB-06-001 trial. Consequently, an adequate assessment of any difference in effects by age group could not be made either. As a result, only valid generalizations to Caucasian adults can be made.

5.0 SUMMARY AND CONCLUSIONS

There were a few, yet significant, deficiencies encountered throughout the statistical review of NDA 22-458, and these review concerns ultimately motivate a final recommendation from the statistical review team that a CR action be taken by DGP. The principal review concerns are summarized below.

Manufacturing

Overall, the primary issue in this NDA review pertained to manufacturing. There were a number of major issues regarding comparability and overall manufacturing quality as determined by the review team from the Division of Therapeutic Proteins (DTP). The consequence of these deficiencies is that the trials discussed in this review can not support the safety and efficacy profile of this biologic product. These specific issues are beyond the scope of this review hence refer to the review document provided by DTP for details.

Level of Evidence

The major statistical issue in this NDA review pertained to the level of evidence presented by the sponsor for the effectiveness of ELEYSO. The development program for this original biologic was ultimately determined by the statistical reviewer as being incomplete.

VPRIV was the latest Type 1 Gaucher Disease treatment approved by the FDA on February 26, 2010, and the main components of its clinical development program, excluding extension studies, consisted of four clinical trials: TKT032 (an analogous study to PB-06-001 with similar results); HGT-GCB-039 (a 'head-to-head' non-inferiority study between VPRIV and CERZYME); TKT034 (an analogous study to PB-06-002 with similar results); and TKT025 (a dose escalation Phase 1 study). The primary basis for the efficacy claim ultimately reflected in the approved product label for VPRIV was

the joint positive results from the TKT032 and HGT-GCB-039 studies respectively. Protalix Biotherapeutics, Ltd., however, did not include a ‘head-to-head’ study between ELELYSO and the previously approved FDA treatments for Type 1 Gaucher Disease (i.e. CERESYME or VPRIV). The absence of an active control study within the development program of ELELYSO lowers the level of evidence compared to that previously demonstrated for VPRIV.

In addition, both PB-06-002 and PB-06-003 were unfinished studies at the time of this NDA submission (April 26, 2010) hence the sponsor only presented interim results within abbreviated CSRs for each study and did not identify the specific ELELYSO doses for patients who participated in the PB-06-002 trial. The clinical datasets for both the PB-06-002 and PB-06-003 studies were also not submitted by the sponsor (only the analysis datasets were submitted).

PB-06-001 Study Design

This study design is more observational in nature. The use of a within-dose comparison (formally assessed by a one sample *t*-test) is not traditionally an acceptable approach for establishing efficacy. Inferential results (e.g. p-values) from this within-group comparison are not statistically valid, therefore have no basis regarding any efficacy claim and thus should not be emphasized. Nonetheless, the change from baseline in each endpoint was determined, by clinical judgment, to be clinically meaningful.

PB-06-001 Patient Population

It was determined by the clinical review team that the patient population studied within the PB-06-001 trial was a relative healthy one which ultimately compromises the interpretability of the study results pertaining to safety. This specific issue is beyond the scope of this review hence refer to the review document provided by the clinical review team for details.

PB-06-002 Study Design

The efficacy results from study PB-06-002 are marginally supportive at best due to the open-label switchover design utilized by the sponsor. This study could have been designed as a double-blind randomized withdrawal or double-blind randomized add-on study which would have resulted in much more useful and supportive efficacy data.

Due to the orphan nature of Type I Gaucher Disease, and the limitations of the submitted clinical studies, the determination of the clinical effectiveness of ELELYSO[®] will rely more on clinical judgment than on statistical rigor usually required for larger studies. The efficacy results from all three clinical studies within the ELELYSO development program were positive in that they each showed a clinically meaningful change from baseline, based primarily on clinical judgment with supportive statistical methodology, in the endpoints of interest (i.e. spleen volume, hemoglobin concentration, liver volume, and platelet count). This was principally established in study PB-06-001 with additional marginal support from studies PB-06-002 and PB-06-003. Although Type 1 Gaucher Disease is a rare and potentially serious and life threatening condition, the application deficiencies described below motivate a statistical recommendation that the sponsor

conduct at least one additional adequate and well-controlled study in order to obtain regulatory approval.

This additional trial should be a randomized, controlled, and properly powered ‘head-to-head’ study which compares ELELYSO with at least one of the currently marketed treatments for Type 1 Gaucher Disease (i.e. CEREZYME[®] or VPRIV[®] or both individually in a three arm trial). This study should recruit patients which are representative of the true Type 1 Gaucher Disease patient population and be of high quality with subsequent compelling and positive results pertaining to the risk/benefit profile of this original biologic. In addition, final CSRs for studies PB-06-002 and PB-06-003 should be submitted with proper identification of ELELYSO dose for patients who participated in the PB-06-002 study. Finalized clinical datasets along with corresponding analysis datasets (with appropriate metadata for each) should also be submitted for both the PB-06-002 and PB-06-003 studies.

6.0 REFERENCES

[1] **E9** Statistical Principles for Clinical Trials Guidance for Industry:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BEHRANG D VALI
02/24/2011

MICHAEL E WELCH
02/24/2011
Concur with review.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 22-458	Applicant: Protalix Biotherapeutics, Ltd.	Stamp Date: 26APR2010
Drug Name: (b) (4) (taliglucerase alpha)	NDA/BLA Type: Type 1 NDA; 505(b)(1)	Indication: Type I Gaucher Disease

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	This was an electronic submission by the sponsor.
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			This electronic submission was eCTD compliant and of satisfactory quality.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			There was only one complete clinical study report (CSR), and this corresponded to the sponsor's sole adequate and well-controlled study. The CSRs for the two supportive studies in addition to both the ISE and ISS were abbreviated reports.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).		X		No subgroup analyses for gender, race and age (e.g. geriatric) were presented for the sole adequate and well-controlled study or the two supportive studies.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			All data sets provided were of satisfactory quality but were not compliant with CDISC standards. Appropriate data definition files in Define.PDF format were included.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the statistical perspective, please state below the reasons and provide comments to be sent to the Applicant.

N/A

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The designs utilized were adequate.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			The endpoints and methods of analysis were specified in the CSRs (including the protocols and Statistical Analysis Plans (SAPs)).
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	There were no traditional interim analyses conducted.
Appropriate references for novel statistical methodology (if present) are included.		X		The statistical methodology was not novel per se hence no references were presented.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Safety datasets were submitted for each study individually; however this data can be integrated.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			Multiple missing data handling strategies were administered by the sponsor which included Multiple Imputation (MI) for primary analysis purposes. For sensitivity analysis purposes, Mixed Model Repeated Measures (MMRM), Last Observation Carried Forward (LOCF), and Worst Case Imputation (i.e. no-change from baseline) were utilized.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Please communicate below any additional requests to the Applicant for the 74-day letter (or any time point following Day 74 within the review cycle).

- (1) Clarify the randomization methodology administered (i.e. simple or adaptive, stratified or non-stratified, blocks utilized or not utilized, etc.) for the PB-06-001 study.

Background

Pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21, Part 314 of the Code of Federal Regulations, Protalix Ltd. has submitted this New Drug Application (NDA) for (b) (4) (taliglucerase alfa). The active ingredient in (b) (4) [delivery by intravenous (IV) infusion every two weeks] is taliglucerase alfa. This is the first prescription product to have taliglucerase alfa as its active ingredient. (b) (4) has undergone clinical development under IND 69,703 in patients with Type 1 (i.e. non-neurological) Gaucher Disease, and has been developed specifically to establish safety and efficacy in this patient population. Currently, there are effective FDA-approved treatment options for patients with Type 1 Gaucher disease; however, due to product shortages caused by manufacturing issues, this serious and life threatening condition still remains as one with an unmet medical need.

Protalix Ltd. obtained Fast Track designation from the Agency on August 24, 2009, and the final component of their rolling submission (which officially starts the PDUFA clock) was delivered on April 26, 2010. The review cycle established by the Division of Gastroenterology Products (DGP) was a standard 10 month cycle. The application also qualifies for Orphan Exception under section 736(a)(1)(E) of the Federal Food, Drug and Cosmetic Act. Protalix Ltd. is currently in the process of obtaining *Orphan Designation* from the Office of Orphan Products Development (OOPD).

This NDA was submitted electronically in eCTD format. The submission was sent via the FDA Electronic Submissions Gateway (ESG) and its content along with the electronic data sets and labeling information have been stored in the electronic document room (EDR) at this path location: <\\Cdsub1\evsprod\NDA022458>. The submission can consequently be accessed directly at the previous path specified.

Brief Overview and Summary of Relevant Trials

(b) (4) has been studied by Protalix Ltd. for the treatment of Type I Gaucher Disease, and its clinical efficacy and safety has been principally evaluated through three studies: a Phase III, multicenter, randomized, double-blind, and parallel dose-group study (PB-06-001) which serves as the lone adequate and well controlled study of this clinical development program as per 21 CFR 314.126; a Phase III, multicenter, open-label, switchover study (PB-06-002); and a Phase III, multicenter, double-blind, parallel dose-group study (PB-06-003) which is a long term extension study of patients from trials PB-06-001 and PB-06-002.

The following table presents information on the three relevant trials contained in the submission.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Type of Study; Phase	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Regimen; Route	Number of Dosed Subjects	Patient Diagnosis	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety; Phase III	PB-06-001	To assess the safety and efficacy of taliglucerase alfa in treatment naïve patients	Multicenter, randomized, double-blind, parallel dose-group	taliglucerase alpha 60 units/kg and 30 units/kg; every two weeks; IV infusion	60 units/kg: 16 30 units/kg: 16 Total: 32	Patients with Type I Gaucher Disease	38 weeks	Complete; Full
Efficacy and Safety; Phase III	PB-06-002	To assess the safety and efficacy of taliglucerase alfa in patients previously treated with Imiglucerase (CEREZYME®)	Multicenter, open-label, switchover	taliglucerase alpha equivalent to Imiglucerase dose; every two weeks; IV infusion	Total: 24	Patients with Type I Gaucher Disease	38 weeks	Ongoing; Abbreviated
Efficacy and Safety; Phase III	PB-06-003	To extend the assessment of the safety and efficacy of taliglucerase alpha in PB-06-001 and PB-06-002 patients who completed 9 months of treatment	Multicenter, double-blind, parallel dose-group, extension	taliglucerase alpha 60 units/kg and 30 units/kg (PB-06-001 patients), and dose equivalent to Imiglucerase dose (PB-06-002 patients); every two weeks; IV infusion	60 units/kg: 14 30 units/kg: 12 PB-06-002 dose: 3 Total: 29	Patients with Type I Gaucher Disease	64 weeks	Ongoing; Abbreviated

Review Issues

All review issues determined so far have been captured above in the additional requests to the Applicant for the 74-day letter (or any time point following Day 74 within the review cycle).

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22458	ORIG-1	PROTALIX LTD	PLANT CELL EXPRESSED RECOMBINANT HUMAN G

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/s/

BEHRANG D VALI
08/12/2010

MILTON C FAN
08/12/2010