

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205494Orig1s000**

**STATISTICAL REVIEW(S)**



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/BLA #:** NDA 205494

**Drug Name:** CERDEGLA™ (eliglustat/Genz-112638) 84 mg in capsule form to be administered orally twice per day (BID) with or without food

**Indication(s):** The long-term treatment of adult patients with Gaucher Disease Type 1 (GD1)

**Applicant:** Genzyme Corporation

**Date(s):** Stamp Date: September 20, 2013  
PDUFA Goal Date: August 20, 2014

**Review Priority:** Priority with Major Amendment under the PDUFA V Program

**Biometrics Division:** Division of Biometrics III

**Statistical Reviewer:** Benjamin P. Vali, M.S.

**Concurring Reviewers:** Freda Cooner, Ph.D.

**Medical Division:** Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Clinical Team:** Medical Reviewer: Karyn Berry, M.D.  
Medical Team Leader: Lara Dimick, M.D., F.A.C.S.

**Project Manager:** Jessica Benjamin, M.P.H.

**Keywords:** NDA review, Clinical Studies

# TABLE OF CONTENTS

<b>1</b>	<b>EXECUTIVE SUMMARY .....</b>	<b>4</b>
<b>2</b>	<b>INTRODUCTION .....</b>	<b>5</b>
2.1	OVERVIEW.....	5
2.2	DATA SOURCES .....	8
<b>3</b>	<b>STATISTICAL EVALUATION .....</b>	<b>8</b>
3.1	DATA AND ANALYSIS QUALITY .....	8
3.1.1	Study GZGD02507 (ENGAGE) .....	8
3.1.2	Study GZGD02607 (ENCORE).....	9
3.2	EVALUATION OF EFFICACY .....	9
3.2.1	Study GZGD02507 (ENGAGE).....	9
3.2.2	Study GZGD02607 (ENCORE).....	29
3.3	EVALUATION OF SAFETY .....	54
3.3.1	Study GZGD02507 (ENGAGE).....	54
3.3.2	Study GZGD02607 (ENCORE).....	54
<b>4</b>	<b>FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>54</b>
4.1	GENDER AND GEOGRAPHIC REGION .....	54
4.1.1	Study GZGD02507 (ENGAGE) .....	54
4.1.2	Study GZGD02607 (ENCORE).....	57
4.2	OTHER SPECIAL/SUBGROUP POPULATIONS .....	58
<b>5</b>	<b>SUMMARY AND CONCLUSIONS .....</b>	<b>60</b>
5.1	STATISTICAL ISSUES .....	60
5.2	COLLECTIVE EVIDENCE .....	61
5.3	CONCLUSIONS AND RECOMMENDATIONS .....	61
<b>6</b>	<b>APPENDIX .....</b>	<b>62</b>

## LIST OF TABLES

Table 1 Summary Information for Relevant Clinical Trials .....	7
Table 2 Summary Information for Previous Products Approved by FDA for GD1 .....	11
Table 3 Disposition – ENGAGE .....	18
Table 4 Demographic and Baseline Characteristics – ENGAGE .....	19
Table 5 Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) – ENGAGE .....	20
Table 6 Summary of Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) – ENGAGE .....	21
Table 7 Summary of Percentage Change from Baseline to Week 39 in Liver Volume (MN) – ENGAGE .....	22
Table 8 Summary of Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) – ENGAGE .....	23
Table 9 Disposition – ENCORE .....	41
Table 10 Demographic and Baseline Characteristics – ENCORE .....	42
Table 11 Summary of Proportion of Patients who were Stable at Week 52 – ENCORE .....	43
Table 12 Summary of Percentage Change from Baseline to Week 52 in Spleen Volume (MN) – ENCORE .....	45
Table 13 Summary of Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) – ENCORE .....	46
Table 14 Summary of Percentage Change from Baseline to Week 52 in Liver Volume (MN) – ENCORE .....	47
Table 15 Summary of Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) – ENCORE .....	48
Table 16 Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by Gender – ENGAGE .....	55
Table 17 Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by Geographic Region – ENGAGE .....	56
Table 18 Summary of Proportion of Patients who were Stable at Week 52 by Gender – ENCORE .....	57
Table 19 Summary of Proportion of Patients who were Stable at Week 52 by Geographic Region – ENCORE .....	58
Table 20 Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by CYP2D6 Metabolizer Status – ENGAGE .....	59
Table 21 Summary of Proportion of Patients who were Stable at Week 52 by CYP2D6 Metabolizer Status – ENCORE .....	60
Table 22 Relevant Timeline and Comments for ENGAGE and ENCORE .....	62

## LIST OF FIGURES

Figure 1 Study Diagram ENGAGE .....	14
Figure 2 Mean ( $\pm$ SD) Spleen Volume (MN) over Time – ENGAGE .....	24
Figure 3 Mean ( $\pm$ SD) Hemoglobin Level (g/dL) over Time – ENGAGE .....	26
Figure 4 Mean ( $\pm$ SD) Liver Volume (MN) over Time – ENGAGE .....	27
Figure 5 Mean ( $\pm$ SD) Platelet Count ( $10^9/L$ ) over Time – ENGAGE .....	28
Figure 6 Study Diagram ENCORE .....	32
Figure 7 Disposition – ENCORE .....	40
Figure 8 Mean ( $\pm$ SD) Spleen Volume (MN) over Time – ENCORE .....	49
Figure 9 Mean ( $\pm$ SD) Hemoglobin Level (g/dL) over Time – ENCORE .....	51
Figure 10 Mean ( $\pm$ SD) Liver Volume (MN) over Time – ENCORE .....	52
Figure 11 Mean ( $\pm$ SD) Platelet Count ( $10^9/L$ ) over Time – ENCORE .....	53

## 1 EXECUTIVE SUMMARY

The applicant submitted the results from the GZGD02507 (ENGAGE) and GZGD02607 (ENCORE) trials to support the efficacy of CERDEGLA™ (eliglustat), a novel substrate reduction therapy (SRT), for the treatment of Gaucher Disease Type 1 (GD1) in adult patients (the proposed indication). In the pivotal ENGAGE trial, eliglustat was demonstrated to be superior to placebo with respect to the Week 39 change from baseline in spleen volume, hemoglobin level, liver volume, and platelet count, respectively. The currently ongoing Open-Label Treatment Period suggests a sustained efficacy profile with respect to the aforementioned four parameters. The key supportive ENCORE trial demonstrated that patients who had reached therapeutic goals with enzyme replacement therapy (ERT) CEREZYME®, the most widely used ERT for treating adults with GD1, remained stable 52 weeks after switching to oral treatment with eliglustat. The currently ongoing Long-Term Treatment Period suggests that this maintained clinical response is durable.

Overall, the designs of both the ENGAGE and ENCORE trials were deemed adequate from a statistical perspective for the proposed indication, and the applicant's corresponding statistical analysis plans deemed appropriate. One issue pertaining to the ENCORE study is the non-inferiority margin of 25% that was pre-specified for the primary efficacy assessment. This margin was deemed clinically unacceptable by the clinical review team. There was also no agreement on the non-inferiority margin of 15%, proposed for the additionally requested assessment of percentage change from baseline in spleen volume. Neither of these margins was acceptable from a statistical perspective. Each margin was chosen by the applicant based on the data from phase 2 study GZGD00304, which was an open-label study in 26 treatment-naïve adult GD1 patients who received monotherapy with eliglustat. It was not feasible to assess assay sensitivity when evaluating the proposed non-inferiority margins without a placebo-controlled trial with CEREZYME. Note that a placebo-controlled trial with CEREZYME has never been conducted. In addition, the aforementioned hypothetical placebo-controlled trial with CEREZYME would have to utilize the same trial design and also be in the same population of patients as those studied in ENCORE to ensure constancy. The differences between the GZGD00304 and ENCORE study designs and patient populations ultimately precluded the constancy assumption from being met. Further details are presented below in Section 3.2.2.1.

## 2 INTRODUCTION

### 2.1 Overview

On September 20, 2013, the Genzyme Corporation submitted this New Drug Application (NDA) for CERDELGA™ (eliglustat) in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 of the Code of Federal Regulations (CFR), Part 314.50. The active pharmaceutical ingredient (API) of eliglustat (84 mg in capsule form to be administered orally twice per day [BID] with or without food) is Genz-112638 which is a water soluble, white to off-white powder. Genz-112638 is considered a New Molecular Entity (NME). Effective on January 2, 2004, the applicant had initiated the clinical development of eliglustat under IND 67,589 for the treatment of GD1 in adult patients (the proposed indication. Eliglustat has been developed to establish safety and efficacy in this patient population. The applicant obtained *Orphan Designation* for eliglustat treatment of adult GD1 patients from the Office of Orphan Products Development (OOPD) on September 17, 2008.

Gaucher Disease is a rare lysosomal storage disorder, with prevalence of 1 in 50,000 live births, caused by a deficiency of the enzyme acid- $\beta$ -glucosidase (also known as glucocerebrosidase). This deficiency results in the over-accumulation of glucosylceramide (GL-1), an important component in animal muscle and nerve cell membranes, in tissue macrophages that become engorged and are typically found in liver, spleen, and bone marrow. As a type of inherited sphingolipidoses, Gaucher Disease is a multi-systemic and heterogeneous disorder that is serious and chronically debilitating given the persistent and irreversible morbidity that will develop over time in the majority of patients. The classic manifestations of Gaucher Disease are organomegaly (i.e., organ enlargement), hematological abnormalities, and bone disease. Symptoms specifically for GD1 may begin in early childhood but typically onset later on in life, and they are non-neurological unlike Gaucher Disease Type 2 (GD2) or Gaucher Disease Type 3 (GD3).

Eliglustat is a novel SRT and its mechanism of action differs from that of the ERTs, which augment acid- $\beta$ -glucosidase activity and are commonly used to treat GD1. Eliglustat is a highly selective and potent inhibitor of glucosylceramide synthase, the enzyme which produces GL-1, and this mechanism of action is hypothesized to reverse the GD1 disease process.

There were a series of communications and meetings between the applicant and the Division of Gastroenterology and Inborn Errors Products (DGIEP) throughout eliglustat's clinical development program. The relevant industry meetings are as follows: A Pre-IND meeting was held on December 15, 2003 for issues pertaining to non-clinical toxicology and cardiology related clinical safety. An End of Phase 2 (EOP2) meeting was held on February 5, 2009 in order to discuss planned phase 3 studies of the clinical program. Almost two years later on April 12, 2011, an important Type C advice meeting was held regarding clinical study enrollment challenges in the aforementioned phase 3 program and consequential alternative NDA filing strategies. Please see details regarding this Type C meeting below in Sections 3.2.1.1 and 3.2.2.1. Finally, the pre-NDA meeting between the applicant and DGIEP was held on May 21, 2013 primarily for discussing the format of the NDA submission. On September 20, 2013,

Genzyme submitted the NDA under the PDUFA V Program. This is a priority review; however, the review cycle was extended due to clinical pharmacology and biopharmaceutics issues.

This application includes data from four clinical safety and efficacy studies. The clinical efficacy and safety of eliglustat has been primarily evaluated in two trials. Study GZGD02507 (ENGAGE) is a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study in treatment-naïve GD1 patients. The ENGAGE study provides the main basis for the efficacy assessments. Study GZGD02607 (ENCORE) is a phase 3, multinational, multicenter, randomized, open-label, active-controlled, parallel group study in GD1 patients previously treated with ERT. The ENCORE study provides the key supportive evidence for the efficacy assessments of eliglustat, specifically for patients who were ERT exposed. A parallel dose group phase 3 study, GZGD03109 (EDGE), and an open-label proof-of-concept phase 2 study, GZGD00304 also provided supportive efficacy data. Table 1 below presents summary information on the two primary clinical trials ENGAGE and ENCORE which are the main focus of this NDA review.

**Table 1**  
**Summary Information for Relevant Clinical Trials**

<b>Type of Study; Phase</b>	<b>Study Identifier</b>	<b>Objective(s) of the Study</b>	<b>Study Design and Type of Control</b>	<b>Test Product(s); Regimen; Route</b>	<b>Number of Dosed Patients</b>	<b>Patient Diagnosis</b>	<b>Duration of Treatment</b>
Safety and Efficacy; Phase 3	GZGD02507 (ENGAGE)	To confirm the efficacy and safety of eliglustat after 39 weeks of treatment in treatment-naïve patients with GD1	Multinational, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group	Eliglustat; 50 mg and 100 mg BID; Capsules administered orally	Total: 40	GD1	39 weeks plus extension up to 6 years
Safety and Efficacy; Phase 3	GZGD02607 (ENCORE)	To demonstrate that, in patients with GD1 who have been stabilized with ERT, the majority of patients who receive eliglustat remain stable after 52 weeks of treatment	Multinational, Multicenter, Randomized, Open-label, Active-controlled, Parallel group	Eliglustat; 50 mg, 100 mg, and 150 mg BID; Capsules administered orally Cerezyme; Variable dose based on a patient's previous stable dose history; Intravenous (IV) every other week (QOW)	Total: 160	GD1	52 weeks plus extension up to 5.5 years

Source: Reviewer's Table.

## 2.2 Data Sources

This NDA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic datasets and labeling information, is located in the Center for Drug Evaluation and Research (CDER) electronic document room (EDR) at the location: [\\CDSESUB1\evsprod\NDA205494](#). Sequences 0000, 0011, 0012, and 0026 contain all the contents relevant for this review.

The clinical study report (CSR), clinical datasets and analysis datasets were reviewed separately for the ENGAGE and ENCORE studies. For each of these two studies, the clinical/tabulation datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard, and the analysis datasets were compliant to the CDISC/ADaM v.1.0 implementation guide standard. Adequate data definition files (in define.xml and define.pdf formats), a reviewer's guide and software code (.txt, .sas, and .pdf formats in triplicate) were also submitted for each study.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

#### 3.1.1 Study GZGD02507 (ENGAGE)

This study utilized an electronic Case Report Form (eCRF) within an Electronic Data Capture (EDC) system, and the submitted data quality appeared to be adequate. It was possible to reproduce the primary analysis dataset (along with the results presented within the CSR), specifically the primary endpoint values, from the original data source. It was also possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 8.6 of the CSR. The blinding/unblinding procedures were well documented within the protocol and in Section 8.4.6 of the CSR.

The original statistical analysis plan (SAP) was finalized on October 28, 2010. An amendment to the SAP was made on August 11, 2011. This amendment incorporated additional inferential analyses for assessing the change from baseline at Week 39 in the four efficacy parameters of interest (i.e., spleen volume, hemoglobin concentration, liver volume, and platelet count) exclusively within the eliglustat treatment group without comparison to the placebo group. These additional analyses were deemed exploratory by the review team. Further information regarding the purpose of this SAP amendment and further details are provided below in Section 3.2.1.1. The SAP, along with the amendment, was submitted, and all relevant analyses were finalized before the Double-Blind Treatment Period (see below in Section 3.2.1.1) was completed on July 18, 2012. Database hard-lock for the Double-Blind Treatment Period was on August 17, 2012, and the study was officially unblinded on September 17, 2012.

### **3.1.2 Study GZGD02607 (ENCORE)**

This study utilized an eCRF within an EDC system, and the submitted data quality appeared to be adequate. It was possible to reproduce the primary analysis dataset (along with the results presented within the CSR), specifically the primary endpoint values, from the original data source. It was also possible to verify the randomized treatment assignments, and the applicant submitted documentation of data quality control/assurance procedures within Section 8.6 of the CSR.

The original statistical analysis plan (SAP) was finalized on November 19, 2010. An amendment to the SAP was made on August 11, 2011. Note that this SAP amendment occurred on the same day as that of the ENGAGE SAP amendment. This amendment incorporated an additional non-inferiority analysis (as recommended by DGIEP in its responses to questions for the April 12, 2011 Type C advice meeting), which specifically assessed the difference in the percentage change from baseline at Week 52 in spleen volume between the eliglustat and CERZYME treatment groups. Although this additional analysis was requested by DGIEP, its result should be considered exploratory and supportive only. Further information regarding the purpose of this SAP amendment and further details are provided below in Section 3.2.2.1. The SAP, along with the amendment, was submitted, and all relevant analyses were finalized in advance of the Primary Analysis Treatment Period (see below in Section 3.2.2.1) completion which was on November 9, 2012. Database hard-lock for the Primary Analysis Treatment Period was on December 7, 2012.

## **3.2 Evaluation of Efficacy**

### **3.2.1 Study GZGD02507 (ENGAGE)**

#### **3.2.1.1 Background, Study Design and Endpoints**

##### **Background**

It was agreed at the EOP2 meeting on February 5, 2009 that the phase 3 efficacy and safety study GZGD02507 (ENGAGE) would be the main basis for the efficacy assessments of eliglustat. This study was designed as a multinational (with a total of 12 participating countries), multicenter (with a total of 18 participating sites), randomized, double-blind, placebo-controlled, parallel group trial evaluating the efficacy and safety of eliglustat in treatment-naïve patients with GD1. The original ENGAGE trial protocol was finalized after the EOP2 meeting on March 31, 2009, and the trial was subsequently started on November 5, 2009. The original protocol incorporated all important suggestions and comments from DGIEP at the EOP2 meeting. These suggestions and comments included the design of the study itself, the control to be used (i.e., placebo), and the endpoints to be measured and subsequently analyzed. The study has been amended seven times since the original protocol, and the final amendment was made on February 5, 2013. All of the protocol amendments were either administrative or contained minor changes which had no notable impact on the originally pre-specified study endpoints and corresponding analyses.

On April 12, 2011, a critical face-to-face Type C advice meeting was held between Genzyme and DGIEP. Genzyme was having difficulties in recruiting patients for the ENGAGE study. At the time of the Type C advice meeting, there had been five previous products approved by the FDA for the treatment of GD1, and four of these products were still on the market. The details of these products are presented in Table 2 below.

**Table 2**  
**Summary Information for Previous Products Approved by FDA for GD1**

<b>Brand Name</b>	<b>Generic Name</b>	<b>NDA Number</b>	<b>Approval Date</b>	<b>Product Type</b>	<b>Route of Administration</b>	<b>Dose and Regimen</b>	<b>Developer/Manufacturer</b>
CEREDASE®	alglucerase	020-057	05Apr1991	ERT	Intravenous (IV) infusion	60 Units/kg body weight every other week (QOW)	Genzyme Corporation
CEREZYME®	imiglucerase	020-367	23May1994	ERT	IV infusion	60 Units/kg body weight QOW	Genzyme Corporation
ZAVESCA®	miglustat	021-348	31Jul2003	SRT	Oral Capsules	100 mg three times per day (TID) at regular intervals with or without food	Actelion Pharmaceuticals, Inc.
VPRIV®	velaglucerase alpha	22-575	26Feb2010	ERT	IV infusion	60 Units/kg body weight QOW	Shire Human Genetic Therapies, Inc.
ELELYSO™	taliglucerase alpha	22-458	01May2012	ERT	IV infusion	60 Units/kg body weight QOW	Protalix, Ltd./ Pfizer, Inc.

Source: Reviewer's Table generated from information gathered from <http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/>.

Note: Marketing and Manufacturing of CEREDASE® was discontinued by Genzyme after CEREZYME® was approved.

Consequently, when the ENGAGE protocol was initiated in late 2009, the medical need for GD1 was met not only by three different ERTs (i.e., CERZYZME, VPRIV, and ELELYSO) but also by another SRT (i.e., ZAVESCA). A further obstacle to recruitment was that ENGAGE was designed as a placebo-controlled study as stated previously. For all the product development, including the five previously approved products for GD1, there was no known attempt to study treatment-naïve GD1 patients using a placebo-controlled trial. The ENGAGE study was the first reported trial, and Genzyme expectedly incurred a large amount of risk in patient recruitment by attempting to recruit a difficult study population when other medical treatments were available. This risk was realized in that only 16 patients had been recruited in a roughly one and a half year period between November 5, 2009 and April 12, 2011. This was well below the 36 patient target study size (sample size calculations in the original protocol presented below in this section). The planned recruitment period was a total of two years.

Genzyme utilized this face-to-face Type C advice meeting to communicate its ENGAGE recruitment issues to DGIEP and to discuss possible strategies, such as shifting the burden of establishing the main basis for efficacy claims from ENGAGE to the GZGD02607 (ENCORE) study. However, DGIEP did not agree to Genzyme's proposed contingency plans. DGIEP reiterated that Genzyme should continue to recruit patients for the ENGAGE study as best as possible and, as agreed upon previously at the EOP2 meeting, that ENGAGE would continue to serve as the pivotal study while ENCORE was to remain as the key supportive study. Genzyme acknowledged DGIEP's position and agreed to continue recruiting patients for ENGAGE as best as possible. Genzyme, however, stated that they would amend the protocol to include inferential within-treatment group analyses for eliglustat patients in case patient recruitment continued to stall. The division understood the applicant's proposition; however, the division clearly stated that these within-treatment group analyses for eliglustat patients would be deemed as exploratory, and that the originally pre-specified comparative analyses between eliglustat and placebo would still be considered confirmatory. Genzyme subsequently amended the ENGAGE protocol (amendment five) on July 12, 2011, while making the corresponding amendment to the SAP on August 11, 2011 as explained in Section 3.1.1 above, to include these within-treatment group analyses for eliglustat patients.

Fortunately, the patient recruitment issue for ENGAGE did not seem to negatively impact the study or the development program. Over the six months following the Type C advice meeting, Genzyme successfully recruited 24 more patients, the last of which was recruited on October 20, 2011. With a total of 40 patients, this trial surpassed the original 36 patient recruiting target. Please see Table 22 in the Appendix for further timeline details regarding the development program milestone events pertaining to the ENGAGE and ENCORE studies.

### **Study Design and Endpoints**

As stated previously, all of the ENGAGE protocol amendments were either administrative or contained minor changes which had no notable impact on the originally pre-specified study endpoints and corresponding analyses. Consequently this section will cover what was presented within the final ENGAGE protocol which was finalized on February 5, 2013.

The primary objective of this study was to confirm the efficacy and safety of eliglustat after 39 weeks of treatment in treatment-naïve patients with GD1. The secondary objective of this study was to determine the long-term efficacy, safety, and pharmacokinetics (PK) of eliglustat. This phase 3 study consisted of two periods: the Double-Blind Treatment Period (Day 1 to Week 39) and the Open-Label Treatment Period (post-Week 39 [Day 1 of the Open-Label Treatment Period] through study completion). The Double-Blind Treatment Period included a Screening Period (Days -45 to -1), a Dose-Adjustment Period (Day 1 to Week 4), and a Treatment Period (post-Week 4 to Week 39). After the patient (and/or their parent/legal guardian) provided informed consent, the patient underwent Screening assessments and, if all eligibility criteria were met, the patient was randomized. In order to achieve balance between the treatment groups, all patients were stratified based on their screening spleen volume (in multiples of normal [MN]) into one of the two stratification groups. The patients within a given spleen volume stratification group were then randomized in a 1:1 ratio to receive either eliglustat or placebo for 39 weeks.

The two spleen volume stratification groups were as follows:

- Low severity spleen volume (less than or equal to 20 MN)
- High severity spleen volume (greater than 20 MN)

Note that MN was calculated using the following formulae (with one cubic centimeter [cc] equivalent to one milliliter [mL]):

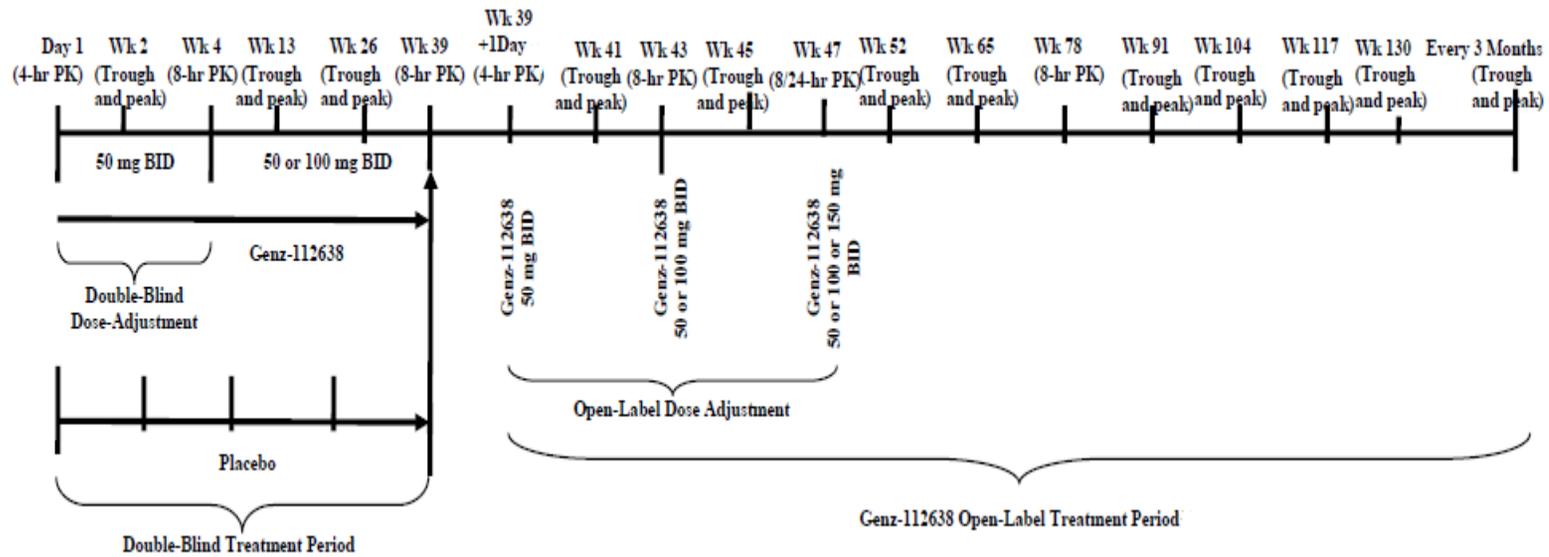
- Spleen MN = volume in cc ÷ (weight in kilogram [kg] × 2)
- Liver MN = volume in cc ÷ (weight in kg × 25)

The randomization was conducted by a third party vendor so that Genzyme was blinded to the treatment assignments. The vendor utilized an Interactive Voice-Response System/Interactive Web-Response System (IVRS/IWRS) for the randomization. In addition, subjects, Investigators, and site personnel were also blinded to the treatment assignments throughout the study until the final analysis was completed for the Double-Blind Primary Analysis Period.

After Week 39 assessments were completed, each patient then entered the Open-Label Treatment Period where all patients received eliglustat from post-Week 39 (Day 1 of the Open-Label Treatment Period) through study completion. Eliglustat and placebo were supplied as 50 mg, 100 mg, and 150 mg capsules. The 150 mg capsules were made available to the sites only for dispensing to patients who had completed the Double-Blind Treatment Period. All doses of eliglustat and placebo were taken orally BID (with water) with or without food.

The Double-Blind Treatment Period ended on July 18, 2012, and the Open-Label Treatment Period is currently ongoing. Each patient's total duration of participation in this study (including both the Double-Blind and Open-Label Treatment Periods) was planned to be at least 130 weeks, and each patient could continue participation for a total of up to six years. The overall study scheme is shown in Figure 1 below. Note that Amendment Seven of this protocol, which was made on February 5, 2013, pertained to an administrative change which was exclusive to the Open-Label Treatment Period.

**Figure 1**  
**Study Diagram ENGAGE**



Source: ENGAGE March 31, 2009 Protocol - Figure 6-1 on pg. 30.

Note: 'Eliglustat' and 'Genz-112638' are used interchangeably/synonymously.

The following primary and secondary endpoints were pre-specified in the order below within the original protocol (with the order unchanged throughout all of the subsequent protocol amendments) by the applicant:

Primary Endpoint: Percentage change from baseline in spleen volume (in MN) at Week 39. Current medical understanding for GD1 purports that a percentage decrease from baseline in spleen volume may indicate an improvement in disease state.

Secondary Endpoints:

- Absolute change from baseline in hemoglobin level (in g/dL) at Week 39. It is currently understood that an absolute increase from baseline in hemoglobin level may indicate an improvement in disease state.
- Percentage change from baseline in liver volume (in MN) at Week 39. It is currently understood that a percentage decrease from baseline in liver volume may indicate an improvement in disease state.
- Percentage change from baseline in platelet count (in  $10^9/L$ ) at Week 39. It is currently understood that a percentage increase from baseline in platelet count may indicate an improvement in disease state.

Allowing for a drop-out rate of 20%, approximately 36 male and female patients would have to be randomized in this study in a 1:1 ratio to receive eliglustat or placebo in order to yield at least 28 evaluable patients at the end of the Double-Blind Treatment Period (39 weeks). This sample size was estimated under the assumption of a 25% decrease in spleen volume in MN for eliglustat and a 5% decrease in spleen volume in MN for placebo at 39 weeks, a common standard deviation of 15% with a two-sided two-sample t-test using a 5% level of significance and 92% power.

Spleen and liver volumes were obtained by magnetic resonance imaging (MRI) at Screening, Weeks 26, 39, 65, 78, 104, 130, every six months thereafter, and at study completion. The image evaluation plan for both organ volumes along with additional information regarding the data acquisition and subsequent analysis usage is as follows:

- The assessment of spleen and liver volume prior to randomization (i.e., Screening) was reviewed by one reader at a central imaging vendor, and was subsequently used as the Baseline assessment value.
- The assessment of spleen and liver volumes at Week 26 and Week 39 were reviewed by two primary readers at the central imaging vendor. These two readers read these images in pairs, and were blinded to patient identifier, treatment, and time point. For a given organ (spleen or liver) at a given time point (Week 26 or Week 39), the average of the two volumes (from each of the two readers) was used as the assessment value at that time point. In the case that there was a discrepancy of more than 5% in organ volume reported by the two readers at that time point, a third blinded reader served as the adjudicator indicating which of the first two values was closest to the adjudicator's value. The value that was closest to, and within 5% of, the adjudicator's value was then averaged with the

adjudicator's value, and this average was subsequently utilized as the assessment value at that time point. In the case that there was a discrepancy of more than 5% between all three readers, all three values were averaged using the arithmetic mean, and this average was subsequently used as the assessment value at that time point.

- If an increase of greater than 30% in spleen volume or liver volume (in MN) was observed, the parameter measurement was repeated approximately four weeks later. The value from the repeated measurement was used in the study analyses using the same procedure described in the second bullet above.

At Screening, Weeks 4, 13, 26, 39, 45, 52, 65, 78, 130, every 12 months thereafter, and at study completion, two assessments of hemoglobin level and platelet count were obtained, and the average value was used at that time point in the analyses involving these secondary efficacy parameters. In the event that a patient was missing one of the two assessments at a particular time point, the single non-missing assessment was consequently used in the analyses at that time point. Note that the Screening value served as the Baseline assessment value for these two parameters.

Throughout the execution of the ENGAGE protocol, an Independent Data Monitoring Committee (DMC) operated according to a DMC Charter. It provided an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. Note that there were no formally planned interim analyses for this study.

Overall, the design of the ENGAGE study and its image evaluation plan was deemed adequate from a statistical perspective, and the estimated sample size was appropriate given the assumptions on the anticipated treatment effect.

### **3.2.1.2 Statistical Methodologies**

#### **3.2.1.2.1 Analysis Sets**

The primary analysis set used for all primary and secondary endpoint analyses was the Full Analysis Set (FAS), which included all randomized patients who received at least one dose of study drug. In this analysis set, patients were analyzed according to the treatment group that they were randomized to receive regardless of the actual treatment received. Due to the fact that this was a randomized and double-blind study, the utilization of the applicant-defined FAS as the primary analysis set appears to be acceptable per the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E9<sup>1</sup>.

As a sensitivity analysis, all analyses were repeated utilizing the Per-Protocol (PP) analysis set, which included all patients in the FAS who completed the study while being compliant with the study medication (i.e., meet at least 80% of drug compliance during the Double-Blind Treatment Period) and without committing any major protocol deviations. In addition, the PP analysis set excluded patients with hematological decline (i.e., decrease in hemoglobin level and/or platelet count) as a result of medically determined etiologies other than Gaucher disease. The PP analysis set definition was finalized prior to database lock and study unblinding.

---

<sup>1</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf>

Another sensitivity analysis was pre-specified to utilize an All-Randomized analysis set, which included all patients who were randomized into the study. Similar to the FAS, patients in this analysis set were analyzed in the treatment group that they were randomized to receive regardless of actual treatment received. However, because all randomized patients dosed at least once (see Table 3 below in Section 3.2.1.3), this analysis set was equivalent to the FAS and thus this sensitivity analysis was equivalent to the primary analysis.

A final sensitivity analysis was conducted by utilizing a Week-39-Completer analysis set, which included all FAS patients who completed 39 weeks of treatment and had non-missing assessments for Baseline and Week 39. Similar to the FAS, patients in this analysis set were analyzed in the treatment group that they were randomized to receive regardless of actual treatment received.

#### **3.2.1.2.2 Multiplicity Adjustment**

In order to control the overall study-wise type I error rate, a step-down/closed sequential testing procedure was pre-specified by the applicant to adjust for the multiple comparisons on the study endpoints presented in the order above within Section 3.2.1.1. Starting with the primary endpoint, the applicant stated that the step-down could only be carried to the next endpoint, within the order presented above, if and only if the current endpoint/step was found to be statistically significant in the comparison of eliglustat to placebo (i.e., p-value less than 0.05). If eliglustat was not statistically significant when compared to placebo at the current endpoint/step (i.e., p-value greater than or equal to 0.05), all hypothesis testing for the subsequent endpoints/steps would be deemed as exploratory.

#### **3.2.1.2.3 Primary Endpoint Analysis**

An Analysis of Covariance (ANCOVA) model was utilized for the Week 39 percentage change from baseline in spleen volume (in MN) with treatment (eliglustat or placebo) and the randomization stratification factor (baseline spleen severity: less than or equal to 20 MN or greater than 20 MN) as factors. A least-squares (LS) estimated mean, confidence interval (CI), and p-value for the treatment effect of eliglustat versus placebo were calculated. Note that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were checked by graphically observing residuals along with a normal quantile-quantile plot.

#### **3.2.1.2.4 Secondary Endpoints Analysis**

The three secondary endpoints were each analyzed, using ANCOVA, in the same manner as previously described for the primary endpoint except that each analysis further adjusted the model by including baseline value as a covariate, i.e., baseline hemoglobin level, baseline liver volume (in MN), and baseline platelet count, respectively. Note that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were checked by graphically observing residuals along with a normal quantile-quantile plot.

### 3.2.1.2.5 Handling of Dropouts/Missing Data

The applicant pre-specified that for the analysis of efficacy endpoints, last observation carried forward (LOCF) was used for patients who had missing data at Week 39 or who withdrew prior to Week 39. A no-change-from-baseline imputation approach was also conducted as a sensitivity analysis.

Although LOCF may not be an acceptable missing data handling strategy for the primary analyses, there was only one patient in the eliglustat group who dropped out of the ENGAGE study (this is further discussed in Sections 3.2.1.3 and 3.2.1.4 below). Consequently, the study results and conclusions were not dependent on the missing data handling strategy.

### 3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

The disposition information for all randomized patients is displayed in Table 3 below. Note that within this review document, all the results presented in the reviewer's tables are agreeable to those reported by the applicant.

**Table 3**  
**Disposition – ENGAGE**  
**(All-Randomized)**

	Eliglustat (N = 20)	Placebo (N = 20)	Total (N = 40)
All-Randomized	20 (100%)	20 (100%)	40 (100%)
Full Analysis Set (FAS)	20 (100%)	20 (100%)	40 (100%)
Week-39-Completer Analysis Set	19 (95.0%)	20 (100%)	39 (97.5%)
Per-Protocol (PP)	18 (91.7%)	20 (100%)	38 (95.0%)
Completed Study	19 (95.0%)	20 (100%)	39 (97.5%)
Discontinued Study Early	1 (5.0%)	0	1 (2.5%)
Adverse Event	0	0	0
Non-Compliant	0	0	0
Wishes to Withdraw	1 (5.0%)	0	1 (2.5%)
Lost to follow-up	0	0	0
Study Terminated by Sponsor	0	0	0
Pregnancy	0	0	0
Decline in Gaucher Disease	0	0	0
Other	0	0	0

Source: Reviewer's Table.

Note: Denominators for percentages are N. In total, 72 patients were screened. Patient 5303, who received treatment with eliglustat 50 mg BID through Week 4 and thereafter received an escalated dose of 100 mg BID, withdrew consent on Day 166. In total, 17 out of the 20 eliglustat patients had their doses escalated from 50 mg BID to 100 mg BID at Week 4 (with the other three remaining at 50 mg BID).

The demographics and baseline characteristics for all randomized patients are presented in Table 4 below.

**Table 4**  
**Demographic and Baseline Characteristics – ENGAGE**  
**(All-Randomized)**

	Eliglustat (N = 20)	Placebo (N = 20)	Total (N = 40)
<b>Age (years)</b>			
n	20	20	40
Mean (SD)	31.6 (11.55)	32.1 (11.26)	31.8 (11.26)
Median	29.1	32.3	30.4
Min, Max	17, 63	16, 60	16, 63
<b>Age Group – n (%)</b>			
< 18	1 (5.0%)	1 (5.0%)	2 (5.0%)
18 to 65	19 (95.0%)	19 (5.0%)	38 (95.0%)
≥ 65	0	0	0
<b>Gender – n (%)</b>			
Female	12 (60.0%)	8 (40.0%)	20 (50.0%)
Male	8 (40.0%)	12 (60.0%)	20 (50.0%)
<b>Race – n (%)</b>			
Asian	1 (5.0%)	0	1 (2.5%)
American Indian or Alaska Native	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	19 (95.0%)	20 (100%)	39 (97.5%)
<b>Weight at Baseline (kg)</b>			
n	20	20	40
Mean (SD)	64.8 (11.74)	68.6 (17.17)	66.7 (14.65)
Median	67.4	64.8	66.4
Min, Max	40, 82	46, 102	40, 102
<b>CYP2D6 Metabolizer Status – n (%)</b>			
Poor	0	0	0
Intermediate	1 (5.0%)	2 (10.0%)	3 (7.5%)
Extensive	18 (90.0%)	18 (90.0%)	36 (90.0%)
Ultra-Rapid	1 (5.0%)	0	1 (2.5%)
Unknown	0	0	0
<b>Spleen Severity Group</b>			
Low (≤ 20 MN)	16 (80.0%)	17 (85.0%)	33 (82.5%)
High (> 20 MN)	4 (20.0%)	3 (15.0%)	7 (17.5%)

Source: Reviewer's Table.

Note: Denominators for percentages are N.

There was no significant imbalance between the treatment groups regarding the presented demographic and baseline characteristics.

### 3.2.1.4 Results and Conclusions

The results displayed in this section correspond to the endpoint testing order specified in Section 3.2.1.1 above.

**Table 5**  
**Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) –**  
**ENGAGE**  
**(FAS)**

Time Point	Eliglustat (N = 20)	Placebo (N = 20)	Treatment Difference (Eliglustat – Placebo)
<b>Baseline Spleen Volume (MN)</b>			
n	20	20	
Mean (SD)	13.89 (5.929)	12.50 (5.959)	
Median	12.09	11.05	
Min, Max	5.9, 28.4	6.3, 25.3	
<b>Week 39 Spleen Volume (MN)</b>			
n	20	20	
Mean (SD)	10.17 (5.065)	12.84 (6.395)	
Median	8.34	10.97	
Min, Max	4.1, 21.9	6.6, 26.2	
<b>Absolute Change from Baseline to Week 39</b>			
n	20	20	
Mean (SD)	-3.72 (2.377)	0.35 (1.050)	
Median	-3.02	0.34	
Min, Max	-9.1, 0.0	-1.8, 2.3	
<b>% Change from Baseline to Week 39</b>			
n	20	20	
Mean (SD)	-27.58 (12.591)	2.07 (8.777)	
Median	-29.03	4.20	
Min, Max	-51.5, 0.0	-20.9, 13.7	
LS Mean (SEM) [1]	-27.77 (2.37)	2.26 (2.37)	-30.03 (3.35)
95% CI [1]	-32.57, -22.97	-2.54, 7.06	-36.82, -23.24
p-value [1]	NA	NA	<0.0001

Source: Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation; LS = least squares; SEM = standard error of the mean; CI = confidence interval; NA = not applicable.

[1]: Derived from ANCOVA model adjusted for baseline spleen severity ( $\leq 20$  MN or  $> 20$  MN). Treatment effect defined as: (% Change from Baseline to Week 39, Eliglustat) – (% Change from Baseline to Week 39, Placebo).

It can be observed from Table 5 above that eliglustat showed superior improvement in the percentage change from baseline for spleen volume at Week 39 when compared to placebo. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals along with the pertinent normal quantile-quantile plot. This analysis was repeated utilizing the PP and Week-39-Completer analysis sets, and the conclusions were consistent. From the 40 patients who were

originally randomized, there was only one dropout, and a sensitivity analysis consequently showed that this dropout did not impact the study conclusions. It is important to note that no single site influenced or drove the overall study results. There were no patients who were designated as outliers (i.e., by having studentized residual values greater than three). An additional sensitivity analysis was conducted by replacing the baseline spleen severity category (i.e., less than or equal to 20 MN or greater than 20 MN), a factor in the original ANCOVA model, with the covariate of baseline spleen volume (in MN). The study conclusion from this additional sensitivity analysis was consistent with the findings from the primary analysis.

**Table 6**  
**Summary of Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) –**  
**ENGAGE**  
**(FAS)**

Time Point	Eliglustat (N = 20)	Placebo (N = 20)	Treatment Difference (Eliglustat – Placebo)
Baseline Hemoglobin Level (g/dL)			
n	20	20	
Mean (SD)	12.05 (1.816)	12.75 (1.629)	
Median	12.05	12.90	
Min, Max	8.2, 15.3	9.7, 16.3	
Week 39 Hemoglobin Level (g/dL)			
n	20	20	
Mean (SD)	12.78 (1.561)	12.17 (2.010)	
Median	12.95	12.25	
Min, Max	8.9, 15.3	7.9, 15.0	
Absolute Change from Baseline to Week 39			
n	20	20	
Mean (SD)	0.73 (1.093)	-0.058 (0.890)	
Median	0.70	-0.65	
Min, Max	-1.5, 3.2	-2.5, 0.7	
LS Mean (SEM) [1]	0.69 (0.23)	-0.54 (0.23)	1.22 (0.32)
95% CI [1]	0.23, 1.14	-1.00, -0.08	0.57, 1.88
p-value [1]	NA	NA	0.0006

Source: Reviewer's Table.

Note: SD = standard deviation; LS = least squares; SEM = standard error of the mean; CI = confidence interval; NA = not applicable.

[1]: Derived from ANCOVA model adjusted for baseline spleen severity ( $\leq 20$  MN or  $> 20$  MN) and baseline hemoglobin level (g/dL). Treatment effect defined as: (Absolute Change from Baseline to Week 39, Eliglustat) – (Absolute Change from Baseline to Week 39, Placebo).

It can be observed from Table 6 above that eliglustat showed superior improvement in the absolute change from baseline for hemoglobin level at Week 39 when compared to placebo. This analysis was repeated utilizing the PP and Week-39-Completer analysis sets, and the conclusions were consistent. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals along with the pertinent normal quantile-quantile plot.

**Table 7**  
**Summary of Percentage Change from Baseline to Week 39 in Liver Volume (MN) –**  
**ENGAGE**  
**(FAS)**

Time Point	Eliglustat (N = 20)	Placebo (N = 20)	Treatment Difference (Eliglustat – Placebo)
<b>Baseline Liver Volume (MN)</b>			
n	20	20	
Mean (SD)	1.44 (0.354)	1.36 (0.280)	
Median	1.36	1.29	
Min, Max	0.9, 2.2	0.9, 2.0	
<b>Week 39 Liver Volume (MN)</b>			
n	20	20	
Mean (SD)	1.35 (0.280)	1.39 (0.309)	
Median	1.25	1.32	
Min, Max	0.9, 1.9	0.9, 2.0	
<b>Absolute Change from Baseline to Week 39</b>			
n	20	20	
Mean (SD)	-0.09 (0.113)	0.03 (0.106)	
Median	-0.07	0.01	
Min, Max	-0.4, 0.1	-0.2, 0.3	
<b>% Change from Baseline to Week 39</b>			
n	20	20	
Mean (SD)	-5.45 (6.886)	1.70 (8.004)	
Median	-5.23	0.54	
Min, Max	-19.0, 9.1	-14.29, 18.25	
LS Mean (SEM) [1]	-5.20 (1.64)	1.44 (1.64)	-6.64 (2.33)
95% CI [1]	-8.53, -1.87	-1.89, 4.78	-11.37, -1.91
p-value [1]	NA	NA	0.0072

Source: Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation; LS = least squares; SEM = standard error of the mean; CI = confidence interval; NA = not applicable.

[1]: Derived from ANCOVA model adjusted for baseline spleen severity ( $\leq 20$  MN or  $> 20$  MN) and baseline liver volume (MN). Treatment effect defined as: (% Change from Baseline to Week 39, Eliglustat) – (% Change from Baseline to Week 39, Placebo).

It can be observed from Table 7 above that eliglustat showed superior improvement in the percentage change from baseline for liver volume at Week 39 when compared to placebo. This analysis was repeated utilizing the PP and Week-39-Completer analysis sets, and the conclusions were consistent. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals along with the pertinent normal quantile-quantile plot.

**Table 8**  
**Summary of Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) –**  
**ENGAGE**  
**(FAS)**

Time Point	Eliglustat (N = 20)	Placebo (N = 20)	Treatment Difference (Eliglustat – Placebo)
<b>Baseline Platelet Count (10<sup>9</sup>/L)</b>			
n	20	20	
Mean (SD)	75.05 (14.095)	78.48 (22.611)	
Median	78.75	76.25	
Min, Max	50.5, 98.5	50.5, 128.5	
<b>Week 39 Platelet Count (10<sup>9</sup>/L)</b>			
n	20	20	
Mean (SD)	98.95 (28.372)	71.50 (25.157)	
Median	101.50	66.25	
Min, Max	40.0, 161.0	36.0, 125.5	
<b>Absolute Change from Baseline to Week 39</b>			
n	20	20	
Mean (SD)	23.90 (22.595)	-6.98 (15.394)	
Median	21.00	-6.00	
Min, Max	-11.0, 70.5	-44.5, 22.5	
<b>% Change from Baseline to Week 39</b>			
n	20	20	
Mean (SD)	31.71 (31.801)	-8.77 (19.187)	
Median	29.17	-7.88	
Min, Max	-21.6, 87.2	-51.7, 29.8	
LS Mean (SEM) [1]	32.00 (5.95)	-9.06 (5.95)	41.06 (8.44)
95% CI [1]	19.94, 44.06	-21.12, 3.00	23.95, 58.17
p-value [1]	NA	NA	<0.0001

Source: Reviewer's Table.

Note: SD = standard deviation; LS = least squares; SEM = standard error of the mean; CI = confidence interval; NA = not applicable.

[1]: Derived from ANCOVA model adjusted for baseline spleen severity ( $\leq 20$  MN or  $> 20$  MN) and baseline platelet count (10<sup>9</sup>/L). Treatment effect defined as: (% Change from Baseline to Week 39, Eliglustat) – (% Change from Baseline to Week 39, Placebo).

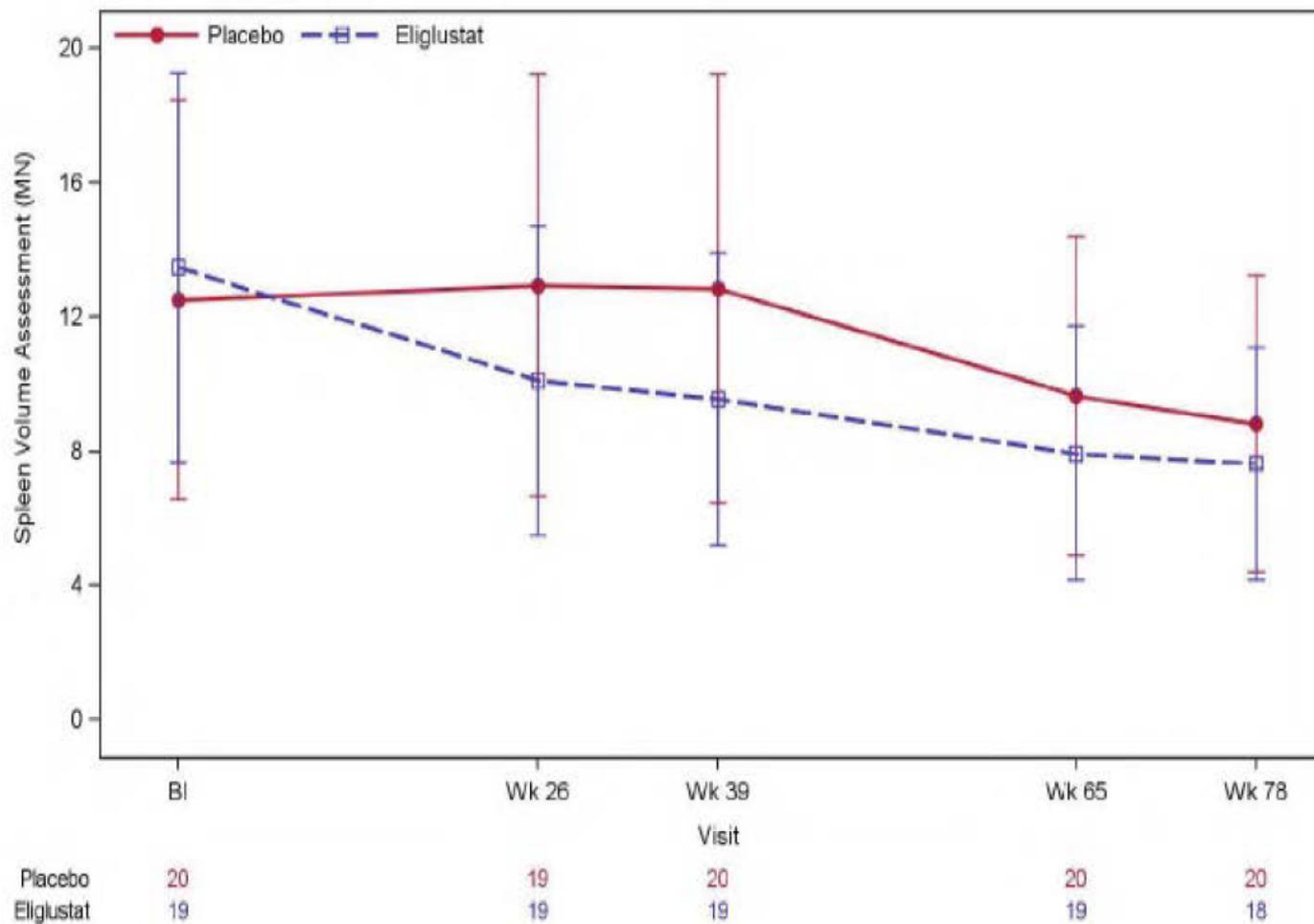
It can be observed from Table 8 above that eliglustat showed superior improvement in the percentage change from baseline for platelet count at Week 39 when compared to placebo. This analysis was repeated utilizing the PP and Week-39-Completer analysis sets, and the conclusions were consistent. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals along with the pertinent normal quantile-quantile plot.

As stated previously in Section 3.2.1.1, after Week 39 assessments were completed, each patient then entered the Open-Label Treatment Period where all patients received eliglustat from post-Week 39 (Day 1 of the Open-Label Treatment Period) through study completion. Each patient's

total duration of participation in this study (including both the Double-Blind and Open-Label Treatment Periods) was planned to be at least 130 weeks, and each patient could continue participation for a total of up to six years. This Open-Label Treatment Period was ongoing at the time of NDA filing, and the most up-to-date submission by the applicant includes a total exposure of 78 weeks.

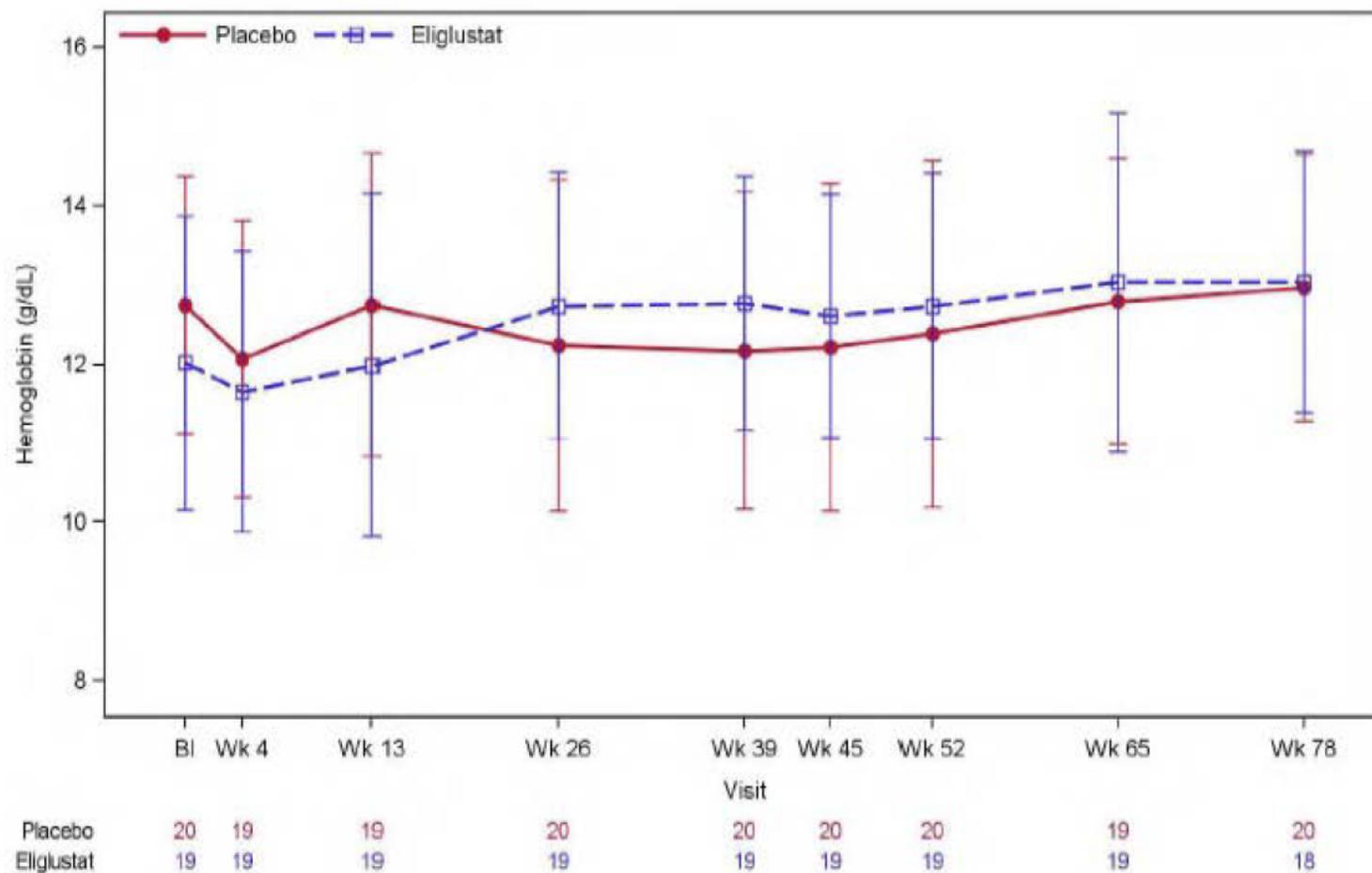
Figures 2, 3, 4, and 5 below present the spleen volume, hemoglobin level, liver volume, and platelet count data, respectively, from baseline through Week 78. Note that patients who were randomized at Baseline to placebo for the Double-Blind Treatment Period are displayed as placebo patients within these figures although they all began the eliglustat treatment the day after Week 39. It appears that patients who were randomized at Baseline to eliglustat for the Double-Blind Treatment Period continued improving in all four efficacy parameters after Week 39. It also appears that patients who were randomized at Baseline to placebo for the Double-Blind Treatment Period started improving in all four efficacy parameters after Week 39 when these patients began exclusive treatment with eliglustat.

**Figure 2**  
**Mean ( $\pm$  SD) Spleen Volume (MN) over Time – ENGAGE**  
**(FAS)**



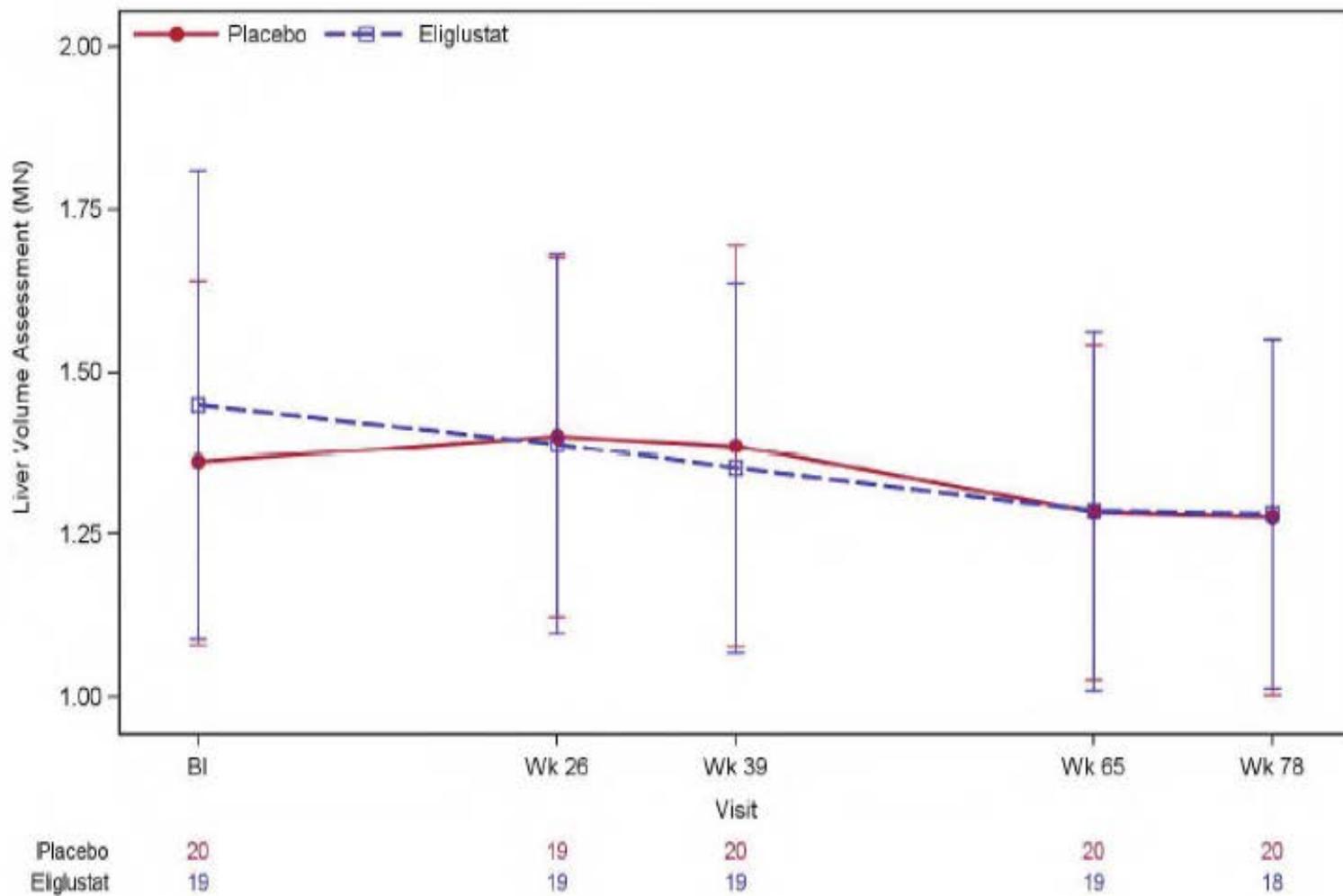
Source: January 10, 2014 Information Request Submission - Figure 2.1.1 on pg. 12.

**Figure 3**  
**Mean ( $\pm$  SD) Hemoglobin Level (g/dL) over Time – ENGAGE**  
**(FAS)**



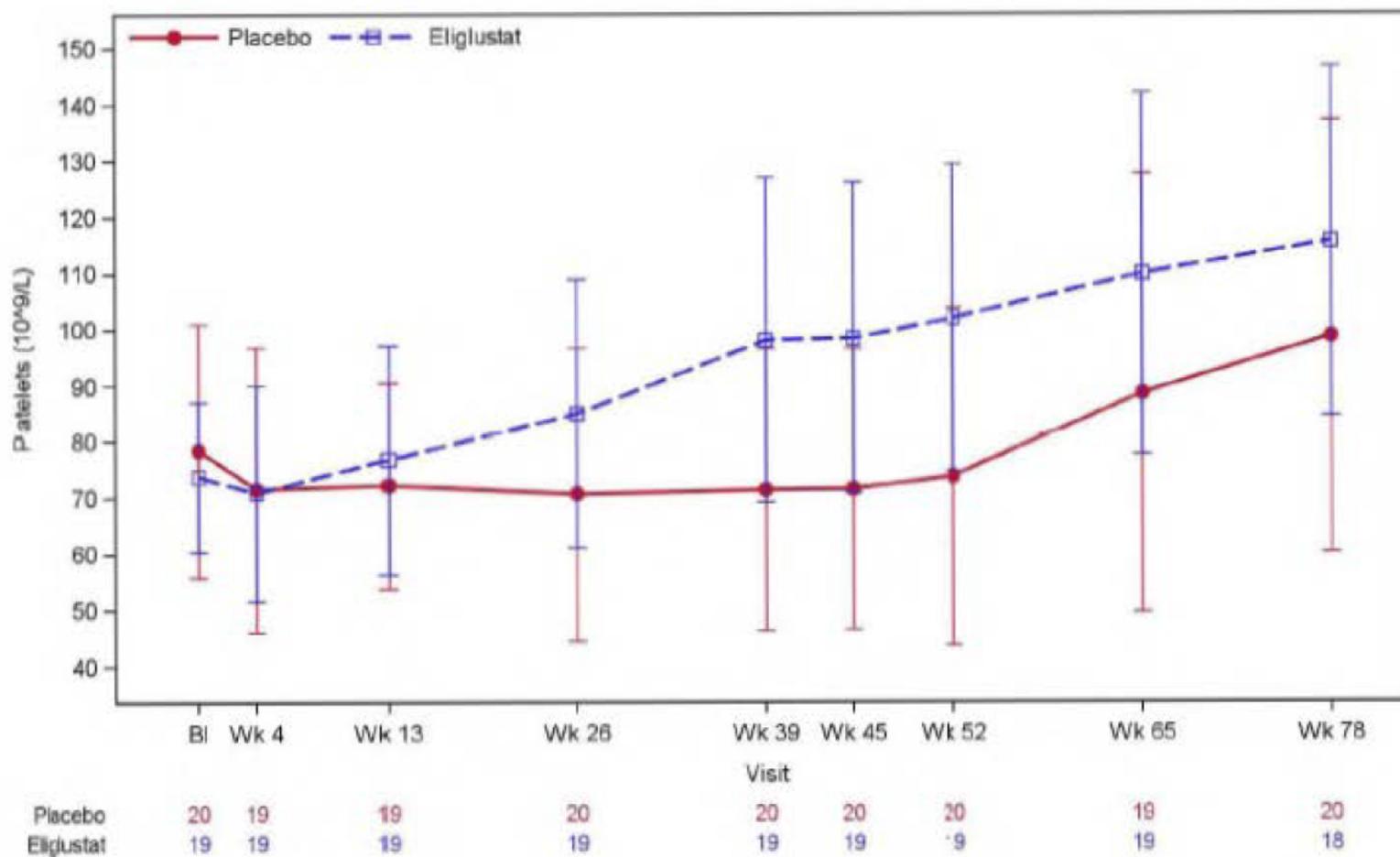
Source: January 10, 2014 Information Request Submission - Figure 2.5.1 on pg. 20.

**Figure 4**  
**Mean ( $\pm$  SD) Liver Volume (MN) over Time – ENGAGE**  
**(FAS)**



Source: January 10, 2014 Information Request Submission - Figure 2.3.1 on pg. 16.

**Figure 5**  
**Mean ( $\pm$  SD) Platelet Count ( $10^9/L$ ) over Time – ENGAGE**  
**(FAS)**



Source: January 10, 2014 Information Request Submission - Figure 2.6.1 on pg. 22.

## 3.2.2 Study GZGD02607 (ENCORE)

### 3.2.2.1 Background, Study Design and Endpoints

#### **Background**

It was agreed at the EOP2 meeting on February 5, 2009 that phase 3 efficacy and safety study GZGD02607 (ENCORE) would provide the key supportive evidence for the efficacy assessments of eliglustat, specifically for patients who were previously ERT-exposed. This study was designed as a multinational (with a total of 12 participating countries), multicenter (with a total of 34 participating sites), randomized, open-label, active-controlled, parallel group non-inferiority trial to evaluate the efficacy and safety of eliglustat in patients with GD1 who had been treated with ERT for at least three years and were currently stabilized on it. Note that CERZYME is the most widely used ERT for treating adults with GD1. The original ENCORE trial protocol was finalized after the EOP2 meeting on May 22, 2009, and the trial was subsequently started on September 10, 2009. The original protocol incorporated all important suggestions and comments made by DGIEP at the EOP2 meeting. These suggestions and comments included the design of the study itself and the endpoints to be measured and subsequently analyzed. The study has been amended seven times since the original protocol, and the final amendment was made on January 31, 2013. Amendment one was administrative and was only applicable to sites within the United Kingdom (UK). This amendment was finalized on August 7, 2009. Amendment two was the result of additional communications between DGIEP and Genzyme after the EOP2 meeting along with parallel communications between the European Medicines Agency (EMA) and Genzyme during that same time period; however, this was a major amendment in that it changed the primary objective of the study from a within-treatment group efficacy assessment exclusively in eliglustat patients to a comparative non-inferiority efficacy assessment between the eliglustat and CERZYME treatment groups. In addition, this amendment changed the duration of the Primary Analysis Treatment Period from 39 weeks to 52 weeks (study design explained below). This amendment was finalized on October 5, 2009 and was prior to the first patient administered the first dose on October 13, 2009. All of the remaining protocol amendments were either administrative or contained minor changes which had no notable impact on the study endpoints and corresponding analyses pre-specified within amendment two.

As explained previously in Section 3.2.1.1 above, on April 12, 2011, a critical face-to-face Type C advice meeting was held between Genzyme and DGIEP. Genzyme was having difficulties in recruiting patients for the ENGAGE study, and the applicant utilized this face-to-face Type C advice meeting to communicate its ENGAGE recruitment issues to DGIEP and to discuss possible strategies such as shifting the burden of establishing the main basis for efficacy claims from ENGAGE to ENCORE. Note that at the time, a total of 98 patients were already recruited for the ENCORE study. However, as previously stated, DGIEP did not agree to Genzyme's proposed contingency plans. DGIEP's position was that Genzyme should continue to recruit patients for the ENGAGE study as best as possible and, as agreed upon previously at the EOP2 meeting, that Study ENGAGE would continue to serve as the pivotal study of the development

program while Study ENCORE remain as the key supportive study. Genzyme acknowledged DGIEP's position and agreed to continue recruiting patients for ENGAGE as best as possible.

The Division, in its responses to questions for this Type C advice meeting, communicated to Genzyme that the non-inferiority margin pre-specified for the primary efficacy assessment in Study ENCORE (see below) was clinically unacceptable. The Division understood, however, that a sample size needed to power ENCORE based on a smaller non-inferiority margin could result in a larger, and hence more difficult, recruitment target. The Division subsequently recommended that Genzyme conduct an additional non-inferiority analysis which specifically assessed the difference between the eliglustat and CEREZYME treatment groups in the change from baseline at Week 52 in either spleen volume or in hemoglobin level. In order to adhere to DGIEP's request, Genzyme chose to conduct this analysis for spleen volume using percentage change, and subsequently amended the ENCORE protocol (amendment five) accordingly on July 6, 2011, while making the corresponding amendment to the SAP on August 11, 2011 as explained above in Section 3.1.2. Note that although this additional analysis was recommended by DGIEP, the results should be considered exploratory and supportive. It should be noted that the non-inferiority margin proposed for this additional assessment was also not officially agreed upon by DGIEP (see details below).

As stated previously, the patient recruitment difficulty for ENGAGE did not seem to last or impact the development program. Genzyme was able to sufficiently recruit for the ENGAGE study over the six months following the Type C advice meeting while maintaining its successful recruitment rate for ENCORE. Please see Table 22 in the Appendix for further timeline details regarding the development program milestone events pertaining to the ENGAGE and ENCORE studies.

### **Study Design and Endpoints**

The primary objective of this study was to assess the efficacy and safety of eliglustat compared with CEREZYME after 52 weeks of treatment in patients with GD1 who had reached therapeutic goals with ERT. The secondary objective of this study was to demonstrate that, in patients with GD1 who had reached therapeutic goals with ERT, the majority of patients who received eliglustat would remain stable after 52 weeks of treatment. This phase 3 study included a Screening Period (Days -45 to -1), a Primary Analysis Treatment Period (Day 1 to Week 52), a Long-Term Treatment Period (post-Week 52 through study completion), and a Safety Follow-Up Period (30 to 37 days after the patient's last dose of treatment). Note that the first eight weeks of the Primary Analysis Treatment Period was a Dose-Adjustment Period for patients randomized to receive eliglustat. After the patient (and/or their parent/legal guardian) provided informed consent each patient underwent Screening assessments to determine study eligibility. If all eligibility criteria were met, the patient was stratified into one of two groups based on the patient's stable ERT dose prior to any unanticipated treatment interruption (such as switching to another ERT), dose reduction, or regimen change (such as every other week dosing [QOW] to every week dosing [QW]). The two groups were as follows:

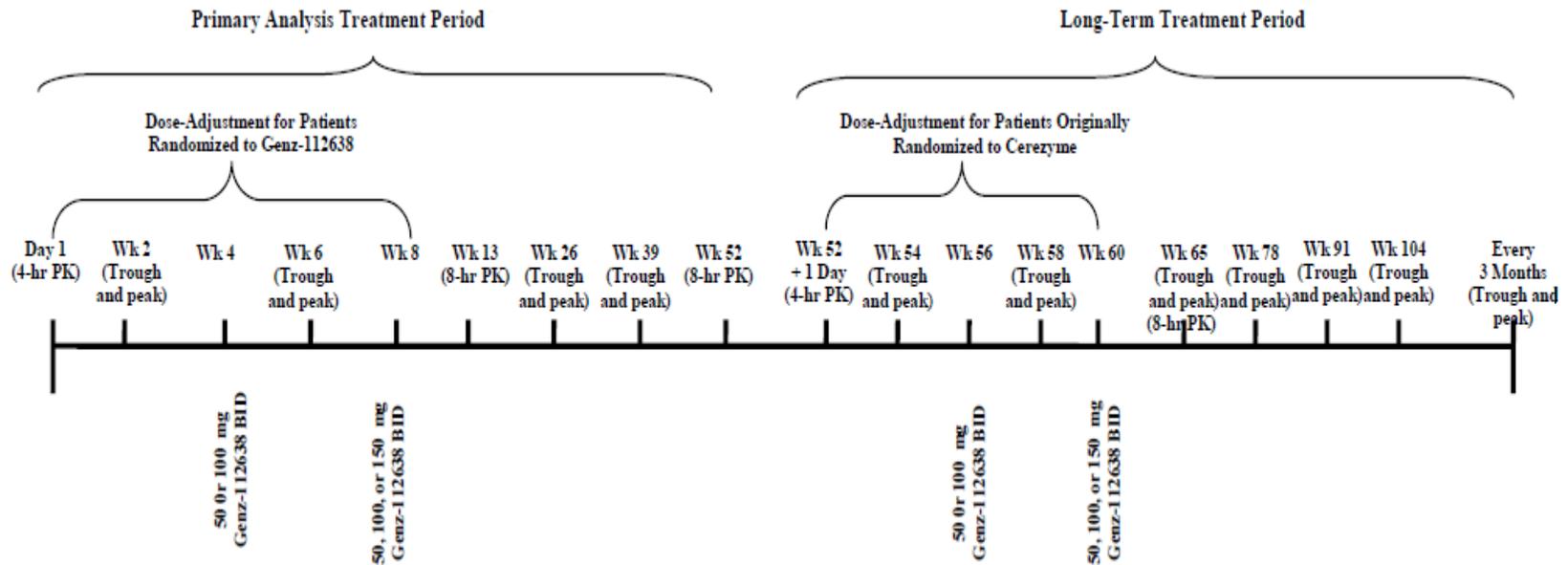
- less than 35 U/kg/QOW
- greater than or equal to 35 U/kg/QOW

The patients in each stratum were then randomized in a 2:1 ratio to receive eliglustat or to receive CEREZYME at their current stable ERT dose, respectively, for 52 weeks (i.e., the Primary Analysis Treatment Period). Note that an Interactive Voice-Response System/Interactive Web-Response System (IVRS/IWRS) was utilized for the randomization.

After Week 52 assessments were completed, each patient then entered the Long-Term Treatment Period where all patients received eliglustat from post-Week 52 (Day 1 of the Long-Term Treatment Period) through study completion. Eliglustat was supplied as 50 mg, 100 mg, and 150 mg capsules. The 150 mg capsules were made available to the sites only for dispensing to patients who had completed the Primary Analysis Treatment Period. All doses of eliglustat were taken orally BID (with water) with or without food. CEREZYME was administered as an IV, in a QOW regimen equivalent to the patient's stable CEREZYME dose.

The Primary Analysis Treatment Period ended on November 9, 2012, and the Long-Term Treatment Period is currently ongoing. Each patient's total duration of participation in this study (including both the Primary Analysis and Long-Term Treatment Periods) was planned to be at least 104 weeks, and each patient could continue participation for a total of up to 5.5 years. The overall study scheme is shown in Figure 6 below. (Note that Amendment Seven of this protocol, which was made on January 31, 2013, pertained to an administrative change which was exclusive to the Long-Term Treatment Period.)

**Figure 6**  
**Study Diagram ENCORE**



Source: ENCORE October 5, 2009 Protocol - Figure 6-1 on pg. 28.

Note: 'Eliglustat' and 'Genz-112638' are used interchangeably/synonymously.

The following primary endpoint was pre-specified by the applicant.

Primary Endpoint: Clinical Response (success/failure) after 52 weeks of study treatment (i.e., the Primary Analysis Treatment Period). For a patient to be considered to have demonstrated a clinically meaningful response to treatment with eliglustat or CEREZYME, the patient must have remained stable in hematological parameters (i.e., hemoglobin levels and platelet counts), and organ volumes (i.e., spleen and liver volumes in MN). As described previously in Section 3.2.1.1 above, MN was calculated using the following formulae (with one cc equivalent to one mL):

- Spleen MN = volume in cc ÷ (weight kg × 2)
- Liver MN = volume in cc ÷ (weight in kg × 25)

A patient must have met the following criteria in each hematological and organ volume parameter in order to have been considered a success:

*Stable Hematological Parameters*

- Hemoglobin level did not decrease greater than 1.5 g/dL from Baseline.  
and
- Platelet count did not decrease greater than 25% from Baseline.

*Stable Organ Volume*

- Spleen volume (in MN) did not increase greater than 25% from Baseline.  
and
- Liver volume (in MN) did not increase greater than 20% from Baseline.

An impartial Independent Adjudication Board (IAB), blinded to the patient treatment assignments, was established to adjudicate treatment failures. For all patients, the IAB confirmed that failure to meet the primary endpoint during the 52-week Primary Analysis Treatment Period was attributed to a decline in Gaucher disease. The IAB included experts in relevant biomedical fields who were independent of the Genzyme Corporation and the ENCORE study. The IAB evaluated the treatment failures according to the guidelines set in a separate charter.

Approximately 150 male and female patients were planned to be randomized in this study in order to yield at least 120 evaluable patients at the end of 52 weeks. This sample size was based on expected responder/stability rates of 95% for the CEREZYME treatment group and 85% for the eliglustat treatment group (each based on data from the GZGD00304 phase 2 study), a power of 85%, a one-sided significance level of 0.025, a non-inferiority margin of 25%, and a 20% non-evaluable/drop-out rate. The margin of 25% was pre-specified by the applicant to be well below the expected difference that would exist between CEREZYME treatment and no treatment. The margin accounts for a 10% difference between the active-comparator (CEREZYME) and test treatment arms (eliglustat) as well as an additional 15% for the inherent variability in estimating the difference between these two treatments.

As stated previously, at the April 12, 2011 Type C meeting DGIEP recommended that Genzyme conduct an additional non-inferiority analysis which specifically assessed the difference between the eliglustat and CERZYZME treatment groups in the change from baseline at Week 52 in either spleen volume or in hemoglobin level. In order to adhere to DGIEP's request, Genzyme chose to conduct this analysis for spleen volume using percentage change, and subsequently amended the ENCORE protocol (amendment five) accordingly. This supplemental analysis utilized a non-inferiority margin of 15%. Note that although this additional analysis was recommended by DGIEP, the results should be considered exploratory.

The secondary endpoints included the following: hemoglobin level, platelet count, and spleen and liver volumes (in MN). Note that the applicant did not pre-specify a multiplicity adjustment in the ENCORE protocol for controlling the overall study-wise type I error rate. Consequently all of these subsequent analyses should be considered exploratory.

Spleen and liver volumes were obtained by MRI at Screening, Weeks 26, 52, 78, 104, every six months thereafter, and at study completion. The image evaluation plan for both organ volumes along with additional information regarding the data acquisition and subsequent analysis usage was very similar to what was utilized for the ENGAGE study. It is as follows:

- The assessment of spleen and liver volume prior to randomization (i.e., Screening) was reviewed by one reader at a central imaging vendor, and was subsequently used as the Baseline assessment value.
- The assessment of spleen and liver volumes at Week 26 and Week 52 were reviewed by two primary readers at the central imaging vendor. These two readers read these images in pairs, and were blinded to patient identifier, treatment, and time point even though ENCORE was an open-label study. For a given organ (spleen or liver) at a given time point (Week 26 or Week 52), the average of the two volumes (from each of the two readers) was used as the assessment value at that time point. In the case that there was a discrepancy of more than 5% in organ volume reported by the two readers at that time point, a third blinded reader served as the adjudicator indicating which of the first two values was closest to the adjudicator's value. The value that was closest to, and within 5% of, the adjudicator's value was then averaged with the adjudicator's value, and this average was subsequently utilized as the assessment value at that time point. In the case that there was a discrepancy of more than 5% between all three readers, all three values were averaged using the arithmetic mean, and this average was subsequently used as the assessment value at that time point.
- If an increase of greater than 25% in spleen volume or greater than 20% in liver volume, in MN, was observed, the parameter measurement was repeated approximately four weeks later. The value from the repeated measurement was used in the study analyses using the same procedure described in the second bullet above.

At Screening, Weeks 13, 26, 39, 52, 65, 78, 91, 104, every 12 months thereafter, and at study completion, two assessments of hemoglobin level and platelet count were obtained, and the average value was used at that time point in the analyses involving these efficacy parameters. In the event that a patient was missing one of the two assessments at a particular time point, the

single non-missing assessment was consequently used in the analyses at that time point. Note that the Screening value served as the Baseline assessment value for these two parameters.

Throughout the execution of the ENCORE protocol, an Independent DMC operated according to a DMC Charter. It provided an ongoing, independent, and expert review of the safety data in order to provide risk management during the conduct of the study. Note that there were no formally planned interim analyses for this study.

Overall, the design of the ENCORE study and its image evaluation plan was deemed adequate from a statistical perspective, and the estimated sample size was appropriate given the assumptions on the anticipated treatment effect.

Although ENCORE was an open-label study, the design was appropriate per the measurement/evaluation of the endpoint values based on the blinded image evaluations and objective laboratory measures which would not be expected to introduce bias. In addition, a double-blinded study would have been difficult to conduct because a double-dummy (i.e., additional placebo IV QOW for patients randomized to receive eliglustat or additional placebo capsules BID for patients randomized to receive CEREZYME) would have to be instituted in order to ensure study blinding.

As stated previously, the non-inferiority margin of 25% chosen for the primary efficacy assessment was deemed clinically unacceptable by the DGIEP clinical review team. Additionally, as previously stated, the non-inferiority margin of 15%, chosen for the extra requested assessment of percentage change from baseline in spleen volume, was also not officially agreed upon by DGIEP. Neither of these margins was acceptable from a statistical perspective. Each margin was chosen by the applicant based on data from the GZGD00304 phase 2 study, which was an open-label study in 26 treatment-naïve adult GD1 patients who received monotherapy with eliglustat. From a statistical perspective, it was not feasible to assess assay sensitivity when evaluating the proposed non-inferiority margins without a placebo-controlled trial with CEREZYME. Note that a placebo-controlled trial with CEREZYME has never been conducted. In addition, the aforementioned hypothetical placebo-controlled trial with CEREZYME would have to utilize the same trial design and also be in the same population of patients as those studied in ENCORE to ensure constancy. The differences between the GZGD00304 and ENCORE study designs and patient populations preclude the constancy assumption from being met.

### **3.2.2.2 Statistical Methodologies**

#### **3.2.2.2.1 Analysis Sets**

The primary analysis set used for the primary endpoint analysis within this non-inferiority framework was the PP analysis set. This analysis set included all randomized patients who received at least one dose of eliglustat or CEREZYME treatment and who were at least 80% compliant with dosing while having both the Baseline and Week 52 assessments available for

evaluating the primary endpoint. The PP analysis set excluded patients who had any of the following major protocol deviations:

- did not meet all of the inclusion and exclusion criteria;
- were inadvertently given the wrong randomized treatment;
- became pregnant.

The PP analysis set also excluded patients who failed the primary endpoint due to medically determined etiologies other than Gaucher disease, as determined by the blinded review of the IAB. This analysis set definition was finalized prior to database lock.

As a sensitivity analysis, all analyses were repeated utilizing the FAS which included all randomized patients who received at least one dose of eliglustat or CEREZYME treatment. In this analysis set, patients were analyzed according to the treatment group that they were randomized to receive regardless of the actual treatment received.

Another sensitivity analysis was conducted by utilizing an All-Randomized analysis set, which included all patients who were randomized into the study. Similar to the FAS, patients in this analysis set were analyzed according to the treatment group that they were randomized to receive regardless of actual treatment received.

A final sensitivity analysis was conducted by utilizing a Week-52-Completer analysis set, which included all FAS patients who completed 52 weeks of treatment and had non-missing assessments for Baseline and Week 52. Similar to the FAS, patients in this analysis set were analyzed according to the treatment group that they were randomized to receive regardless of actual treatment received.

Overall, the utilization of the applicant defined analysis sets is acceptable. Specifically, per ICH E9, the use of the PP analysis set as the primary analysis set may be preferable as this is a non-inferiority study; however, all analysis sets (specifically both the PP and All-Randomized analysis sets) are utilized for the primary analysis in order to comply with FDA's Guidance for Industry: Non-Inferiority Clinical Trials<sup>2</sup>.

#### **3.2.2.2.2 Multiplicity Adjustment**

As stated above in Section 3.2.2.1, the applicant did not pre-specify a multiplicity adjustment for controlling the overall study-wise type I error. Consequently all subsequent (i.e., non-primary) analyses were considered exploratory.

#### **3.2.2.2.3 Primary Endpoint Analysis**

The primary endpoint was assessed for patients within the eliglustat and CEREZYME treatment groups. The responder/stability rates at Week 52 (i.e., the percentage of patients who were responders or remained stable at Week 52) were assessed for both treatment groups separately. A difference in the responder rates between the eliglustat and CEREZYME groups at Week 52 was calculated for the primary comparison. The applicant specified that if the lower-bound of

---

<sup>2</sup> <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf>

the 95% CI for the difference was within the non-inferiority margin of 25%, then eliglustat treatment would be declared non-inferior to CEREZYME treatment.

The aforementioned 95% CI for the difference in the proportion of patients who were responders at Week 52 was estimated using the method of Agresti and Caffo's adjusted Wald confidence intervals (Agresti, 2000, *American Statistician*; Dann, 2007, *Pharmaceutical Statistics*)<sup>3,4</sup>. The overall estimate was based on a weighted combination of the differences between the eliglustat and CEREZYME groups within the two randomization stratification groups (i.e., less than 35 U/kg/QOW and greater than or equal to 35 U/kg/QOW) with the scaled Mantel-Haenszel weights for each randomization stratum (LaVange, 2005 *Stat Methods Med Res*)<sup>5</sup>.

The Mantel-Haenszel weights were based on the sample sizes of the eliglustat group for randomization stratum one ( $n_{1T}$ ), the eliglustat group for randomization stratum two ( $n_{2T}$ ), the CEREZYME group for randomization stratum one ( $n_{1C}$ ), and the CEREZYME group for randomization stratum two ( $n_{2C}$ ). The Mantel-Haenszel weight for randomization stratum one was

$$W_{MH1} = \frac{n_{1T} n_{1C}}{n_{1T} + n_{1C}}.$$

Similarly, the Mantel-Haenszel weight for randomization stratum two was

$$W_{MH2} = \frac{n_{2T} n_{2C}}{n_{2T} + n_{2C}}.$$

These two Mantel-Haenszel weights were scaled to sum to one. The scaled Mantel-Haenszel weight for randomization stratum one was

$$W_1 = \frac{W_{MH1}}{W_{MH1} + W_{MH2}}.$$

Similarly, the scaled Mantel-Haenszel weight for randomization stratum two was

$$W_2 = \frac{W_{MH2}}{W_{MH1} + W_{MH2}}.$$

<sup>3</sup> Agresti A, Caffo B. Simple and effective confidence intervals for proportions and difference of proportions results from adding two successes and two failures. *American Statistician* 2000; 54 (4): 280-288.

<sup>4</sup> Dann RS, Koch GG. Methods for one-sided testing of the difference between proportions and sample size considerations related to non-inferiority clinical trials. In: *Pharmaceutical Statistics*. John Wiley & Sons; 2007. (www.interscience.wiley.com) DOI: 10.1002/pst.287.

<sup>5</sup> LaVange LM, Durham TA, Koch GG. Randomization-based nonparametric methods for the analysis of multicenter trials. *Statistical Methods Med Res*. 2005; 14:281-301.

The results for the eliglustat and CEREZYME success rates for the two randomization strata were then combined to produce an overall 95% CI for the difference between the eliglustat and CEREZYME success rates using the previously presented scaled Mantel-Haenszel weights for each stratum. The overall weighted difference between the eliglustat and CEREZYME success rates based on the randomization strata was

$$\tilde{d} = w_1(\tilde{p}_{1T} - \tilde{p}_{1C}) + w_2(\tilde{p}_{2T} - \tilde{p}_{2C})$$

where for  $i = 1$  or  $2$ ,

$$\tilde{p}_{iT} = (X_{iT} + 1)/(n_{iT} + 2), \tilde{p}_{iC} = (X_{iC} + 1)/(n_{iC} + 2).$$

The standard error for the difference between the eliglustat and CEREZYME treatment groups within the  $i$ th randomization stratum ( $i = 1$  or  $2$ ) was

$$SE_i = \sqrt{\tilde{p}_{iT}(1 - \tilde{p}_{iT})/\tilde{n}_{iT} + \tilde{p}_{iC}(1 - \tilde{p}_{iC})/\tilde{n}_{iC}}$$

where for  $i = 1$  or  $2$ ,

$$\tilde{n}_{iT} = n_{iT} + 2, \tilde{n}_{iC} = n_{iC} + 2$$

Therefore, the standard error for the overall weighted difference between the eliglustat and CEREZYME success rates based on the randomization strata was

$$SE(\tilde{d}) = \sqrt{w_1^2 SE_1^2 + w_2^2 SE_2^2}$$

Hence, the overall 95% CI for the difference between the eliglustat and CEREZYME success rates for the assessment of the non-inferiority of eliglustat compared to CEREZYME was

$$\tilde{d} \pm 1.96 \times SE(\tilde{d})$$

An ANCOVA model was utilized for the Week 52 percentage change from baseline in spleen volume (in MN) analysis with treatment (eliglustat or CEREZYME) and the randomization stratification factor of pre-study CEREZYME dose groups (less than 35 U/kg/QOW or greater than or equal to 35 U/kg/QOW) as factors. Baseline spleen volume (in MN) was included in the model as a covariate. The LS estimated mean, 95% CI, and p-value for the treatment effect of eliglustat versus CEREZYME were calculated. Note that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were checked by graphically observing residuals along with a normal quantile-quantile plot. If the lower-bound of the 95% CI for the difference was within the applicant-proposed non-inferiority margin of 15%, then eliglustat treatment would be declared non-inferior to CEREZYME treatment. As stated previously, this additionally requested analysis was considered exploratory.

For the secondary endpoint of the study, if the lower bound of an exact 95% CI (using the Clopper-Pearson method) in the eliglustat group alone was strictly greater than 50%, this would suggest that the majority of eliglustat patients were successful in maintaining stability after 52 weeks of treatment irrespective of whether or not the non-inferiority of eliglustat relative to CEREZYME was demonstrated. The exact 95% CIs for the eliglustat and CEREZYME treatment groups were also derived for each of the two pre-study CEREZYME dose groups used to stratify the randomization within the eliglustat and CEREZYME treatment groups, respectively. Note that because there was no multiplicity adjustment approach pre-specified by the applicant, as stated previously, this secondary analysis of the study was deemed as exploratory.

#### **3.2.2.2.4 Secondary Endpoints Analysis**

Because the applicant did not pre-specify a multiplicity adjustment method for controlling the overall study-wise significance level, the secondary efficacy endpoints were only summarized descriptively by treatment group at Baseline and at Week 52. Specifically, change and/or percentage change from baseline values were summarized.

#### **3.2.2.2.5 Handling of Dropouts/Missing Data**

For the analysis of the primary endpoint, imputing missing as ‘failure’ was implemented for patients who had missing data at Week 52 or who withdrew prior to Week 52.

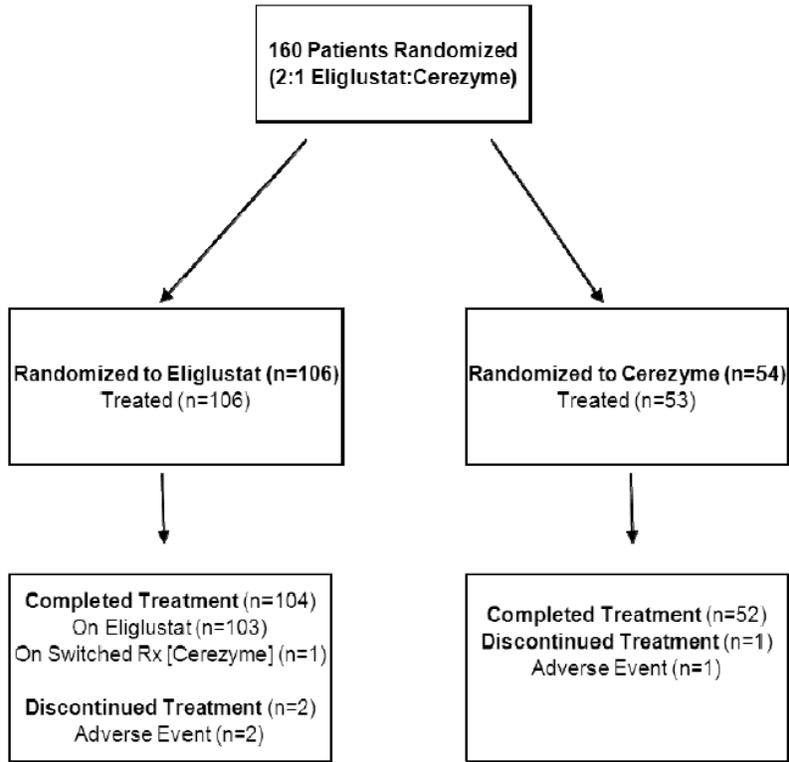
Regarding the additional non-inferiority analysis for the percentage change from baseline in spleen volume at Week 52 and all other secondary efficacy endpoint analyses, a no-change-from-baseline imputation approach was utilized.

There were only four patients (two in each treatment group) who dropped out of the ENCORE study (this is further discussed in Sections 3.2.2.3 and 3.2.2.4 below). Consequently, the study results and conclusions were not dependent on the missing data handling strategy.

#### **3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics**

The disposition information for all randomized patients is displayed in Figure 7 and Table 9 below.

**Figure 7**  
**Disposition – ENCORE**



Source: ENCORE CSR - Figure 9-1 on pg. 77.

**Table 9**  
**Disposition – ENCORE**  
**(All-Randomized)**

	Eliglustat (N = 106)	CEREZYME (N = 54)	Total (N = 160)
All-Randomized	106 (100%)	54 (100%)	160 (100%)
Full Analysis Set (FAS)	106 (100%)	53 (98.1%)	159 (99.4%)
Week-52-Completer Analysis Set	104 (98.1%)	52 (96.3%)	156 (97.5%)
Per-Protocol (PP)	99 (93.4%)	47 (87.0%)	146 (91.3%)
Completed Study	104 (98.1%)	52 (96.3%)	156 (97.5%)
Discontinued Study Early	2 (1.9%)	2 (3.7%)	4 (2.5%)
Adverse Event	2 (1.9%)	1 (1.9%)	3 (1.9%)
Non-Compliant	0	1 (1.9%)	1 (0.6%)
Wishes to Withdraw	0	0	0
Lost to follow-up	0	0	0
Study Terminated by Sponsor	0	0	0
Pregnancy	0	0	0
Decline in Gaucher Disease	0	0	0
Other	0	0	0

Source: Reviewer's Table.

Note: Denominators for percentages are N. In total, 206 patients were screened. Patients 2101 and 6903 (eliglustat) discontinued due to adverse event. Patient 2817 was randomized to receive CEREZYME but never dosed. Patient 2916 (CEREZYME) discontinued due to adverse event. Patient 4614 switched from eliglustat back to CEREZYME mid-study for safety reasons. In total at Week 8, 34 out of the 106 eliglustat patients had their doses escalated from 50 mg BID to 100 mg BID, and 51 out of the 106 eliglustat patients had their doses escalated from 50 mg BID to 150 mg BID. The other 21 eliglustat patients remained dosing at 50 mg BID.

The demographics and baseline characteristics for all randomized patients are presented in Table 10 below.

**Table 10**  
**Demographic and Baseline Characteristics – ENCORE**  
**(All-Randomized)**

	Eliglustat (N = 106)	CEREZYME (N = 54)	Total (N = 160)
Age (years)			
n	106	54	160
Mean (SD)	37.4 (14.16)	37.0 (14.97)	37.3 (14.39)
Median	37.2	35.4	36.7
Min, Max	18, 69	18, 66	18, 69
Age Group – n (%)			
< 18	0	0	0
18 to 65	105 (99.1%)	53 (98.1%)	158 (98.8%)
≥ 65	1 (0.9%)	1 (1.9%)	2 (1.3%)
Gender – n (%)			
Female	59 (55.7%)	29 (53.7%)	88 (55.0%)
Male	47 (44.3%)	25 (46.3%)	72 (45.0%)
Race – n (%)			
Asian	1 (0.9%)	1 (1.9%)	2 (1.3%)
American Indian or Alaska Native	1 (0.9%)	0	1 (0.6%)
Black or African American	6 (5.7%)	4 (7.4%)	10 (6.3%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	98 (92.5%)	49 (90.7%)	147 (91.9%)
Weight at Baseline (kg)			
n	106	53	159
Mean (SD)	70.8 (16.82)	67.8 (14.44)	69.8 (16.08)
Median	69.0	65.4	68.0
Min, Max	43, 136	41, 101	41, 136
CYP2D6 Metabolizer Status – n (%)			
Poor	4 (3.8%)	2 (3.7%)	6 (3.8%)
Intermediate	12 (11.3%)	9 (16.7%)	21 (13.1%)
Extensive	84 (79.2%)	39 (72.2%)	123 (76.9%)
Ultra-Rapid	4 (3.8%)	1 (1.9%)	5 (3.1%)
Unknown	2 (1.9%)	3 (5.6%)	5 (3.1%)
Stable Pre-Study CEREZYME Dose Group			
Low (< 35 U/kg/QOW)	43 (40.6%)	22 (40.7%)	65 (40.6%)
High (≥ 35 U/kg/QOW)	63 (59.4%)	32 (59.3%)	95 (59.4%)

Source: Reviewer's Table.

Note: Denominators for percentages are N.

It can be seen that there was no noticeable imbalance between the treatment groups regarding the presented demographic and baseline characteristics.

### 3.2.2.4 Results and Conclusions

The results for the analysis of the primary endpoint are shown below in Table 11.

**Table 11**  
**Summary of Proportion of Patients who were Stable at Week 52 – ENCORE (PP)**

Variable	Eliglustat			CEREZYME		
	Pre-study CEREZYME < 35 U/kg/QOW (N = 38)	Pre-study CEREZYME ≥ 35 U/kg/QOW (N = 61)	Overall (N = 99)	Pre-study CEREZYME < 35 U/kg/QOW (N = 18)	Pre-study CEREZYME ≥ 35 U/kg/QOW (N = 29)	Overall (N = 47)
Patients Stable at Week 52, n (%)	32 (84.2%)	52 (85.2%)	84 (84.8%)	17 (94.4%)	27 (93.1%)	44 (93.6%)
Patients who met Stable Spleen Volume Criteria, n (%)	36 (94.7%)	60 (98.4%)	96 (97.0%)	18 (100%)	29 (100%)	47 (100%)
Patients who met Stable Hemoglobin Level Criteria, n (%)	35 (92.1%)	59 (96.7%)	94 (94.9%)	18 (100%)	29 (100%)	47 (100%)
Patients who met Stable Liver Volume Criteria, n (%)	38 (100%)	57 (93.4%)	95 (96.0%)	17 (94.4%)	27 (93.1%)	44 (93.6%)
Patients who met Stable Platelet Count Criteria, n (%)	36 (94.7%)	56 (91.8%)	92 (92.9%)	18 (100%)	29 (100%)	47 (100%)
Difference in Proportion Stable at Week 52 (Eliglustat – CEREZYME), %	-10.2%	-9.5%	-8.8%			
Primary Endpoint						
95% Agresti and Caffo adjusted CI of Difference in Proportion Stable, % [1]	(-25.2%, 10.2%)	(-21.8%, 6.2%)	(-17.6%, 3.3%)			
Exact 95% CI of Proportion Stable at Week 52, % [2]	(68.7%, 94.0%)	(71.9%, 91.8%)	(75.1%, 90.5%)	(72.7%, 99.9%)	(77.2%, 99.2%)	(82.5%, 98.7%)

Source: Reviewer's Table.

Note: QOW = every other week; CI = confidence interval. Denominators for percentages are N. The primary efficacy criteria for success include stable hematologic parameters and organ volumes as defined in the protocol above. The eliglustat patient (4614) who returned to CEREZYME treatment was counted as a failure.

[1]: If the lower bound of the 95% CI for the difference in the overall columns is within the non-inferiority margin of 25% (i.e., >-25%), then the eliglustat treatment will be declared non-inferior to CEREZYME treatment.

[2]: The lower bound of the exact 95% CI (using the Clopper-Pearson method) for the overall column of the eliglustat group will be used to claim that the majority of the eliglustat patients were successful in maintaining stability after 52 weeks of treatment, irrespective of whether or not the non-inferiority of eliglustat relative to CEREZYME was demonstrated.

It can be observed from Table 11 above that the lower bound of the 95% CI of the difference in the proportion of patients stable at Week 52 (i.e., -17.6%) was above the pre-specified non-inferiority margin of -25%. Consequently, eliglustat is declared non-inferior to CEREZYME treatment. This analysis was repeated utilizing the FAS, Week-52-Completer and All-Randomized analysis sets, and all statistics and corresponding conclusions were consistent. From the 160 patients who were originally randomized, there were only four dropouts (two from each treatment group), and a sensitivity analysis showed that these dropouts did not alter the study conclusions.

It is important to note that no single site influenced or drove the overall study results. It was observed that sites #27 (Investigator Martins), #28 (Investigator Drelichman), and #29 (Investigator Cravo) had a larger number of successes/responders than the other sites. A sensitivity analysis was conducted by removing all patients from these sites from the overall analysis, and the subsequent results and conclusions stood. The Office of Scientific Investigation's (OSI) did not identify any deviations from regulations from these sites/investigators and issued NAI for each of these sites after inspection during the review cycle.

It should also be noted that the EMA suggested a 20% margin for the primary efficacy assessment in their formal communications with Genzyme during the time period which followed the EOP2 meeting with DGIEP. It can be observed that the lower bound of the 95% CI (i.e., -17.6%) was also within this suggested non-inferiority margin.

It can also be observed from Table 11 above that the lower bound of the exact 95% CI in the eliglustat group overall (i.e., 75.1%) was greater than 50%. This result suggests that the majority of eliglustat patients were successful in maintaining stability after 52 weeks of treatment. Note that because there was no multiplicity adjustment pre-specified by the applicant, as stated previously, this analysis was deemed as exploratory.

Tables 12, 13, 14, and 15 below present the descriptive summary of spleen volume, hemoglobin level, liver volume, and platelet count, respectively. Specifically, change and/or percentage change from baseline values are summarized. Note that for Table 12, the ANCOVA model results, corresponding to the additional non-inferiority analysis requested by DGIEP, are presented.

**Table 12**  
**Summary of Percentage Change from Baseline to Week 52 in Spleen Volume (MN) –**  
**ENCORE**  
**(FAS)**

Time Point	Eliglustat (N = 106)	CEREZYME (N = 53)	Treatment Difference (Eliglustat – CEREZYME)
Baseline Spleen Volume (MN)			
n	106	53	
Mean (SD)	3.17 (1.346)	2.74 (1.152)	
Median	2.87	2.24	
Min, Max	1.1, 7.4	1.1, 5.8	
Week 52 Spleen Volume (MN)			
n	106	53	
Mean (SD)	3.04 (1.363)	2.64 (1.059)	
Median	2.93	2.42	
Min, Max	0.9, 7.6	1.1, 5.2	
Absolute Change from Baseline to Week 52			
n	106	53	
Mean (SD)	-0.13 (0.470)	-0.10 (0.299)	
Median	-0.14	-0.10	
Min, Max	-1.7, 1.3	-0.8, 0.7	
% Change from Baseline to Week 52			
n	106	53	
Mean (SD)	-5.11 (14.548)	-3.06 (10.466)	
Median	-6.00	-4.40	
Min, Max	-48.7, 31.8	-22.1, 20.1	
LS Mean (SEM) [1]	-5.00 (1.52)	-3.26 (1.99)	-1.73 (2.52)
95% CI [1]	-8.00, -1.99	-7.21, 0.68	-6.72, 3.25
p-value [1]	NA	NA	0.4924
LS Mean (SEM) [2]	-6.17 (1.59)	-3.21 (2.15)	-2.83 (2.71)
95% CI [2]	-9.17, -2.93	-7.47, 1.06	-8.14, 2.47
p-value [2]	NA	NA	0.2922

Source: Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation; LS = least squares; SEM = standard error of the mean; CI = confidence interval; NA = not applicable.

[1]: Derived from ANCOVA model adjusted for pre-study CEREZYME dose group (< 35 U/kg/QOW or ≥ 35 U/kg/QOW) and baseline spleen volume (MN). Treatment effect defined as: (% Change from Baseline to Week 52, Eliglustat) – (% Change from Baseline to Week 52, CEREZYME).

[2]: Same model as defined in [1] except that the results are based on the PP population.

It can be observed from Table 12 above that the upper bound of the 95% CI of the difference in the percentage change from baseline at Week 52 (i.e., 3.25% and 2.47% for the FAS and PP analysis sets, respectively) was below the pre-specified non-inferiority margin of 15%. As stated previously, this additionally requested analysis was considered exploratory. It should be noted that the ANCOVA model assumptions, i.e., normality and constant variance of residuals, were appropriate based on graphically observing residuals along with the pertinent normal quantile-quantile plot.

**Table 13**  
**Summary of Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) –**  
**ENCORE**  
**(FAS)**

Time Point	Eliglustat (N = 106)	CEREZYME (N = 53)
Baseline Hemoglobin Level (g/dL)		
n	106	53
Mean (SD)	13.61 (1.273)	13.88 (1.30)
Median	13.58	13.90
Min, Max	10.7, 17.3	11.2, 16.6
Week 52 Hemoglobin Level (g/dL)		
n	106	53
Mean (SD)	13.40 (1.267)	13.95 (1.420)
Median	13.35	13.90
Min, Max	10.1, 16.4	11.1, 18.8
Absolute Change from Baseline to Week 52		
n	106	53
Mean (SD)	-0.21 (0.729)	0.079 (0.917)
Median	-0.30	0.15
Min, Max	-2.0, 1.9	-3.5, 2.3

Source: Reviewer's Table.

Note: SD = standard deviation.

It can be seen from Table 13 above that hemoglobin levels remained fairly stable for both treatment groups at Week 52.

**Table 14**  
**Summary of Percentage Change from Baseline to Week 52 in Liver Volume (MN) –**  
**ENCORE**  
**(FAS)**

Time Point	Eliglustat (N = 106)	CEREZYME (N = 53)
Baseline Liver Volume (MN)		
n	106	53
Mean (SD)	0.94 (0.189)	0.92 (0.157)
Median	0.90	0.95
Min, Max	0.5, 1.5	0.6, 1.3
Week 52 Liver Volume (MN)		
n	106	53
Mean (SD)	0.96 (0.181)	0.95 (0.160)
Median	0.93	0.93
Min, Max	0.6, 1.7	0.6, 1.3
Absolute Change from Baseline to Week 52		
n	106	53
Mean (SD)	0.02 (0.0915)	0.03 (0.0957)
Median	0.03	0.040
Min, Max	-0.2, 0.3	-0.2, 0.3
% Change from Baseline to Week 52		
n	106	53
Mean (SD)	2.22 (9.596)	2.80 (10.110)
Median	2.90	4.20
Min, Max	-21.5, 30.0	-26.8, 25.3

Source: Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation.

It can be seen from Table 14 above that liver volume remained reasonably stable for both treatment groups at Week 52.

**Table 15**  
**Summary of Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) –**  
**ENCORE**  
**(FAS)**

Time Point	Eliglustat (N = 106)	CEREZYME (N = 53)
Baseline Platelet Count (10 <sup>9</sup> /L)		
n	106	53
Mean (SD)	203.30 (79.327)	187.51 (56.784)
Median	186.25	174.50
Min, Max	100.5, 511.0	102.0, 339.5
Week 52 Platelet Count (10 <sup>9</sup> /L)		
n	106	53
Mean (SD)	214.49 (83.293)	191.95 (61.902)
Median	200.00	181.00
Min, Max	69.5, 522.0	81.0, 367.5
Absolute Change from Baseline to Week 52		
n	106	53
Mean (SD)	10.22 (40.504)	4.44 (24.106)
Median	8.00	3.50
Min, Max	-149.0, 166.0	-37.5, 94.5
% Change from Baseline to Week 52		
n	106	53
Mean (SD)	4.04 (18.827)	1.76 (13.492)
Median	4.10	2.00
Min, Max	-55.7, 73.1	-32.9, 34.8

Source: Reviewer's Table.

Note: SD = standard deviation.

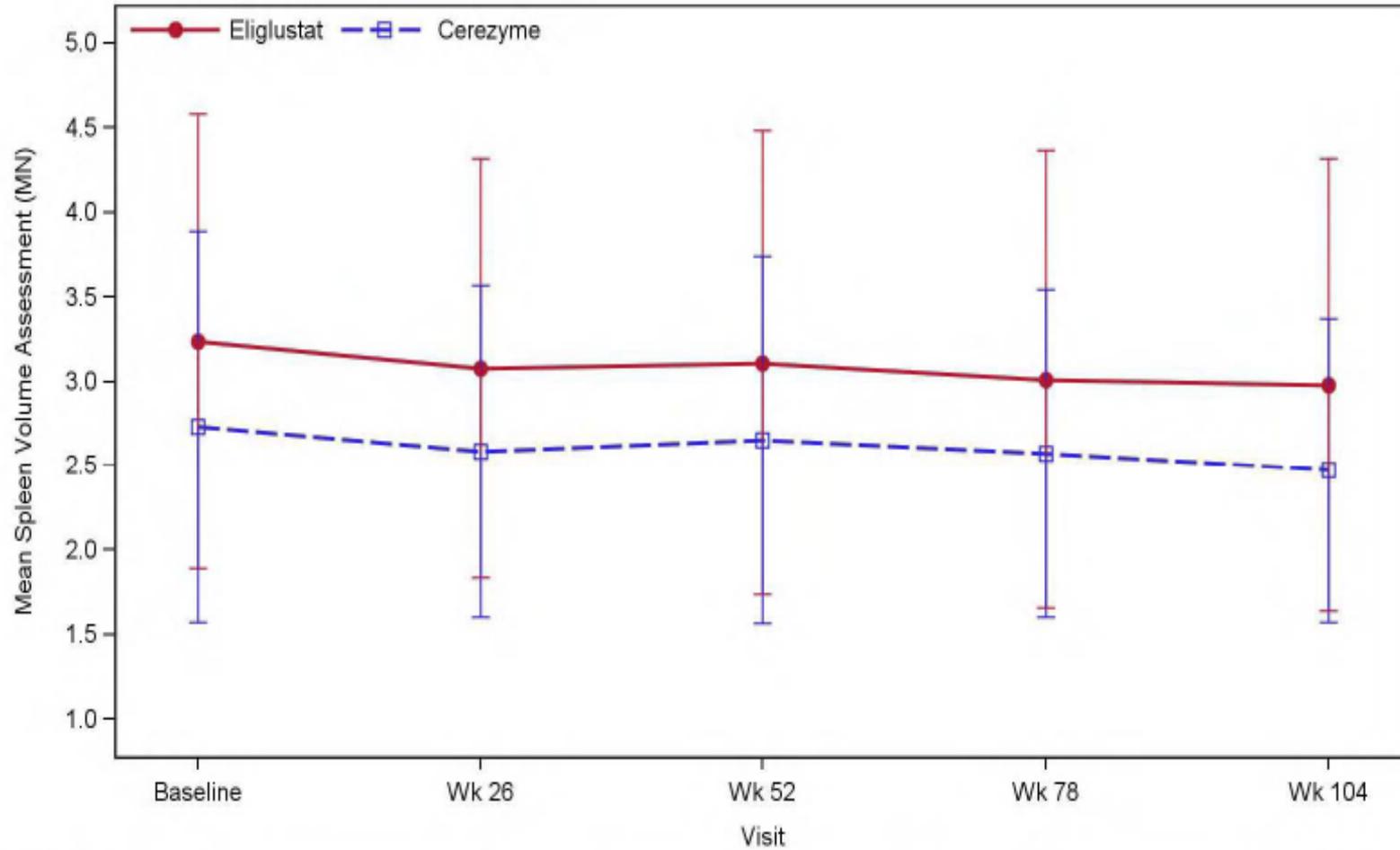
It can be seen from Table 15 above that platelet counts remained reasonably stable at Week 52.

As stated previously in Section 3.2.2.1, after Week 52 assessments were completed, each patient then entered the Long-Term Treatment Period where all patients received eliglustat from post-Week 52 (Day 1 of the Long-Term Treatment Period) through study completion. Each patient's total duration of participation in this study (including both the Primary Analysis and Long-Term Treatment Periods) was planned to be at least 104 weeks, and each patient could continue participation for a total of up to 5.5 years. This Long-Term Treatment Period was ongoing at the time of NDA filing, and the most up-to-date submission by the applicant includes a total exposure of 104 weeks.

Figures 8, 9, 10, and 11 below present the spleen volume, hemoglobin level, liver volume, and platelet count data, respectively, from baseline through Week 104. Note that patients who were randomized at Baseline to continue receiving CEREZYME for the Primary Analysis Treatment Period are displayed as CEREZYME patients within these figures although they all began the eliglustat treatment the day after Week 52. It can be seen that patients who were randomized at

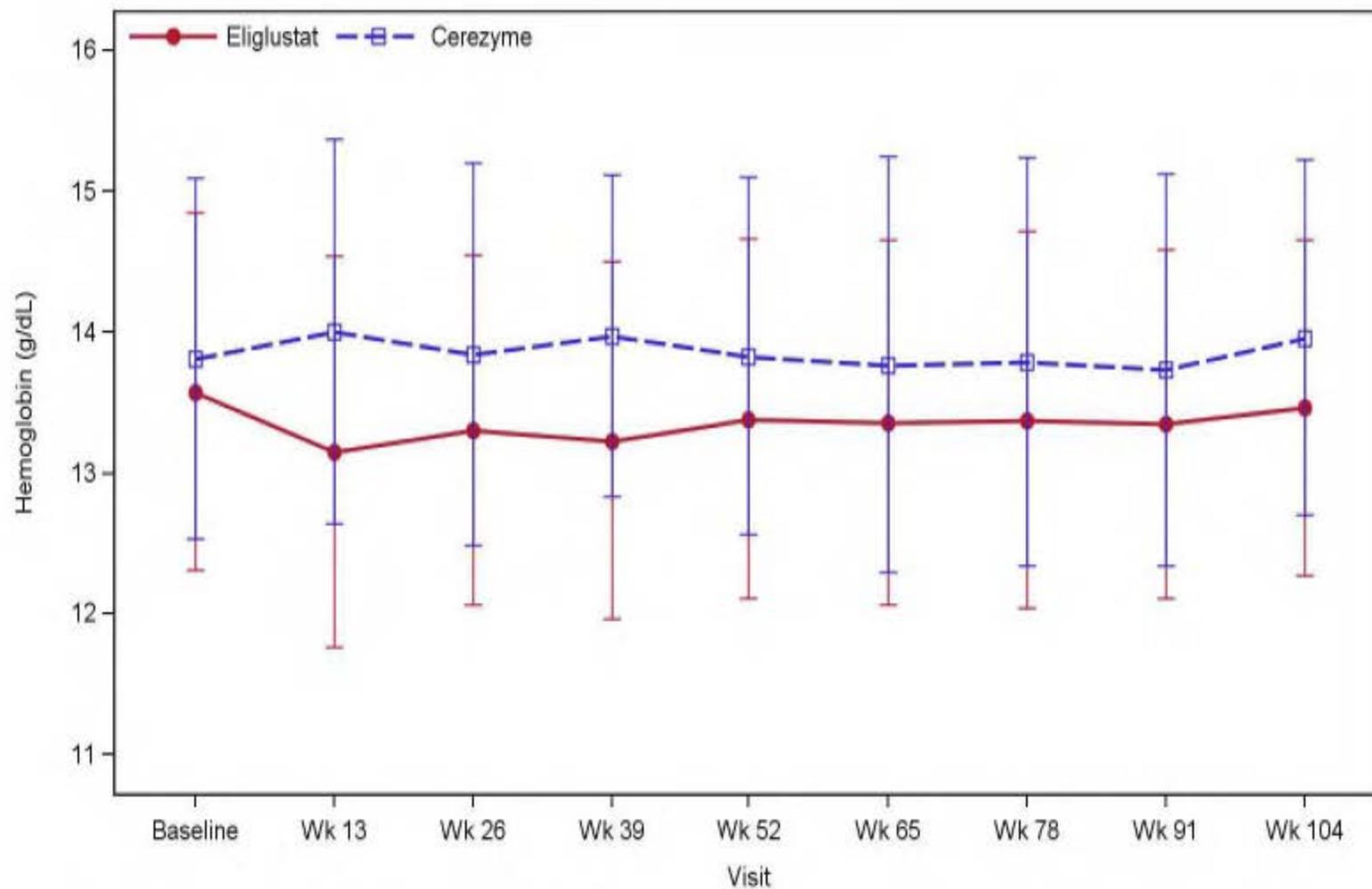
Baseline to eliglustat for the Primary Analysis Treatment Period seemed to maintain their organ volume and hematological parameter values after Week 52. It can also be seen that patients who were randomized at Baseline to continue on CEREZYME for the Primary Analysis Treatment Period seemed to maintain their organ volume and hematological parameter values after Week 52 when these patients began exclusive treatment with eliglustat.

**Figure 8**  
**Mean ( $\pm$  SD) Spleen Volume (MN) over Time – ENCORE (FAS)**



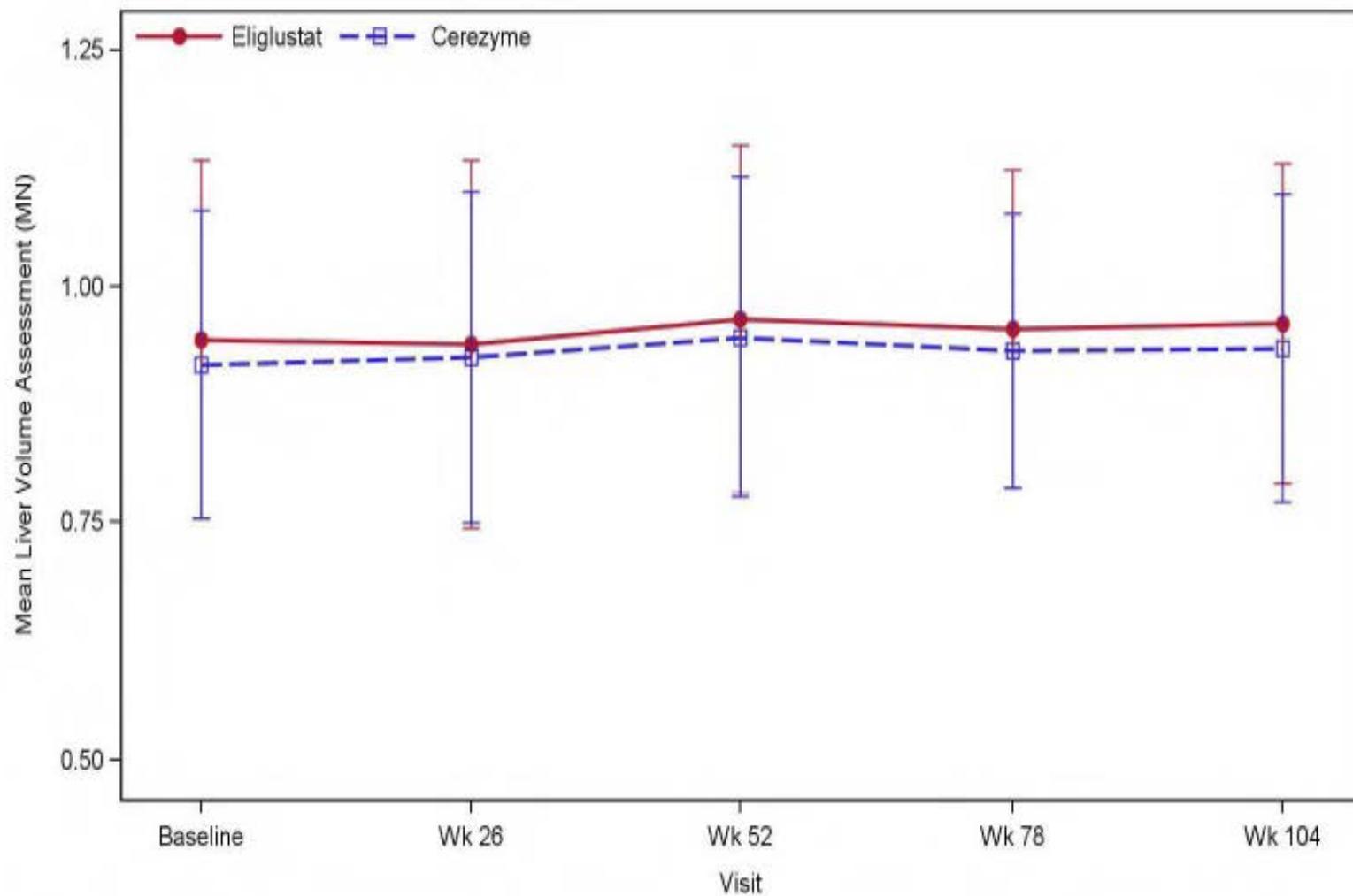
Source: January 10, 2014 Information Request Submission - Figure 3.1.2 on pg. 26.

**Figure 9**  
**Mean ( $\pm$  SD) Hemoglobin Level (g/dL) over Time – ENCORE**  
**(FAS)**



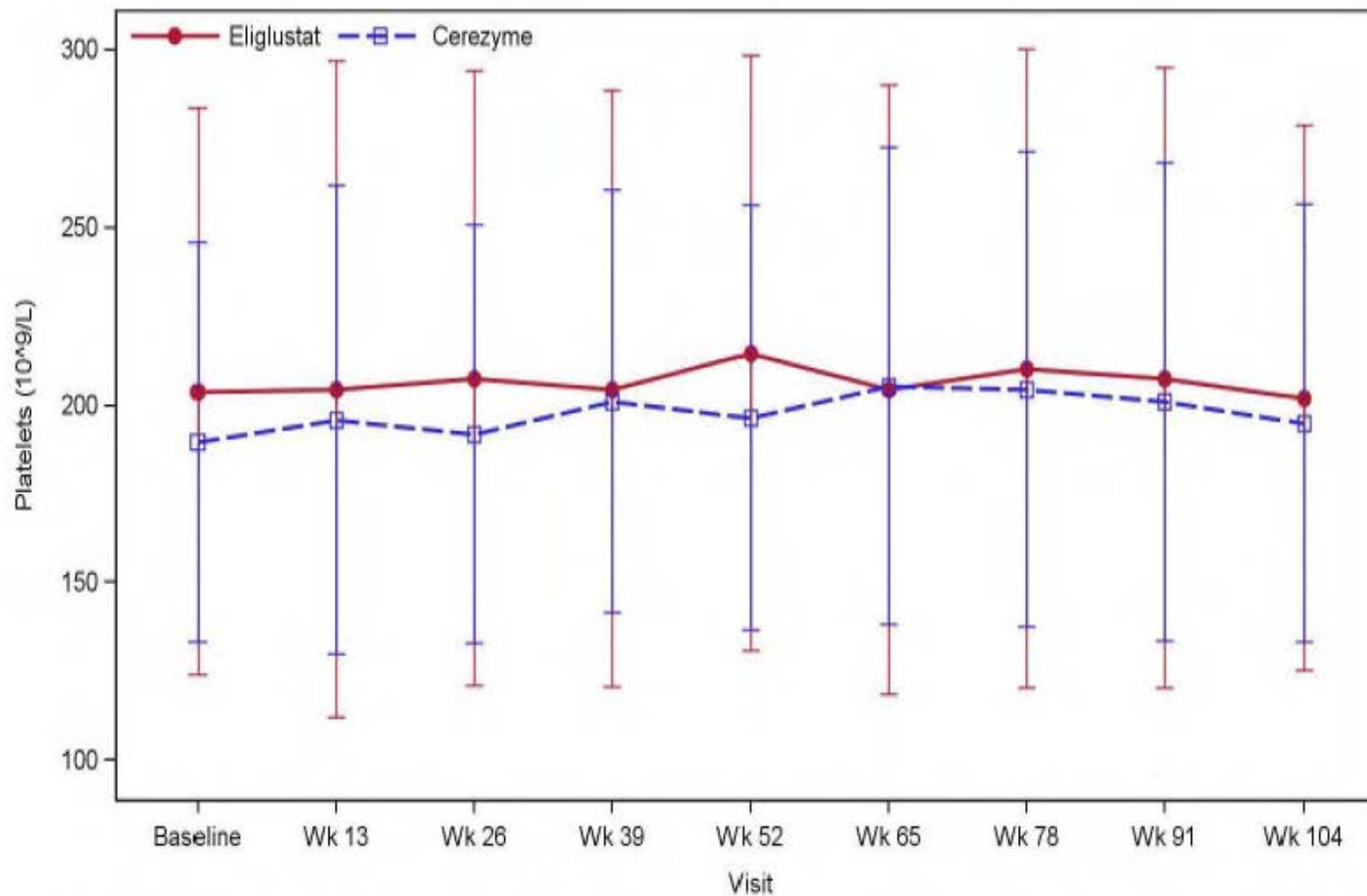
Source: January 10, 2014 Information Request Submission - Figure 3.5.2 on pg. 34.

**Figure 10**  
**Mean ( $\pm$  SD) Liver Volume (MN) over Time – ENCORE**  
**(FAS)**



Source: January 10, 2014 Information Request Submission - Figure 3.3.2 on pg. 30.

**Figure 11**  
**Mean ( $\pm$  SD) Platelet Count ( $10^9/L$ ) over Time – ENCORE (FAS)**



Source: January 10, 2014 Information Request Submission - Figure 3.6.2 on pg. 36.

### **3.3 Evaluation of Safety**

The main safety evaluation by study is presented below. It should be noted that unlike in ERTs, which are all biological products, it is commonly known that there is little to no risk in developing any types of anti-drug antibody when being administered eliglustat. This attribute and the relatively mild adverse events observed during the clinical development program indicate the low risk associated with eliglustat treatment. Please see Section 7 of the clinical review for the full details regarding the safety profile of eliglustat.

#### **3.3.1 Study GZGD02507 (ENGAGE)**

There were no deaths, no serious adverse events (SAE), no treatment discontinuations due to treatment-emergent adverse events (TEAE), and no study withdrawals due to TEAEs. Most of the TEAEs were considered by investigators to be unrelated to the study drug. The only TEAEs occurring in at least 10% of the eliglustat patients were diarrhea and flatulence.

#### **3.3.2 Study GZGD02607 (ENCORE)**

There were no deaths. The SAEs were reported in 11 patients (10%) in the eliglustat group (each with one SAE). The majority of SAEs were classified as such due to hospitalizations for intercurrent illnesses and three SAEs were events for which GD1 patients are commonly known at an increased risk (i.e., hepatocellular carcinoma, cholecystitis and joint dislocation). Two eliglustat patients (2%) discontinued study treatment due to TEAEs within the 52 week treatment period. There were no TEAEs occurring in at least 10% of the eliglustat patients.

## **4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS**

### **4.1 Gender and Geographic Region**

As you can see from Tables 4 and 10 above, the study participants for both ENGAGE and ENCORE were primarily white adults between the ages of 18 and 65. Consequently, no race or age subgroup analyses were conducted. The analyses for the primary endpoint in both ENGAGE and ENCORE were conducted by the gender and geographic region subgroups, and these results are presented within this section. The SAS outputs of gender and geographic region subgroup analyses for the secondary endpoints in both ENGAGE and ENCORE are presented in the Appendix.

#### **4.1.1 Study GZGD02507 (ENGAGE)**

The gender subgroup analysis results are presented in Table 16 below. It was found that the results were consistent across the gender subgroups, and consistent with the overall population as seen in Table 5 above.

**Table 16**  
**Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by**  
**Gender – ENGAGE**  
**(FAS)**

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>Female</i>						
Baseline Spleen Volume (MN)						
Eliglustat	12	13.50	5.300	11.29	7.6	22.9
Placebo	8	14.03	6.367	12.29	6.3	24.5
Week 39 Spleen Volume (MN)						
Eliglustat	12	9.50	5.046	7.57	5.2	21.9
Placebo	8	14.88	6.570	13.87	6.6	24.6
Absolute Change from Baseline to Week 39						
Eliglustat	12	-4.00	2.342	-3.70	-7.0	0.0
Placebo	8	0.85	0.809	0.80	-0.3	2.0
% Change from Baseline to Week 39						
Eliglustat	12	-30.94	13.630	-31.95	-51.5	0.0
Placebo	8	6.46	5.636	7.18	-2.8	13.7
<i>Male</i>						
Baseline Spleen Volume (MN)						
Eliglustat	8	14.49	7.114	13.11	5.9	28.4
Placebo	12	11.48	5.719	9.15	6.8	25.3
Week 39 Spleen Volume (MN)						
Eliglustat	8	11.18	5.262	9.96	4.1	19.3
Placebo	12	11.48	6.176	8.33	7.0	26.2
Absolute Change from Baseline to Week 39						
Eliglustat	8	-3.31	2.526	-2.86	-9.1	-0.7
Placebo	12	0.01	1.084	-0.17	-1.8	2.3
% Change from Baseline to Week 39						
Eliglustat	8	-22.55	9.494	-24.05	-32.2	-7.7
Placebo	12	-0.86	9.457	-2.12	-20.9	13.4

Source: Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation.

The geographic region subgroup analysis results are presented in Table 17 below. It was found that the results were consistent across the geographic region subgroups, and consistent with the overall population as seen in Table 5 above.

**Table 17**  
**Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by**  
**Geographic Region – ENGAGE**  
**(FAS)**

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>North America</i>						
Baseline Spleen Volume (MN)						
Eliglustat	7	13.31	7.801	10.08	5.9	28.4
Placebo	6	9.67	2.273	9.15	7.3	13.1
Week 39 Spleen Volume (MN)						
Eliglustat	7	9.30	5.181	8.26	4.1	19.3
Placebo	6	9.39	3.002	8.33	7.0	14.7
Absolute Change from Baseline to Week 39						
Eliglustat	7	-4.01	2.941	-3.04	-9.1	-1.6
Placebo	6	-0.28	1.163	-0.47	-1.8	1.6
% Change from Baseline to Week 39						
Eliglustat	7	-29.04	9.391	-30.64	-41.3	-18.1
Placebo	6	-3.81	11.413	-5.00	-20.9	12.2
<i>Europe</i>						
Baseline Spleen Volume (MN)						
Eliglustat	7	12.57	5.136	10.33	8.6	22.9
Placebo	8	14.39	7.357	12.63	6.8	25.3
Week 39 Spleen Volume (MN)						
Eliglustat	7	9.35	3.772	7.95	5.6	16.2
Placebo	8	15.05	7.550	12.87	7.1	26.2
Absolute Change from Baseline to Week 39						
Eliglustat	7	-3.23	1.783	-2.90	-6.7	-0.7
Placebo	8	0.66	0.800	0.76	-0.3	2.3
% Change from Baseline to Week 39						
Eliglustat	7	-25.42	9.320	-28.88	-34.7	-7.7
Placebo	8	5.00	5.707	4.55	-2.8	13.4
<i>Other</i>						
Baseline Spleen Volume (MN)						
Eliglustat	6	16.11	4.484	16.05	10.0	21.9
Placebo	6	12.81	6.210	11.20	6.3	22.6
Week 39 Spleen Volume (MN)						
Eliglustat	6	12.15	6.443	10.41	6.1	21.9
Placebo	6	13.35	6.647	12.35	6.6	24.6
Absolute Change from Baseline to Week 39						
Eliglustat	6	-3.96	2.596	-4.03	-7.0	0.0
Placebo	6	0.55	1.123	0.52	-1.0	2.0
% Change from Baseline to Week 39						
Eliglustat	6	-28.39	19.547	-32.35	-51.5	0.0
Placebo	6	4.04	7.544	5.80	-5.5	13.7

Source: Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation.

#### 4.1.2 Study GZGD02607 (ENCORE)

The gender subgroup analysis results are presented in Table 18 below. It was found that the results were consistent across the gender subgroups, and consistent with the overall population as seen in Table 11 above.

**Table 18**  
**Summary of Proportion of Patients who were Stable at Week 52 by Gender – ENCORE (FAS)**

Gender	Eliglustat (N = 106)	CEREZYME (N = 53)
<i>Female</i>		
<i>n</i>	59	28
<i>n (%)</i>	50 (84.7%)	25 (89.3%)
<i>Male</i>		
<i>n</i>	47	25
<i>n (%)</i>	37 (78.7%)	23 (92.0%)

Source: Reviewer's Table.

Note: Denominators for percentages are *n*.

The geographic region subgroup analysis results are presented in Table 19 below. It was found that the results were consistent across the geographic region subgroups, and consistent with the overall population as seen in Table 11 above.

**Table 19**  
**Summary of Proportion of Patients who were Stable at Week 52 by Geographic Region –**  
**ENCORE**  
**(FAS)**

Gender	Eliglustat (N = 106)	CEREZYME (N = 53)
<i>North America</i>		
<i>n</i>	48	24
<i>n (%)</i>	38 (79.2%)	23 (95.8%)
<i>Europe</i>		
<i>n</i>	17	9
<i>n (%)</i>	15 (88.2%)	8 (88.9%)
<i>Other</i>		
<i>n</i>	41	20
<i>n (%)</i>	34 (82.9%)	17 (85.0%)

Source: Reviewer's Table.

Note: Denominators for percentages are *n*.

#### 4.2 Other Special/Subgroup Populations

The special subgroup population of clinical interest was the CYP2D6 metabolizer status at baseline (i.e., poor, intermediate, extensive, ultra-rapid, or unknown). The results of this subgroup analysis for the primary endpoint in both ENGAGE and ENCORE are presented within this section. The SAS outputs of this subgroup analysis for the secondary endpoints in both ENGAGE and ENCORE are presented in the Appendix.

This subgroup analysis result for ENGAGE is presented in Table 20 below. As you can see here and from Table 4 above, the study participants for ENGAGE were primarily extensive metabolizers.

**Table 20**  
**Summary of Percentage Change from Baseline to Week 39 in Spleen Volume (MN) by**  
**CYP2D6 Metabolizer Status – ENGAGE**  
**(FAS)**

Timepoint/ Treatment Group	n	Mean	SD	Median	Min	Max
<i>Intermediate</i>						
Baseline Spleen Volume (MN)						
Eliglustat	1	5.94		5.94	5.9	5.9
Placebo	2	13.63	5.848	13.63	9.5	17.8
Week 39 Spleen Volume (MN)						
Eliglustat	1	4.12		4.12	4.1	4.1
Placebo	2	12.72	5.763	12.72	8.6	16.8
Absolute Change from Baseline to Week 39						
Eliglustat	1	-1.82		-1.82	-1.8	-1.8
Placebo	2	-0.91	0.0849	-0.91	-1.0	-0.9
% Change from Baseline to Week 39						
Eliglustat	1	-30.64		-30.64	-30.6	-30.6
Placebo	2	-7.21	2.475	-7.21	-9.0	-5.5
<i>Extensive</i>						
Baseline Spleen Volume (MN)						
Eliglustat	18	13.99	5.766	12.09	7.6	28.4
Placebo	18	12.37	6.125	11.05	6.3	25.3
Week 39 Spleen Volume (MN)						
Eliglustat	18	10.08	4.800	8.34	5.2	21.9
Placebo	18	12.86	6.615	10.97	6.6	26.2
Absolute Change from Baseline to Week 39						
Eliglustat	18	-3.91	2.439	-3.36	-9.1	0.0
Placebo	18	0.49	1.012	0.55	-1.8	2.3
% Change from Baseline to Week 39						
Eliglustat	18	-28.30	12.681	-29.03	-51.5	0.0
Placebo	18	3.10	8.630	4.86	-20.9	13.7
<i>Ultra-Rapid</i>						
Baseline Spleen Volume (MN)						
Eliglustat	1	20.16		20.16	20.2	20.2
Placebo	0					
Week 39 Spleen Volume (MN)						
Eliglustat	1	17.85		17.85	17.9	17.9
Placebo	0					
Absolute Change from Baseline to Week 39						
Eliglustat	1	-2.31		-2.31	-2.3	-2.3
Placebo	0					
% Change from Baseline to Week 39						
Eliglustat	1	-11.46		-11.46	-11.5	-11.5
Placebo	0					

Source: Reviewer's Table.

Note: MN = multiples of normal; SD = standard deviation.

This subgroup analysis result for ENCORE is presented in Table 21 below. As you can see here and from Table 10 above, the study participants for ENCORE were primarily extensive metabolizers.

**Table 21**  
**Summary of Proportion of Patients who were Stable at Week 52 by CYP2D6 Metabolizer Status – ENCORE (FAS)**

Gender	Eliglustat (N = 106)	CEREZYME (N = 53)
<i>Poor</i>		
<i>n</i>	4	2
<i>n (%)</i>	3 (75.0%)	2 (100 %)
<i>Intermediate</i>		
<i>n</i>	12	9
<i>n (%)</i>	8 (66.7%)	9 (100%)
<i>Extensive</i>		
<i>n</i>	84	38
<i>n (%)</i>	71 (84.5%)	34 (89.5%)
<i>Ultra-Rapid</i>		
<i>n</i>	4	1
<i>n (%)</i>	4 (100%)	1 (100%)
<i>Unknown</i>		
<i>n</i>	2	3
<i>n (%)</i>	1 (50.0%)	2 (66.7%)

Source: Reviewer's Table.

Note: Denominators for percentages are *n*.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

Overall, the designs of both the ENGAGE and ENCORE studies were deemed adequate from a statistical perspective for the proposed indication, and the applicant's corresponding statistical analysis plans deemed appropriate. There were no statistical review issues identified for this application that would preclude product approval.

One issue pertaining to the ENCORE study is the non-inferiority margin of 25% that was pre-specified for the primary efficacy assessment. This margin was deemed clinically unacceptable by the clinical review team. There was also no agreement on the non-inferiority margin of 15%, proposed for the additionally requested assessment of percentage change from baseline in spleen volume. Neither of these margins was acceptable from a statistical perspective. Each margin was chosen by the applicant based on data from the GZGD00304 phase 2 study, which was an open-label study in 26 treatment-naïve adult GD1 patients who received monotherapy with eliglustat. It was not feasible to assess assay sensitivity when evaluating the proposed non-inferiority margins without a placebo-controlled trial with CEREZYME. Note that a placebo-controlled trial with CEREZYME has never been conducted. In addition, the aforementioned hypothetical placebo-controlled trial with CEREZYME would have to utilize the same trial design and also be in the same population of patients as those studied in ENCORE to ensure constancy. The differences between the GZGD00304 and ENCORE study designs and patient populations ultimately precluded the constancy assumption from also being met.

## **5.2 Collective Evidence**

The applicant submitted the results from the ENGAGE and ENCORE trials to support the efficacy of eliglustat for the treatment of GD1 in adult patients. In the pivotal ENGAGE trial eliglustat was demonstrated to be superior to placebo with respect to the Week 39 change from baseline in spleen volume, hemoglobin level, liver volume, and platelet count, respectively. The currently ongoing Open-Label Treatment Period suggests a sustained efficacy profile with respect to the aforementioned four parameters. The key supportive ENCORE trial demonstrated that patients who had reached therapeutic goals with ERT, CEREZYME being the most widely used ERT for treating adults with GD1, remained stable 52 weeks after switching to oral treatment with eliglustat. The currently ongoing Long-Term Treatment Period suggests that this maintained clinical response is durable.

## **5.3 Conclusions and Recommendations**

There is sufficient evidence in supporting the proposed efficacy claims for eliglustat, and the claims reflected within the applicant's submitted product labeling are supported by the results presented in this review.

## 6 APPENDIX

**Table 22**

**Relevant Timeline and Comments for ENGAGE and ENCORE**

(Note: Read this table starting from the upper left side down to the lower right side.)

<u>Milestone</u>	<b>1. February 5, 2009</b> EOP2 Meeting	<b>2. March 31, 2009</b> Original ENGAGE Protocol Finalized	<b>3. May 22, 2009</b> Original ENCORE Protocol Finalized	<b>4. September 10, 2009</b> ENCORE Initiated
<u>Comment</u> (if necessary)	Study Designs, Endpoints and Roles (within the overall clinical development program) are determined separately for the ENGAGE and ENCORE studies.			
<u>Milestone</u>	<b>5. October 5, 2009</b> Amendment Two (major amendment) of ENCORE Protocol	<b>6. November 5, 2009</b> ENGAGE Initiated	<b>7. October 28, 2010</b> Original ENGAGE SAP Finalized	<b>8. November 19, 2010</b> Original ENCORE SAP Finalized
<u>Comment</u> (if necessary)	Primary objective of the study changed to a comparative non-inferiority efficacy assessment. In addition, the duration of the Primary Analysis Treatment Period changed from 39 weeks to 52 weeks. This was considered by the review team to effectively be the initial ENCORE trial protocol due to no patients being dosed at the time.			

<u>Milestone</u>	<b>9. April 12, 2011</b> Type C Advice Meeting	<b>10. July 6, 2011</b> Amendment Five of ENCORE Protocol	<b>11. July 12, 2011</b> Amendment Five of ENGAGE Protocol	<b>12. August 11, 2011</b> Separate Amendments for both the ENGAGE and ENCORE SAPs
<u>Comment</u> (if necessary)	Genzyme disclosed its ENGAGE study recruitment issues to DGIEP. At the time, only 16 patients were recruited for the ENGAGE study while 98 patients were already recruited for the ENCORE study. Alternative strategies were discussed; however, DGIEP ultimately stated that Genzyme needed to adhere to agreements and commitments made at the EOP2 meeting. DGIEP also communicated to Genzyme that the non-inferiority margin chosen for ENCORE's primary efficacy assessment was clinically unacceptable. The Division subsequently recommended that Genzyme choose to conduct an additional non-inferiority analysis.	Incorporated recommendation by DGIEP (at the previous Type C advice meeting) to conduct an additional non-inferiority analysis which specifically assessed the difference in the change from baseline at Week 52 in spleen volume between the two treatment groups. This analysis and its corresponding results are still considered exploratory in nature.	Included inferential within-treatment group analyses for eliglustat patients in case patient recruitment continued to stall (which it ultimately didn't). These are considered exploratory analyses.	SAPs for both studies amended to incorporate changes made by each study protocol's Amendment Five.

<u>Milestone</u>	<b>13. July 18, 2012</b> ENGAGE Double-Blind Treatment Period Complete	<b>14. August 17, 2012</b> ENGAGE Clinical Database Hard-lock for Double-Blind Treatment Period Study Data	<b>15. September 17, 2012</b> ENGAGE officially Unblinded	<b>16. November 9, 2012</b> ENCORE Primary Analysis Treatment Period Complete
<u>Comment</u> (if necessary)	Study is still currently ongoing during its extension phase.			Study is still currently ongoing during its extension phase.

<u>Milestone</u>	<b>17. December 7, 2012</b> ENCORE Clinical Database Hard-lock for Primary Analysis Treatment Period Study Data
<u>Comment</u> (if necessary)	

In the order shown, the following pages present the gender, geographic region, and CYP2D6 metabolizer status subgroup analyses for the ENGAGE study secondary endpoints:

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Female Gender

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Male Gender

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Female Gender

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Male Gender

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by Female Gender

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by Male Gender

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by North America Geographic Region

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Europe Geographic Region

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Other Geographic Region

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by North America Geographic Region

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Europe Geographic Region

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Other Geographic Region

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by North America Geographic Region

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by Europe Geographic Region

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by Other Geographic Region

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Intermediate CYP2D6 Metabolizer Status

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Extensive CYP2D6 Metabolizer Status

Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Ultra-Rapid CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Intermediate CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Extensive CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Ultra-Rapid CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by Intermediate CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by Extensive CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 39 in Platelet Count ( $10^9/L$ ) by Ultra-Rapid CYP2D6 Metabolizer Status

## SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Female Gender – ENGAGE

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	10.8750000	1.2545372	11.0250000	8.1500000	12.7500000
PLACEBO	8	8	11.4062500	1.2551145	11.1500000	9.6500000	13.2000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	11.9291667	1.3087917	12.0750000	8.8500000	13.4500000
PLACEBO	8	8	10.3437500	1.6321409	10.3000000	7.8500000	12.3500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	1.0541667	1.0281179	0.8000000	-0.7000000	3.1500000
PLACEBO	8	8	-1.0625000	0.8551316	-0.8750000	-2.5000000	0.0500000

## SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Male Gender – ENGAGE

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	13.8187500	0.7309180	13.7750000	12.8500000	15.2500000
PLACEBO	12	12	13.6458333	1.1806120	13.3250000	12.1000000	16.3000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	14.0562500	0.9076805	14.2500000	12.5000000	15.3000000
PLACEBO	12	12	13.3875000	1.1150061	13.4000000	11.9500000	15.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	0.2375000	1.0599023	0.3500000	-1.4500000	1.6000000
PLACEBO	12	12	-0.2583333	0.7882182	-0.1750000	-1.4500000	0.7000000

## SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Female Gender – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	1.4641667	0.3736663	1.3600000	0.9300000	2.1800000
PLACEBO	8	8	1.5275000	0.2933915	1.5000000	1.1400000	1.9800000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	1.3508333	0.3015855	1.2350000	0.9100000	1.9000000
PLACEBO	8	8	1.5912500	0.2800733	1.6000000	1.2700000	1.9800000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	-0.1133333	0.0862695	-0.0900000	-0.2800000	0
PLACEBO	8	8	0.0637500	0.1470605	0.0250000	-0.1200000	0.2800000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	-7.0416667	4.3571401	-6.6050000	-13.1000000	0
PLACEBO	8	8	4.8862500	10.4980188	1.5050000	-8.6300000	18.2500000

## SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Male Gender – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	1.3987500	0.3429468	1.3550000	0.9400000	1.9000000
PLACEBO	12	12	1.2500000	0.2176319	1.2100000	0.9300000	1.6900000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	1.3362500	0.2633269	1.2600000	1.0200000	1.8400000
PLACEBO	12	12	1.2491667	0.2532142	1.2100000	0.9000000	1.7600000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	-0.0625000	0.1462630	-0.0450000	-0.3600000	0.1000000
PLACEBO	12	12	-0.000833333	0.0615642	0.0050000	-0.1500000	0.0800000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	-3.0712500	9.3841834	-3.4750000	-18.9500000	9.0900000
PLACEBO	12	12	-0.4250000	5.3126290	0.5400000	-14.2900000	6.2500000

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by Female Gender – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	73.3750000	14.3275402	74.0000000	51.0000000	98.5000000
PLACEBO	8	8	73.2500000	21.2115198	68.5000000	53.5000000	118.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	107.2916667	30.6842115	110.2500000	40.0000000	161.0000000
PLACEBO	8	8	73.6250000	22.5685464	72.5000000	49.5000000	112.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	33.9166667	22.3371209	32.0000000	-11.0000000	70.5000000
PLACEBO	8	8	0.3750000	11.1827354	-5.0000000	-7.0000000	22.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	12	12	45.3383333	31.3155944	41.0800000	-21.5700000	87.1600000
PLACEBO	8	8	0.7262500	15.9268371	-7.2300000	-11.6100000	29.8000000

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by Male Gender – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	77.5625000	14.3064359	80.2500000	50.5000000	93.5000000
PLACEBO	12	12	81.9583333	23.7414658	80.7500000	50.5000000	128.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	86.4375000	20.1767856	90.5000000	42.0000000	106.5000000
PLACEBO	12	12	70.0833333	27.6330117	64.7500000	36.0000000	125.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	8.8750000	13.1005725	6.2500000	-8.5000000	31.5000000
PLACEBO	12	12	-11.8750000	16.2566420	-13.0000000	-44.5000000	12.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	8	8	11.2612500	20.1887511	7.5350000	-16.8300000	49.6100000
PLACEBO	12	12	-15.0933333	19.1119231	-15.4350000	-51.7400000	14.6300000

## SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by North America Geographic Region – ENGAGE

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	12.6357143	1.6861483	11.9500000	10.7000000	15.2500000
PLACEBO	6	6	13.9333333	1.3459817	13.3500000	12.8000000	16.3000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	13.2000000	1.0444297	13.4500000	11.4000000	14.3000000
PLACEBO	6	6	13.1583333	1.0650903	13.1250000	11.9500000	14.8500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	0.5642857	1.0040395	0.4500000	-1.0500000	2.2000000
PLACEBO	6	6	-0.7750000	0.7581227	-1.0250000	-1.1500000	0.7000000

## SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Europe Geographic Region – ENGAGE

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	12.3500000	1.6173538	12.8500000	10.0500000	13.9500000
PLACEBO	8	8	12.2625000	1.2194115	12.5500000	10.3500000	13.8500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	13.0857143	1.4935177	13.1000000	11.1500000	15.3000000
PLACEBO	8	8	11.6562500	2.1406670	12.2250000	7.8500000	14.5500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	0.7357143	1.1484462	0.8500000	-1.4500000	2.1500000
PLACEBO	8	8	-0.6062500	1.0362837	-0.6750000	-2.5000000	0.7000000

## SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Other Geographic Region – ENGAGE

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	11.0250000	2.0277451	11.0250000	8.1500000	13.3500000
PLACEBO	6	6	12.2166667	1.9472202	11.8750000	9.6500000	14.5500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	11.9333333	2.0103897	12.1750000	8.8500000	14.6000000
PLACEBO	6	6	11.8666667	2.4705600	11.5750000	8.9500000	15.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	0.9083333	1.2920591	0.8000000	-0.7000000	3.1500000
PLACEBO	6	6	-0.3500000	0.9071935	-0.1750000	-2.0500000	0.6500000

## SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by North America Geographic Region – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	1.3914286	0.3512088	1.3000000	0.9400000	1.9000000
PLACEBO	6	6	1.2466667	0.2377113	1.2750000	0.9300000	1.6100000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	1.2785714	0.2378675	1.2300000	1.0200000	1.6700000
PLACEBO	6	6	1.2683333	0.3575146	1.2650000	0.9000000	1.8900000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	-0.1128571	0.1356115	-0.0700000	-0.3600000	0.0800000
PLACEBO	6	6	0.0216667	0.1433062	-0.0050000	-0.1500000	0.2800000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	-6.6057143	8.3622961	-5.3800000	-18.9500000	8.5100000
PLACEBO	6	6	0.5733333	10.3163262	-0.2600000	-14.2900000	17.3900000

## SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Europe Geographic Region – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	1.4557143	0.3479395	1.4200000	1.1000000	2.1800000
PLACEBO	8	8	1.4250000	0.2700265	1.3350000	1.1200000	1.8400000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	1.3757143	0.2454830	1.2700000	1.2000000	1.9000000
PLACEBO	8	8	1.4537500	0.2658645	1.4250000	1.1200000	1.7600000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	-0.0800000	0.1183216	-0.0700000	-0.2800000	0.1000000
PLACEBO	8	8	0.0287500	0.1074958	0.0250000	-0.1200000	0.2300000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	-4.3728571	7.2046784	-4.6100000	-12.8400000	9.0900000
PLACEBO	8	8	2.3337500	8.0013658	1.5050000	-8.6300000	18.2500000

## SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Other Geographic Region – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	1.4716667	0.4216831	1.3800000	0.9300000	2.0800000
PLACEBO	6	6	1.3900000	0.3417601	1.2550000	1.1100000	1.9800000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	1.3866667	0.3841701	1.2400000	0.9100000	1.8700000
PLACEBO	6	6	1.4133333	0.3340459	1.3150000	1.0600000	1.9800000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	-0.0850000	0.0952365	-0.0550000	-0.2100000	0
PLACEBO	6	6	0.0233333	0.0765942	0.0100000	-0.0500000	0.1700000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	-5.3700000	5.5211955	-4.5100000	-13.1000000	0
PLACEBO	6	6	1.9800000	6.7192619	0.6250000	-4.5000000	14.9100000

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by North America Geographic Region – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	71.7857143	10.7232502	75.5000000	50.5000000	81.0000000
PLACEBO	6	6	71.0833333	17.5254577	71.0000000	50.5000000	96.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	93.7857143	26.2612788	101.0000000	42.0000000	121.0000000
PLACEBO	6	6	65.7500000	21.1157524	66.2500000	36.0000000	94.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	22.0000000	18.4797186	21.5000000	-8.5000000	48.5000000
PLACEBO	6	6	-5.3333333	10.7082523	-9.5000000	-14.5000000	12.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	28.6900000	26.5959113	31.3000000	-16.8300000	66.9000000
PLACEBO	6	6	-8.4450000	15.5757950	-12.8350000	-28.7100000	14.6300000

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by Europe Geographic Region – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	76.9285714	13.4022031	81.0000000	61.0000000	93.5000000
PLACEBO	8	8	82.6875000	23.4915448	80.0000000	58.0000000	118.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	97.6428571	14.0466908	98.0000000	76.5000000	114.5000000
PLACEBO	8	8	78.7500000	31.3733281	75.5000000	40.5000000	125.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	20.7142857	16.3728870	15.5000000	2.0000000	48.0000000
PLACEBO	8	8	-3.9375000	20.8368449	-4.2500000	-44.5000000	22.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	7	7	29.4342857	25.2037926	25.4100000	2.4700000	72.1800000
PLACEBO	8	8	-4.8225000	26.6800090	-4.6750000	-51.7400000	29.8000000

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by Other Geographic Region – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	76.6666667	19.4542198	82.7500000	51.0000000	98.5000000
PLACEBO	6	6	80.2500000	27.6636042	71.5000000	53.5000000	128.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	106.5000000	43.4315553	108.0000000	40.0000000	161.0000000
PLACEBO	6	6	67.5833333	20.9509347	60.5000000	49.5000000	107.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	29.8333333	33.8668963	31.5000000	-11.0000000	70.5000000
PLACEBO	6	6	-12.6666667	11.0075732	-7.7500000	-31.0000000	-4.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	6	6	37.8800000	46.5413128	43.4100000	-21.5700000	87.1600000
PLACEBO	6	6	-14.3433333	9.8727922	-11.3150000	-32.6300000	-7.1400000

## SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Intermediate CYP2D6 Metabolizer Status – ENGAGE

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	15.2500000	.	15.2500000	15.2500000	15.2500000
PLACEBO	2	2	13.6000000	1.6263456	13.6000000	12.4500000	14.7500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	14.2000000	.	14.2000000	14.2000000	14.2000000
PLACEBO	2	2	12.9500000	0.9899495	12.9500000	12.2500000	13.6500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	-1.0500000	.	-1.0500000	-1.0500000	-1.0500000
PLACEBO	2	2	-0.6500000	0.6363961	-0.6500000	-1.1000000	-0.2000000

## SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Extensive CYP2D6 Metabolizer Status – ENGAGE

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	11.8027778	1.7084110	11.8250000	8.1500000	14.3000000
PLACEBO	18	18	12.6555556	1.6482512	12.9000000	9.6500000	16.3000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	12.6000000	1.5418667	12.9000000	8.8500000	15.3000000
PLACEBO	18	18	12.0833333	2.0928450	12.2500000	7.8500000	15.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	0.7972222	1.0619727	0.7000000	-1.4500000	3.1500000
PLACEBO	18	18	-0.5722222	0.9280312	-0.6500000	-2.5000000	0.7000000

**SAS Output for Absolute Change from Baseline to Week 39 in Hemoglobin Level (g/dL) by Ultra-Rapid CYP2D6 Metabolizer Status – ENGAGE**

Order of output = Baseline, Week 39, and Absolute Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	13.3500000	.	13.3500000	13.3500000	13.3500000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	14.6000000	.	14.6000000	14.6000000	14.6000000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	1.2500000	.	1.2500000	1.2500000	1.2500000

**SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Intermediate CYP2D6 Metabolizer Status – ENGAGE**

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	0.9400000	.	0.9400000	0.9400000	0.9400000
PLACEBO	2	2	1.4500000	0.2121320	1.4500000	1.3000000	1.6000000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	1.0200000	.	1.0200000	1.0200000	1.0200000
PLACEBO	2	2	1.4850000	0.1909188	1.4850000	1.3500000	1.6200000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	0.0800000	.	0.0800000	0.0800000	0.0800000
PLACEBO	2	2	0.0350000	0.0212132	0.0350000	0.0200000	0.0500000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	8.5100000	.	8.5100000	8.5100000	8.5100000
PLACEBO	2	2	2.5500000	1.8384776	2.5500000	1.2500000	3.8500000

## SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Extensive CYP2D6 Metabolizer Status – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	1.4433333	0.3403804	1.3600000	0.9300000	2.1800000
PLACEBO	18	18	1.3511111	0.2900890	1.2700000	0.9300000	1.9800000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	1.3355556	0.2583482	1.2450000	0.9100000	1.9000000
PLACEBO	18	18	1.3750000	0.3215633	1.3050000	0.9000000	1.9800000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	-0.1077778	0.1088742	-0.0800000	-0.3600000	0.1000000
PLACEBO	18	18	0.0238889	0.1117844	0	-0.1500000	0.2800000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	-6.5322222	6.2085061	-5.8600000	-18.9500000	9.0900000
PLACEBO	18	18	1.6050000	8.4447709	0	-14.2900000	18.2500000

## SAS Output for Percentage Change from Baseline to Week 39 in Liver Volume (MN) by Ultra-Rapid CYP2D6 Metabolizer Status – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	1.8400000	.	1.8400000	1.8400000	1.8400000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	1.8400000	.	1.8400000	1.8400000	1.8400000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	0	.	0	0	0

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	0	.	0	0	0

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by Intermediate CYP2D6 Metabolizer Status – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	78.0000000		78.0000000	78.0000000	78.0000000
PLACEBO	2	2	81.0000000	21.2132034	81.0000000	66.0000000	96.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	86.0000000		86.0000000	86.0000000	86.0000000
PLACEBO	2	2	69.2500000	18.7383297	69.2500000	56.0000000	82.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	8.0000000		8.0000000	8.0000000	8.0000000
PLACEBO	2	2	-11.7500000	2.4748737	-11.7500000	-13.5000000	-10.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	10.2600000		10.2600000	10.2600000	10.2600000
PLACEBO	2	2	-14.6050000	0.7707464	-14.6050000	-15.1500000	-14.0600000

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by Extensive CYP2D6 Metabolizer Status – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	74.4722222	14.7623052	77.5000000	50.5000000	98.5000000
PLACEBO	18	18	78.1944444	23.3257866	76.2500000	50.5000000	128.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	100.7222222	29.4164931	104.2500000	40.0000000	161.0000000
PLACEBO	18	18	71.7500000	26.1923035	66.2500000	36.0000000	125.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	26.2500000	22.5579320	25.2500000	-11.0000000	70.5000000
PLACEBO	18	18	-6.4444444	16.1717700	-5.5000000	-44.5000000	22.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	18	18	34.8288889	31.9672211	33.5500000	-21.5700000	87.1600000
PLACEBO	18	18	-8.1166667	20.1734298	-7.4000000	-51.7400000	29.8000000

## SAS Output for Percentage Change from Baseline to Week 39 in Platelet Count (10<sup>9</sup>/L) by Ultra-Rapid CYP2D6 Metabolizer Status – ENGAGE

Order of output = Baseline, Week 39, Absolute Change from Baseline to Week 39, and Percentage Change from Baseline to Week 39

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	82.5000000	.	82.5000000	82.5000000	82.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	80.0000000	.	80.0000000	80.0000000	80.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	-2.5000000	.	-2.5000000	-2.5000000	-2.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
ELIGLUSTAT	1	1	-3.0300000	.	-3.0300000	-3.0300000	-3.0300000

In the order shown, the following pages present the gender, geographic region, and CYP2D6 metabolizer status subgroup analyses for the ENCORE study secondary endpoints:

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Female Gender

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Male Gender

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Female Gender

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Male Gender

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Female Gender

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Male Gender

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Female Gender

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Male Gender

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by North America Geographic Region

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Europe Geographic Region

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Other Geographic Region

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by North America Geographic Region

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Europe Geographic Region

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Other Geographic Region

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by North America Geographic Region

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Europe Geographic Region

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Other Geographic Region

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by North America Geographic Region

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Europe Geographic Region

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Other Geographic Region

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Poor CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Intermediate CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Extensive CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Ultra-Rapid CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Unknown CYP2D6 Metabolizer Status

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Poor CYP2D6 Metabolizer Status

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Intermediate CYP2D6 Metabolizer Status

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Extensive CYP2D6 Metabolizer Status

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Ultra-Rapid CYP2D6 Metabolizer Status

Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Unknown CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Poor CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Intermediate CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Extensive CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Ultra-Rapid CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Unknown CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Poor CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Intermediate CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Extensive CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Ultra-Rapid CYP2D6 Metabolizer Status

Percentage Change from Baseline to Week 52 in Platelet Count ( $10^9/L$ ) by Unknown CYP2D6 Metabolizer Status

## SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Female Gender – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	2.6570833	1.1523303	2.2300000	1.1400000	5.3400000
ELIGLUSTAT	41	41	2.8712195	1.0803152	2.5600000	1.0600000	5.6600000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	2.6316667	1.0799987	2.3550000	1.1300000	4.8800000
ELIGLUSTAT	41	41	2.7424390	1.1602969	2.4700000	0.8500000	6.0600000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	-0.0254167	0.3077404	0.0200000	-0.6500000	0.6900000
ELIGLUSTAT	41	41	-0.1287805	0.3768899	-0.2000000	-1.0600000	0.8300000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	0.3820833	10.8696286	0.8950000	-15.4600000	22.2700000
ELIGLUSTAT	41	41	-5.4434146	12.7341365	-7.1700000	-38.5500000	25.9300000

## SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Male Gender – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	21	21	2.8342857	1.1725637	2.8800000	1.4200000	5.7700000
ELIGLUSTAT	36	36	3.5047222	1.5418995	3.1900000	1.4400000	7.4300000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	21	21	2.6519048	1.0603189	2.7300000	1.2000000	5.1600000
ELIGLUSTAT	36	36	3.3744444	1.5095060	3.1450000	1.2400000	7.5900000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	21	21	-0.1823810	0.2716782	-0.1300000	-0.7600000	0.2700000
ELIGLUSTAT	36	36	-0.1302778	0.5626137	-0.0800000	-1.6800000	1.2500000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	21	21	-5.7576190	8.7169295	-5.4300000	-19.7900000	10.7400000
ELIGLUSTAT	36	36	-2.3352778	15.5224441	-2.0400000	-31.1100000	37.5500000

**SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Female Gender – ENCORE**

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	13.0303571	1.0525401	13.1000000	11.2000000	16.0000000
ELIGLUSTAT	59	59	12.9720339	0.9943058	13.0500000	10.7000000	14.9000000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	13.0660714	1.0670185	13.0000000	11.0500000	16.8500000
ELIGLUSTAT	59	59	12.7661017	1.0367157	12.7500000	10.0500000	15.3500000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	0.0357143	0.8328729	0.1750000	-1.4500000	1.9500000
ELIGLUSTAT	59	59	-0.2059322	0.7990881	-0.2500000	-1.9500000	1.9000000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Male Gender – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	14.8200000	0.8250000	14.8000000	13.1000000	16.5500000
ELIGLUSTAT	47	47	14.4170213	1.1239622	14.5000000	12.3000000	17.2500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	14.9480000	1.0669739	14.9000000	13.0000000	18.8000000
ELIGLUSTAT	47	47	14.2138298	1.0605424	14.4500000	11.9000000	16.3500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	0.1280000	1.0186879	0.1500000	-3.4500000	2.2500000
ELIGLUSTAT	47	47	-0.2031915	0.6307694	-0.3000000	-1.4000000	1.3500000

## SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Female Gender – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	0.9200000	0.1583713	0.9200000	0.5600000	1.1800000
ELIGLUSTAT	59	59	0.9332203	0.1954344	0.9100000	0.5600000	1.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	0.9732143	0.1618196	0.9600000	0.6700000	1.3100000
ELIGLUSTAT	59	59	0.9525424	0.1852360	0.9500000	0.5700000	1.6600000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	0.0532143	0.0977167	0.0600000	-0.2400000	0.2000000
ELIGLUSTAT	59	59	0.0193220	0.0990448	0.0300000	-0.2300000	0.1800000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	6.5292857	10.6176645	6.7250000	-23.5300000	28.1700000
ELIGLUSTAT	59	59	2.8318644	10.1135552	3.4100000	-19.3300000	25.4000000

## SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Male Gender – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	0.9252000	0.1581697	0.9600000	0.6500000	1.2500000
ELIGLUSTAT	47	47	0.9455319	0.1804801	0.8900000	0.5300000	1.3800000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	0.9196000	0.1566706	0.9300000	0.6200000	1.2500000
ELIGLUSTAT	47	47	0.9638298	0.1782469	0.9200000	0.6400000	1.4400000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	-0.0056000	0.0848076	-0.0200000	-0.1600000	0.2600000
ELIGLUSTAT	47	47	0.0182979	0.0820212	0.0200000	-0.1300000	0.2700000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	-0.1844000	9.0474025	-2.0000000	-16.1600000	28.8900000
ELIGLUSTAT	47	47	2.5370213	9.5608149	2.4400000	-12.3600000	35.0600000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Female Gender – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	194.3214286	57.3101074	181.7500000	111.5000000	316.5000000
ELIGLUSTAT	59	59	212.8474576	80.9793106	190.0000000	104.5000000	511.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	200.7142857	63.2836689	185.7500000	81.0000000	367.5000000
ELIGLUSTAT	59	59	228.0847458	83.8333812	219.0000000	95.0000000	522.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	6.3928571	29.0017104	1.5000000	-37.5000000	94.5000000
ELIGLUSTAT	59	59	15.2372881	42.6090240	12.5000000	-98.5000000	166.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	28	28	3.8260714	15.8090697	1.1900000	-28.0000000	41.6300000
ELIGLUSTAT	59	59	8.7828814	22.3116228	8.3600000	-34.3200000	107.7900000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Male Gender – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	179.8800000	56.3595748	167.0000000	102.0000000	339.5000000
ELIGLUSTAT	47	47	191.3085106	76.3647250	178.5000000	100.5000000	401.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	182.1400000	60.0592624	167.0000000	103.5000000	337.5000000
ELIGLUSTAT	47	47	195.3404255	80.1292506	176.0000000	69.5000000	373.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	2.2600000	17.4171372	7.5000000	-35.0000000	35.5000000
ELIGLUSTAT	47	47	4.0319149	36.7284992	6.5000000	-149.0000000	111.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	25	25	1.4404000	11.9392146	3.9200000	-24.3100000	30.6200000
ELIGLUSTAT	47	47	2.6108511	17.2729498	2.6100000	-42.6900000	49.8900000

## SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by North America Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	18	18	2.2933333	0.9371044	1.9650000	1.1400000	4.1100000
ELIGLUSTAT	36	36	2.8372222	1.0404384	2.6000000	1.0600000	4.8800000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	18	18	2.1955556	0.7979328	1.9800000	1.2000000	3.6600000
ELIGLUSTAT	36	36	2.6705556	0.8911339	2.5900000	0.8500000	4.4300000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	18	18	-0.0977778	0.2633842	-0.1200000	-0.4500000	0.4700000
ELIGLUSTAT	36	36	-0.1666667	0.4590300	-0.1800000	-1.3000000	1.0100000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	18	18	-2.3616667	11.6290631	-5.6500000	-18.5200000	22.2700000
ELIGLUSTAT	36	36	-4.1747222	14.8951819	-6.6800000	-26.6400000	37.5500000

## SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Europe Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	8	8	2.4300000	0.8697619	2.1900000	1.5700000	4.2300000
ELIGLUSTAT	12	12	3.5558333	1.6861115	3.0200000	1.8600000	7.2900000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	8	8	2.3950000	0.7185501	2.2100000	1.5600000	3.4700000
ELIGLUSTAT	12	12	3.3833333	1.6828889	3.0000000	1.6700000	7.4100000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	8	8	-0.0350000	0.3498163	0.0450000	-0.7600000	0.2700000
ELIGLUSTAT	12	12	-0.1725000	0.4944809	-0.0700000	-1.6800000	0.1700000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	8	8	0.1825000	11.3454960	2.6550000	-17.9700000	11.8800000
ELIGLUSTAT	12	12	-4.8266667	9.7854041	-2.0400000	-31.1100000	5.5000000

## SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Other Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	19	19	3.2931579	1.2470590	3.1700000	1.2800000	5.7700000
ELIGLUSTAT	29	29	3.4165517	1.4746798	3.0000000	1.4400000	7.4300000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	19	19	3.1668421	1.1918662	2.9600000	1.1300000	5.1600000
ELIGLUSTAT	29	29	3.3510345	1.6166397	3.3100000	1.1500000	7.5900000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	19	19	-0.1263158	0.3203680	-0.1300000	-0.6500000	0.6900000
ELIGLUSTAT	29	29	-0.0655172	0.4820165	-0.1600000	-1.0600000	1.2500000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	19	19	-3.7205263	8.7339500	-5.1000000	-19.7900000	16.9100000
ELIGLUSTAT	29	29	-3.4151724	14.9604213	-6.2800000	-38.5500000	31.0200000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by North America Geographic Region – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	14.0062500	1.2355524	14.0000000	11.2500000	16.5500000
ELIGLUSTAT	48	48	13.7302083	1.2851749	13.6750000	10.7000000	17.2500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	14.1062500	1.6055144	14.2500000	11.6000000	18.8000000
ELIGLUSTAT	48	48	13.5135417	1.1963037	13.5250000	10.0500000	16.3500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	0.1000000	0.8118685	-0.0250000	-1.2500000	2.2500000
ELIGLUSTAT	48	48	-0.2166667	0.7514053	-0.2750000	-1.8000000	1.9000000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Europe Geographic Region – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	13.5611111	1.5824778	13.8000000	11.2000000	15.8000000
ELIGLUSTAT	17	17	13.8588235	1.2946084	14.0500000	11.6500000	16.6500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	13.8388889	1.5878007	13.9000000	11.0500000	16.3000000
ELIGLUSTAT	17	17	13.5823529	1.4188399	13.7000000	10.9500000	16.3500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	0.2777778	0.9273993	0.3500000	-1.1500000	1.9500000
ELIGLUSTAT	17	17	-0.2764706	0.4657379	-0.3000000	-0.9000000	0.7000000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Other Geographic Region – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	13.8575000	1.2997242	13.8500000	11.2000000	16.4500000
ELIGLUSTAT	41	41	13.3731707	1.2408212	13.3000000	11.5000000	17.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	13.8225000	1.1323561	13.5250000	12.0500000	15.6000000
ELIGLUSTAT	41	41	13.2121951	1.2923709	13.0000000	10.3000000	16.1500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	-0.0350000	1.0533281	0.2500000	-3.4500000	1.6500000
ELIGLUSTAT	41	41	-0.1609756	0.7930568	-0.2500000	-1.9500000	1.3000000

## SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by North America Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	0.8633333	0.1736730	0.8650000	0.5600000	1.1800000
ELIGLUSTAT	48	48	0.8945833	0.1717365	0.8800000	0.5300000	1.4900000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	0.8925000	0.1665050	0.9000000	0.6200000	1.2500000
ELIGLUSTAT	48	48	0.9083333	0.1520825	0.9100000	0.6000000	1.3200000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	0.0291667	0.0971738	0.0500000	-0.2400000	0.2000000
ELIGLUSTAT	48	48	0.0137500	0.0945679	0.0100000	-0.1900000	0.2700000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	4.3104167	11.1490294	6.2800000	-23.5300000	28.1700000
ELIGLUSTAT	48	48	2.4160417	10.8911281	1.1050000	-15.4500000	35.0600000

## SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Europe Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	0.9566667	0.1489966	0.9900000	0.7300000	1.2500000
ELIGLUSTAT	17	17	1.0223529	0.2038544	0.9900000	0.7600000	1.4000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	0.9888889	0.1287871	0.9800000	0.7700000	1.1300000
ELIGLUSTAT	17	17	1.0541176	0.1871516	1.0000000	0.8200000	1.4300000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	0.0322222	0.0954958	0.0200000	-0.1300000	0.1900000
ELIGLUSTAT	17	17	0.0317647	0.0683040	0.0500000	-0.1000000	0.1500000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	4.0411111	9.6762395	2.5000000	-10.4000000	21.8400000
ELIGLUSTAT	17	17	3.7200000	7.0211413	3.8500000	-10.0000000	15.3100000

## SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Other Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	0.9780000	0.1148271	0.9600000	0.7000000	1.1900000
ELIGLUSTAT	41	41	0.9556098	0.1898953	0.9700000	0.5600000	1.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	0.9960000	0.1502069	0.9500000	0.7200000	1.3100000
ELIGLUSTAT	41	41	0.9751220	0.1949375	0.9400000	0.5700000	1.6600000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	0.0180000	0.0984405	0.0100000	-0.1600000	0.2600000
ELIGLUSTAT	41	41	0.0195122	0.0973897	0.0300000	-0.2300000	0.1600000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	1.9195000	10.0743852	1.0150000	-16.1600000	28.8900000
ELIGLUSTAT	41	41	2.6124390	9.6875832	3.0900000	-19.3300000	19.4800000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by North America Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	206.5625000	57.4818142	197.2500000	110.5000000	316.5000000
ELIGLUSTAT	48	48	206.1875000	89.2656581	188.2500000	101.5000000	511.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	212.7083333	66.9366860	202.5000000	103.5000000	367.5000000
ELIGLUSTAT	48	48	219.0000000	94.2851605	214.2500000	92.0000000	522.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	6.1458333	30.3853795	-1.5000000	-37.5000000	94.5000000
ELIGLUSTAT	48	48	12.8125000	32.5433631	11.2500000	-91.5000000	72.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	24	24	3.1087500	15.8811672	-0.4950000	-24.3100000	41.6300000
ELIGLUSTAT	48	48	6.6000000	17.1643708	3.6450000	-22.6500000	52.9900000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Europe Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	182.3888889	66.3017617	165.5000000	102.0000000	339.5000000
ELIGLUSTAT	17	17	198.9117647	73.6608010	186.0000000	100.5000000	349.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	179.6111111	68.3478135	170.0000000	117.0000000	337.5000000
ELIGLUSTAT	17	17	205.1176471	74.6229123	188.5000000	69.5000000	359.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	-2.7777778	17.1557409	-7.0000000	-30.0000000	22.5000000
ELIGLUSTAT	17	17	6.2058824	59.0198745	4.0000000	-149.0000000	166.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	-1.3088889	11.2422812	-3.9500000	-18.8100000	14.7100000
ELIGLUSTAT	17	17	6.2488235	30.9564967	2.6100000	-42.6900000	107.7900000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Other Geographic Region – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	166.9500000	45.3657360	161.2500000	104.5000000	258.5000000
ELIGLUSTAT	41	41	201.7317073	70.4585958	190.0000000	106.0000000	401.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	172.6000000	45.6726338	169.5000000	81.0000000	265.5000000
ELIGLUSTAT	41	41	210.7073171	74.3553105	187.0000000	90.0000000	396.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	5.6500000	17.8562240	7.7500000	-31.5000000	35.5000000
ELIGLUSTAT	41	41	8.9756098	40.1462874	8.0000000	-98.5000000	111.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	20	20	4.0155000	13.0767578	4.6950000	-28.0000000	30.6200000
ELIGLUSTAT	41	41	5.3139024	18.9582115	5.0000000	-34.3200000	49.8900000

**SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Poor CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	2.8800000	1.9091883	2.8800000	1.5300000	4.2300000
ELIGLUSTAT	3	3	3.4000000	1.1220963	3.9400000	2.1100000	4.1500000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	2.5950000	1.2374369	2.5950000	1.7200000	3.4700000
ELIGLUSTAT	3	3	2.9133333	1.1132984	3.0700000	1.7300000	3.9400000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	-0.2850000	0.6717514	-0.2850000	-0.7600000	0.1900000
ELIGLUSTAT	3	3	-0.4866667	0.3426855	-0.3800000	-0.8700000	-0.2100000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	-2.7750000	21.4889751	-2.7750000	-17.9700000	12.4200000
ELIGLUSTAT	3	3	-15.0500000	8.8877050	-18.0100000	-22.0800000	-5.0600000

**SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Intermediate CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	6	6	3.2183333	1.4901331	2.6800000	1.9600000	5.7700000
ELIGLUSTAT	10	10	2.3370000	0.7115406	2.1900000	1.4700000	4.0000000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	6	6	3.0783333	1.1874749	2.7700000	1.9500000	5.1600000
ELIGLUSTAT	10	10	2.2480000	0.5044645	2.1550000	1.6500000	3.1100000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	6	6	-0.1400000	0.4062512	-0.2250000	-0.6100000	0.4700000
ELIGLUSTAT	10	10	-0.0890000	0.3554793	-0.1150000	-0.8900000	0.4500000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	6	6	-1.1733333	14.2168810	-8.0000000	-12.5600000	22.2700000
ELIGLUSTAT	10	10	-1.4610000	14.6019789	-5.5800000	-22.2500000	30.6100000

**SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Extensive CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	33	33	2.5496970	1.0421597	2.2200000	1.1400000	5.3400000
ELIGLUSTAT	59	59	3.3054237	1.3924653	2.9900000	1.0600000	7.4300000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	33	33	2.4781818	1.0198022	2.2700000	1.1300000	4.7700000
ELIGLUSTAT	59	59	3.1677966	1.4274937	3.1400000	0.8500000	7.5900000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	33	33	-0.0715152	0.2668113	-0.0700000	-0.6500000	0.6900000
ELIGLUSTAT	59	59	-0.1376271	0.5020556	-0.1600000	-1.6800000	1.2500000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	33	33	-2.4627273	9.5584312	-3.6600000	-19.7900000	16.9100000
ELIGLUSTAT	59	59	-4.3884746	14.5275505	-6.4900000	-38.5500000	37.5500000

**SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Ultra-Rapid CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	2.6800000	.	2.6800000	2.6800000	2.6800000
ELIGLUSTAT	3	3	3.3533333	2.1069963	2.8700000	1.5300000	5.6600000

---

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	2.5300000	.	2.5300000	2.5300000	2.5300000
ELIGLUSTAT	3	3	3.4100000	2.2229035	2.9700000	1.4400000	5.8200000

---

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	-0.1500000	.	-0.1500000	-0.1500000	-0.1500000
ELIGLUSTAT	3	3	0.0566667	0.1305118	0.1000000	-0.0900000	0.1600000

---

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	-5.6000000	.	-5.6000000	-5.6000000	-5.6000000
ELIGLUSTAT	3	3	0.1433333	5.2264743	2.8300000	-5.8800000	3.4800000

**SAS Output for Percentage Change from Baseline to Week 52 in Spleen Volume (MN) by Unknown CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	3.8000000	1.2055289	3.1700000	3.0400000	5.1900000
ELIGLUSTAT	2	2	2.6200000	0.5374012	2.6200000	2.2400000	3.0000000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	3.6266667	1.1184960	3.2700000	2.7300000	4.8800000
ELIGLUSTAT	2	2	2.7850000	0.7707464	2.7850000	2.2400000	3.3300000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	-0.1733333	0.3552933	-0.3100000	-0.4400000	0.2300000
ELIGLUSTAT	2	2	0.1650000	0.2333452	0.1650000	0	0.3300000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	-4.0933333	10.8474436	-5.9700000	-13.8800000	7.5700000
ELIGLUSTAT	2	2	5.5000000	7.7781746	5.5000000	0	11.0000000

**SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Poor CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	14.6000000	1.6970563	14.6000000	13.4000000	15.8000000
ELIGLUSTAT	4	4	13.4000000	0.7527727	13.4000000	12.7000000	14.1000000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	14.2250000	2.9344931	14.2250000	12.1500000	16.3000000
ELIGLUSTAT	4	4	13.1625000	0.3772157	13.3250000	12.6000000	13.4000000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	-0.3750000	1.2374369	-0.3750000	-1.2500000	0.5000000
ELIGLUSTAT	4	4	-0.2375000	0.6725263	-0.4500000	-0.7500000	0.7000000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Intermediate CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	13.6166667	1.0831090	13.7500000	11.2500000	15.1000000
ELIGLUSTAT	12	12	13.5916667	1.4784564	13.7500000	11.0500000	16.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	13.8777778	1.3451559	13.8500000	11.6000000	15.4000000
ELIGLUSTAT	12	12	13.0916667	1.9460722	13.7000000	10.0500000	15.5500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	0.2611111	0.8188322	0.2000000	-1.1500000	1.6500000
ELIGLUSTAT	12	12	-0.5000000	0.8455767	-0.4250000	-1.9500000	1.0500000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Extensive CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	13.9842105	1.3248715	14.0250000	11.2000000	16.5500000
ELIGLUSTAT	84	84	13.6595238	1.2843937	13.5750000	10.7000000	17.2500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	14.0328947	1.4238450	13.9250000	11.0500000	18.8000000
ELIGLUSTAT	84	84	13.5089286	1.1770179	13.3500000	11.1000000	16.3500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	0.0486842	0.9583549	0.1500000	-3.4500000	2.2500000
ELIGLUSTAT	84	84	-0.1505952	0.7115863	-0.2500000	-1.8000000	1.9000000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Ultra-Rapid CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	13.2000000	.	13.2000000	13.2000000	13.2000000
ELIGLUSTAT	4	4	12.6875000	0.7717675	12.8500000	11.7000000	13.3500000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	14.2500000	.	14.2500000	14.2500000	14.2500000
ELIGLUSTAT	4	4	12.4000000	1.0824355	12.5500000	10.9500000	13.5500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	1.0500000	.	1.0500000	1.0500000	1.0500000
ELIGLUSTAT	4	4	-0.2875000	0.9285966	-0.7000000	-0.8500000	1.1000000

## SAS Output for Absolute Change from Baseline to Week 52 in Hemoglobin Level (g/dL) by Unknown CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, and Absolute Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	13.0000000	1.8000000	13.0000000	11.2000000	14.8000000
ELIGLUSTAT	2	2	14.0500000	1.2020815	14.0500000	13.2000000	14.9000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	12.9000000	1.2010412	12.5000000	11.9500000	14.2500000
ELIGLUSTAT	2	2	13.5750000	1.3788582	13.5750000	12.6000000	14.5500000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	-0.1000000	0.7365460	-0.5000000	-0.5500000	0.7500000
ELIGLUSTAT	2	2	-0.4750000	0.1767767	-0.4750000	-0.6000000	-0.3500000

**SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Poor CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	1.0350000	0.1060660	1.0350000	0.9600000	1.1100000
ELIGLUSTAT	4	4	0.9800000	0.1685230	0.9100000	0.8700000	1.2300000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	1.0700000	0.1555635	1.0700000	0.9600000	1.1800000
ELIGLUSTAT	4	4	0.9475000	0.1123610	0.9750000	0.8000000	1.0400000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	0.0350000	0.0494975	0.0350000	0	0.0700000
ELIGLUSTAT	4	4	-0.0325000	0.1322561	-0.0200000	-0.1900000	0.1000000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	3.1550000	4.4618438	3.1550000	0	6.3100000
ELIGLUSTAT	4	4	-2.2650000	12.5035822	-2.1800000	-15.4500000	10.7500000

**SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Intermediate CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	0.9122222	0.1738374	0.9100000	0.7000000	1.2500000
ELIGLUSTAT	12	12	0.8625000	0.1059266	0.8750000	0.7000000	1.0400000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	0.8922222	0.1190355	0.9200000	0.7200000	1.1200000
ELIGLUSTAT	12	12	0.8800000	0.1165411	0.9000000	0.7100000	1.0900000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	-0.0200000	0.1219631	0.0200000	-0.2400000	0.1500000
ELIGLUSTAT	12	12	0.0175000	0.0708552	0.0250000	-0.0900000	0.1800000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	-0.6688889	12.8472706	2.8600000	-23.5300000	19.2300000
ELIGLUSTAT	12	12	2.1941667	7.8540394	2.7600000	-8.6500000	19.7800000

## SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Extensive CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	0.9165789	0.1621357	0.9550000	0.5600000	1.1900000
ELIGLUSTAT	84	84	0.9509524	0.2011390	0.9100000	0.5300000	1.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	0.9515789	0.1730103	0.9350000	0.6200000	1.3100000
ELIGLUSTAT	84	84	0.9709524	0.1923577	0.9350000	0.5700000	1.6600000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	0.0350000	0.0886155	0.0400000	-0.1600000	0.2600000
ELIGLUSTAT	84	84	0.0200000	0.0942568	0.0300000	-0.2300000	0.2700000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	4.2623947	9.8078454	4.6500000	-16.1600000	28.8900000
ELIGLUSTAT	84	84	2.9095238	10.1795156	2.9100000	-19.3300000	35.0600000

**SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Ultra-Rapid CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	0.9100000	.	0.9100000	0.9100000	0.9100000
ELIGLUSTAT	4	4	0.8675000	0.0763217	0.8850000	0.7600000	0.9400000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	0.9600000	.	0.9600000	0.9600000	0.9600000
ELIGLUSTAT	4	4	0.9125000	0.1490805	0.9600000	0.7000000	1.0300000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	0.0500000	.	0.0500000	0.0500000	0.0500000
ELIGLUSTAT	4	4	0.0450000	0.0793725	0.0600000	-0.0600000	0.1200000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	5.4900000	.	5.4900000	5.4900000	5.4900000
ELIGLUSTAT	4	4	4.6725000	9.3793119	6.4700000	-7.8900000	13.6400000

**SAS Output for Percentage Change from Baseline to Week 52 in Liver Volume (MN) by Unknown CYP2D6 Metabolizer Status – ENCORE**

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	0.9566667	0.1026320	0.9300000	0.8700000	1.0700000
ELIGLUSTAT	2	2	0.9400000	0.1555635	0.9400000	0.8300000	1.0500000

**The SAS System**

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	0.9833333	0.1159023	1.0400000	0.8500000	1.0600000
ELIGLUSTAT	2	2	0.9700000	0.1838478	0.9700000	0.8400000	1.1000000

**The SAS System**

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	0.0266667	0.1436431	-0.0300000	-0.0800000	0.1900000
ELIGLUSTAT	2	2	0.0300000	0.0282843	0.0300000	0.0100000	0.0500000

**The SAS System**

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	3.4800000	16.1625246	-2.8000000	-8.6000000	21.8400000
ELIGLUSTAT	2	2	2.9800000	2.5173001	2.9800000	1.2000000	4.7600000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Poor CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	164.5000000	88.3883476	164.5000000	102.0000000	227.0000000
ELIGLUSTAT	4	4	189.8750000	110.8176994	153.0000000	104.5000000	349.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	219.2500000	144.6033368	219.2500000	117.0000000	321.5000000
ELIGLUSTAT	4	4	185.0000000	65.8229950	196.0000000	95.0000000	253.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	54.7500000	56.2149891	54.7500000	15.0000000	94.5000000
ELIGLUSTAT	4	4	-4.8750000	103.0771354	28.5000000	-149.0000000	72.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	2	2	28.1700000	19.0353145	28.1700000	14.7100000	41.6300000
ELIGLUSTAT	4	4	10.3450000	44.3416926	15.5400000	-42.6900000	52.9900000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Intermediate CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	197.5555556	80.6064686	191.0000000	104.5000000	339.5000000
ELIGLUSTAT	12	12	202.7083333	55.3719111	191.0000000	117.0000000	322.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	196.5000000	77.0032467	183.5000000	103.5000000	337.5000000
ELIGLUSTAT	12	12	231.8333333	55.7675098	212.7500000	132.0000000	320.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	-1.0555556	23.3270825	-2.0000000	-37.5000000	32.0000000
ELIGLUSTAT	12	12	29.1250000	51.6721582	13.2500000	29.0000000	166.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	9	9	1.3000000	14.1800573	-0.5900000	-13.7100000	30.6200000
ELIGLUSTAT	12	12	17.7991667	31.6067207	7.2250000	-8.9900000	107.7900000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Extensive CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	190.2763158	51.8009049	175.7500000	110.0000000	316.5000000
ELIGLUSTAT	84	84	204.5416667	82.9290308	185.7500000	100.5000000	511.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	192.6578947	57.2738921	183.5000000	81.0000000	367.5000000
ELIGLUSTAT	84	84	214.0297619	87.9116942	187.7500000	69.5000000	522.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	2.3815789	19.9144909	3.0000000	-35.0000000	51.0000000
ELIGLUSTAT	84	84	9.4880952	34.2185548	8.5000000	-98.5000000	111.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	38	38	1.2410526	12.5951479	1.8000000	-28.0000000	36.7700000
ELIGLUSTAT	84	84	4.9188095	16.5643572	4.2100000	-34.3200000	49.8900000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Ultra-Rapid CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	164.0000000		164.0000000	164.0000000	164.0000000
ELIGLUSTAT	4	4	189.5000000	76.7409061	158.7500000	137.5000000	303.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	212.5000000		212.5000000	212.5000000	212.5000000
ELIGLUSTAT	4	4	192.3750000	99.4395755	157.0000000	117.0000000	338.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	48.5000000		48.5000000	48.5000000	48.5000000
ELIGLUSTAT	4	4	2.8750000	28.2588482	4.0000000	-32.0000000	35.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	1	1	29.5700000		29.5700000	29.5700000	29.5700000
ELIGLUSTAT	4	4	-0.8700000	14.9436408	3.1400000	-21.4800000	11.7200000

## SAS Output for Percentage Change from Baseline to Week 52 in Platelet Count (10<sup>9</sup>/L) by Unknown CYP2D6 Metabolizer Status – ENCORE

Order of output = Baseline, Week 52, Absolute Change from Baseline to Week 52, and Percentage Change from Baseline to Week 52

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	145.5000000	15.6204994	137.5000000	135.5000000	163.5000000
ELIGLUSTAT	2	2	209.0000000	1.4142136	209.0000000	208.0000000	210.0000000

### The SAS System

The MEANS Procedure

Analysis Variable : AVAL Analysis Value							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	144.3333333	17.6091832	154.5000000	124.0000000	154.5000000
ELIGLUSTAT	2	2	184.0000000	43.1335137	184.0000000	153.5000000	214.5000000

### The SAS System

The MEANS Procedure

Analysis Variable : CHG Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	-1.1666667	15.7823741	-9.0000000	-11.5000000	17.0000000
ELIGLUSTAT	2	2	-25.0000000	44.5477272	-25.0000000	-56.5000000	6.5000000

### The SAS System

The MEANS Procedure

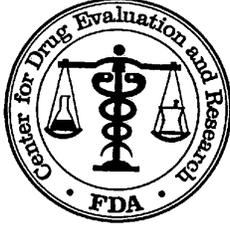
Analysis Variable : PCHG Percent Change from Baseline							
Planned Treatment Group, Period 1	N Obs	N	Mean	Std Dev	Median	Minimum	Maximum
CEREZYME	3	3	-0.5433333	11.2741755	-5.5000000	-8.4900000	12.3600000
ELIGLUSTAT	2	2	-11.8850000	21.2344166	-11.8850000	-26.9000000	3.1300000

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

/s/  
-----

BEHRANG VALI  
07/22/2014

FREDA COONER  
07/22/2014



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

### Statistical Review and Evaluation

#### CARCINOGENICITY STUDIES

**IND/NDA Number:** NDA 205-494

**Drug Name:** Genz-112638

**Applicant:** Sponsor: Genzyme Corporation  
153 Second Avenue Waltham, MA 02451 USA  
Test Facility: (b) (4)  
(b) (4)

**Documents Reviewed:** Electronic data submitted on November, 2013, Also include the sponsor's reports submitted.

**Review Priority:** Standard

**Biometrics Division:** Division of Biometrics -6

**Statistical Reviewer:** Min Min, Ph.D.

**Concurring Reviewer:** Karl Lin, Ph.D.

**Medical Division:** Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Reviewing Pharmacologist:** Sruthi King Ph.D.

**Project Manager:** Jessica Benjamin

**Keywords:** Carcinogenicity, Dose response

**Table of Contents**

1 ..... Background 3

2 ..... Rat Study 3

    2.1. Sponsor's analyses..... 3

        2.1.1. Survival analysis..... 3

        2.1.2. Tumor data analysis..... 5

    2.2. Reviewer's analyses ..... 6

        2.2.1. Survival analysis..... 7

        2.2.2. Tumor data analysis..... 7

3 ..... Mouse Study 9

    3.1. Sponsor's analyses..... 9

        3.1.1. Survival analysis..... 9

        3.1.2. Tumor data analysis..... 10

    3.2. Reviewer's analyses ..... 11

        3.2.1. Survival analysis..... 11

        3.2.2. Tumor data analysis..... 11

4 ..... Evaluation of validity of the designs of rat and mouse studies 12

    4.1. Rat Study..... 13

    4.2. Mouse Study ..... 15

5 ..... Summary 16

6 ..... Appendix 18

7 ..... References: 41

## 1. Background

In this submission, the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to further assess the carcinogenic potential of Genz-112638 in rats and mice, when administered daily oral administration (gavage) to rats for at least 103 weeks and by dietary admixture to mice for up to 105/106 weeks. The test item is indicated for the treatment of lysosomal storage diseases.

Three groups of 50 male and 50 female Sprague-Dawley rats received the test item, Genz-112638 (batch No. T1136) and two control groups of 50 males and 50 females received the vehicle (drinking water). Three groups of 60 male and 60 female CD1 mice received the test item, Genz-112638 (batch No. T1136) and two control groups of 60 males and 60 females received untreated diet.

Results of this review have been discussed with the reviewing pharmacologist Dr. King who suggested doing analysis for rat and mouse studies.

## 2. Rat Study

Three groups of 50 male and 50 female Sprague-Dawley rats received the test item, Genz-112638 (batch No. T1136) at the dose-levels of 10, 25 or 75 mg/kg/day in males for 105 weeks, or 5, 15 or 50 mg/kg/day in females for 103 weeks, by gavage, under a dosage-volume of 5 ml/kg. In addition, two control groups of 50 males and 50 females received the vehicle (drinking water) only under the same experimental conditions.

Mortality and clinical signs were checked daily and any animal showing signs of poor clinical condition, especially when death appeared imminent, was humanely sacrificed after a blood smear was prepared (whenever possible). In addition, detailed clinical observations were made once a week until the end of the study. After 6 months of treatment, all animals were palpated every 2 weeks in order to record the time of onset, location, size, appearance and progression of palpable masses. On completion of the treatment period all surviving animals were euthanized and submitted to a full macroscopic *post-mortem* examination. Designated tissues were preserved in an appropriate fixative and processed for microscopic examination. A peer review was performed on at least 10% of the histological slides from each group and on all slides from identified target organs and tumors.

### 2.1. Sponsor's analyses

Mortality data and tumor rates were compared between control group 1 and control group 2 using Chi Square test or Fisher's Exact test (if the conditions for the validity of Chi Square test are not satisfied).

- if comparisons of the dual controls show no major differences in mortality and tumor rate, then the data of the two controls were combined to form a single control group in subsequent analysis of survival data and tumor incidences,
- if the data show evidences of major differences in mortality or tumor incidence between the identical controls, then two tests for survival data and for each tumor/organ combination were carried out: control 1 *vs.* treated groups and control 2 *vs.* treated groups.

#### 2.1.1. Survival analysis

Analysis of survival data was performed separately for each sex. Survival probability functions were estimated by the Kaplan-Meier technique. Survival curves were compared by the log-rank procedure, according to Peto's method (Peto *et al.*, 1980).

**Sponsor's findings:** The Kaplan-Meier product-limit survival curves from the sponsor's report are presented in Figure 1 and Figure 2 for males and females, respectively. Sponsor's analysis showed that there were no difference between the two control groups by using Chi-Square test, *i.e.* no association between controls and the number of unscheduled deaths in both sexes (p-value=0.5465 in females and p-value=0.2241 in males). Two controls were combined to form a single control group in subsequent analysis of survival data. There were no statistically significant differences between survival curves of treatment groups in both males and females when compared to the combined data from the two control groups (p-value=0.1644 in females and p-value=0.7851 in males).

In conclusion, the test item, Genz-112638, was administered orally (gavage) for 103/105 weeks to rats, at 10, 25 or 75 mg/kg/day for males and 5, 15, 50 mg/kg/day for females had no effect on the overall survival. The survival rates to scheduled sacrifice (Week 105 for males and Week 103 for females) were 36, 48, 44, 40, and 48% in males and 48, 42, 30, 30, and 50% in females given 0 (two control groups separately), 10, 25, or 75 mg/kg/day for males and 5, 15, or 50 mg/kg/day, respectively.

Figure 1: Kaplan-Meier plot of Survival in Male Rats

Figure 1. Survival rate in males - principal animals

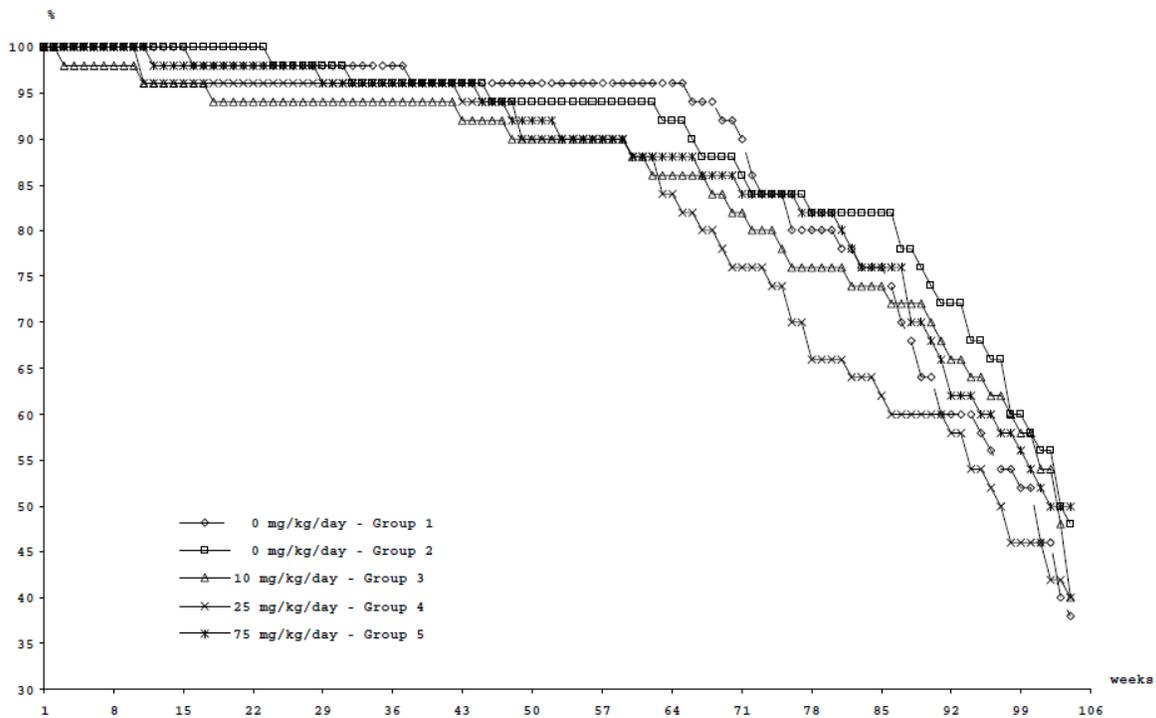
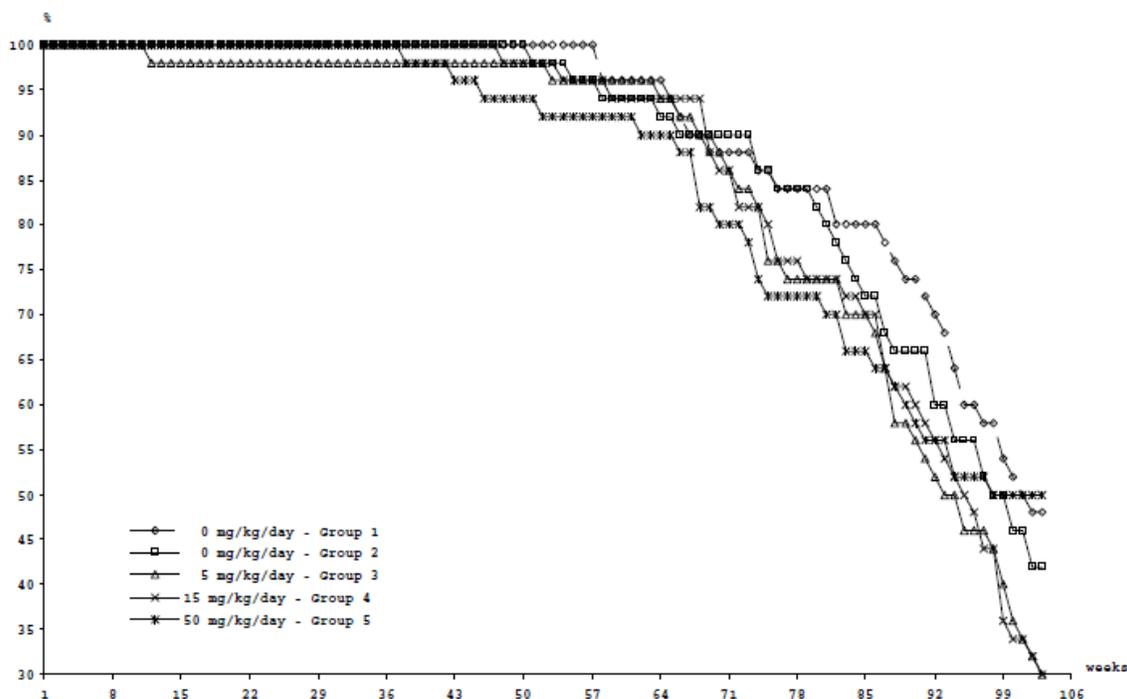


Figure 2: Kaplan-Meier plot of Survival in Female Rats

Figure 2. Survival rate in females - principal animals



### 2.1.2. Tumor data analysis

As the comparison of dual controls showed no major differences in mortality or tumor rate, the data of the two controls were combined to form a single control group in subsequent analysis of tumor incidences.

Statistical analysis of tumor incidences was performed using both Peto's Test and the Poly-3 Test. In both cases, for common tumors, a result was considered significant if  $p < 0.005$ , and for rare tumors if  $p < 0.025$ . Statistical analysis of tumor incidences was based on the principles outlined by Peto *et al.* (1980). Peto's method corrects for longevity (and hence for the period of time at risk) and applies statistical approaches appropriate to the cause of death ("context of observation"). The results are split into time-intervals based on time-of-death or time-to-tumor-detection. The expected frequencies of tumors are calculated using death rate calculations (for fatal tumors) and prevalence calculations (for non-fatal "incidental" tumors). The final test statistic for each type of tumor combines trend scores across the fatal and non-fatal categories.

The Poly-3 test (modified method by Bieler and Williams) was used to evaluate the overall dose-related trends in tumor incidence. This test is a method of weighting an animal's time at risk that does not require tumor lethality or cause-of-death information.

This statistical analysis was performed as follows:

1. for each tumor type encountered in the study; where appropriate, tumors were also grouped for analysis, following the principles outlined by McConnell *et al.* (1986),

2. separately for males and females,
  3. Poly-3 test provided a one-tailed p-value, and a decision rule was applied as follows (FDA, 2001):
    - for common tumors, a result is considered significant if  $p < 0.005$ ,
    - for rare tumors (those which are found in less than 1% of control animals), a result is considered significant if  $p < 0.025$ . The Poly-3 test was performed using SAS software version 9.2 (SAS Institute Inc).
- A one-tailed exact test was used to analyze any tumour type for which there was 12 or less tumour bearing animals (over all groups). The statistical decision rule was applied, as above.

**Sponsor's findings:** Trend test statistics, conducted according to Poly-3 test (modified method by Bieler and Williams), revealed statistically significantly higher incidences of:

- granulocytic leukemia in males treated at 10 mg/kg/day (2/50 *versus* 0/100),
- odontoma in male rats treated at 25 mg/kg/day (a single rat; 1/50 *versus* 0/100),
- mammary gland adenomas in females treated at 15 or 50 mg/kg/day.

Neoplasms with statistical significance by the Poly-3 test when compared to controls

Organ	Neoplasm	Benign or malignant	Rare*/common tumor	Sex	Week of onset	Dose-level mg/kg/day	Trend	p-value
Hemolymphoreticular system	Leukemia; granulocytic	Malignant	rare tumor	male	18	10	increase	0.02153
Mammary gland	Adenoma	Benign	rare tumor	female	103	15	increase	0.01817
Mammary gland	Adenoma	Benign	rare tumor	female	75	50	increase	0.01872
Teeth	Odontoma	Benign	rare tumor	male	105	25	increase	0.00014

\*: found in less than 1% of control animals.

These neoplasms were not dose-related and the incidences were close to the ones observed in <sup>(b) (4)</sup> control data or in the literature. A relationship to treatment was therefore considered to be unlikely. In addition, the total incidences of mammary gland adenocarcinomas, fibroadenomas and fibromas were very similar among the different groups and therefore a relationship to treatment was excluded. The number of primary neoplasms was marginally lower in males and females treated at 75 and 50 mg/kg/day, respectively. This was associated with lower numbers in benign and malignant neoplasms in females. As these differences were marginal and did not correlate with statistically significant differences on microscopic examination, a relationship to treatment was considered to be unlikely.

No increases in tumor incidence were observed in any male or female groups that were attributed to treatment with Genz-112638. Consequently, under the experimental conditions of this study, Genz-112638 did not prove to be carcinogenic, at doses as high as 75 mg/kg/day in the males and 50 mg/kg/day in the females.

## 2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically. As the comparison of dual controls showed no major differences in

mortality or tumor rate, the data of the two controls were combined to form a single control group in subsequent survival and tumor analyses.

### 2.2.1. Survival analysis

The survival distributions of animals in all five treatment groups (three treated groups and two dual control groups) were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix for five treatment groups in males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for five treatment groups in males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for the set of combined dual controls with three treated groups in males and females, respectively.

**Reviewer's findings:** The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared individually treated groups with the combined control groups. Also the test results showed no statistically significant difference in mortality in both females and males when compared between dual controls. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

### 2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of each of the two vehicle control groups and combined vehicle control groups with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for the combined dual controls with three treated groups in males and females, respectively.

According to pharmacologist request, we have the following tumor combinations in rat and mouse studies:

#### Rat:

- Adrenal medullas benign and malignant pheochromocytoma.
- Kidney tubule adenoma and carcinoma for male rats only.
- Liver hepatocellular adenoma and carcinoma.
- Lung bronchio-alveolar adenoma and carcinoma for male rats only.
- Mammary gland adenocarcinoma and adenocarcinoma arising in fibroden for female rats only.
- Mammary gland fibroadenoma and adenoma plus fibroma for female rats only.
- Pancreas acinar cell adenocarcinoma and adenoma plus islet cell adenoma.
- Pituitary gland pars distalis and intermedia adenoma.
- Prostate adenocarcinoma and adenoma for male rats only.
- Skin benign and malignant basal cell tumor for male rats only.
- Skin squamous cell papilloma and carcinoma plus keratoacanthoma for male rats only.
- Thyroid follicular cell b-adenoma and carcinoma
- Thyroid c-cell b-adenoma and carcinoma.

**Mouse:**

- Colon adenocarcinoma and adenoma for male mice only.
- Duodenum adenocarcinoma and adenoma for male mice only.
- Liver hepatocellular adenoma and carcinoma.
- Lung bronchio-alveolar adenoma and carcinoma for male mice only.
- Mammary gland adenocarcinoma and adenoma plus squamous cell carcinoma for female mice only.
- Ovaries tubulostromal adenoma and benign granulose cell tumor plus mixed sex cord and stromal tumor for female mice only.
- Prostate adenocarcinoma and adenoma for male rats only.
- Skin squamous cell carcinoma and papilloma plus benign hair follicle tumor for female mice only.
- Uterus endometrial stromal polyp and sarcoma for female mice only.

**Multiple testing adjustment:** Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level  $\alpha=0.025$  for rare tumors and  $\alpha=0.005$  for common tumors for a submission with two species, and a significance level  $\alpha=0.05$  for rare tumors and  $\alpha=0.01$  for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of significance level  $\alpha=0.05$  for rare tumors and  $\alpha=0.01$  for common tumors, in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

**Reviewer’s findings:** Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship and/or pair-wise comparisons between the combined vehicle controls and each of individual treated groups.

**Tumor Types with P-Values  $\leq 0.05$  for Dose Response Relationship or Pair-wise Comparisons (Combined controls, low, medium and high dose groups)**

Sex	Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
			Cont	Low	Med	High				
			N=102	N=55	N=53	N=51				
Male	SKIN	FIBROMA	2	1	2	4	0.029	0.711	0.371	0.086
			[69]	[30]	[30]	[31]	.	.	.	.

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, none of the incidence of any tested tumor types in either sex was considered to have statistically significant positive dose relationship. Also based on the same proposed level of significance, none of the pair-wise comparisons of treated groups with the combined controls was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

### 3. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. Three groups of 60 male and 60 female CD1 mice received the test item, Genz-112638 (batch No. T1136), at dose-levels of 10, 25 or 75 mg/kg/day by dietary admixture for 105/106 weeks. In addition, two control groups of 60 males and 60 females received untreated diet under the same experimental conditions.

The animals were checked daily for mortality and clinical signs. In addition, detailed clinical observations were made once a week until the end of the study. After 6 months of treatment, all animals were palpated every 2 weeks in order to record the time of onset, location, size, appearance and progression of palpable masses. A blood smear was prepared on moribund principal animals before sacrifice, whenever possible. A macroscopic *post-mortem* examination was performed on moribund principal and satellite animals and the required tissues were preserved from principal animals only for a microscopic examination.

#### 3.1. Sponsor's analyses

As comparisons of the dual controls did not show major differences in mortality and tumor rate, then the data of the two controls were combined to form a single control group in subsequent survival and tumor analyses.

##### 3.1.1. Survival analysis

Survival data from the mouse study were analyzed by the sponsor using the same statistical methodologies that were used to analyze the survival data from the rat study. All statistical analysis was performed for males and females separately.

**Sponsor's findings:** Kaplan-Meier product limit survival curves are presented in Figure 3 (males) and Figure 4 (females). Sponsor's analysis showed no effect of the test item treatment was observed on the overall survival rates of males and females, apart from minimally reduced survival rates in males given 25 or 75 mg/kg/day when compared to controls. There were no indications of a test item treatment-related effect in the mortality or in the causes of death observed in males or females.

**Figure 3: Kaplan-Meier plot of Survival in Male Mice**

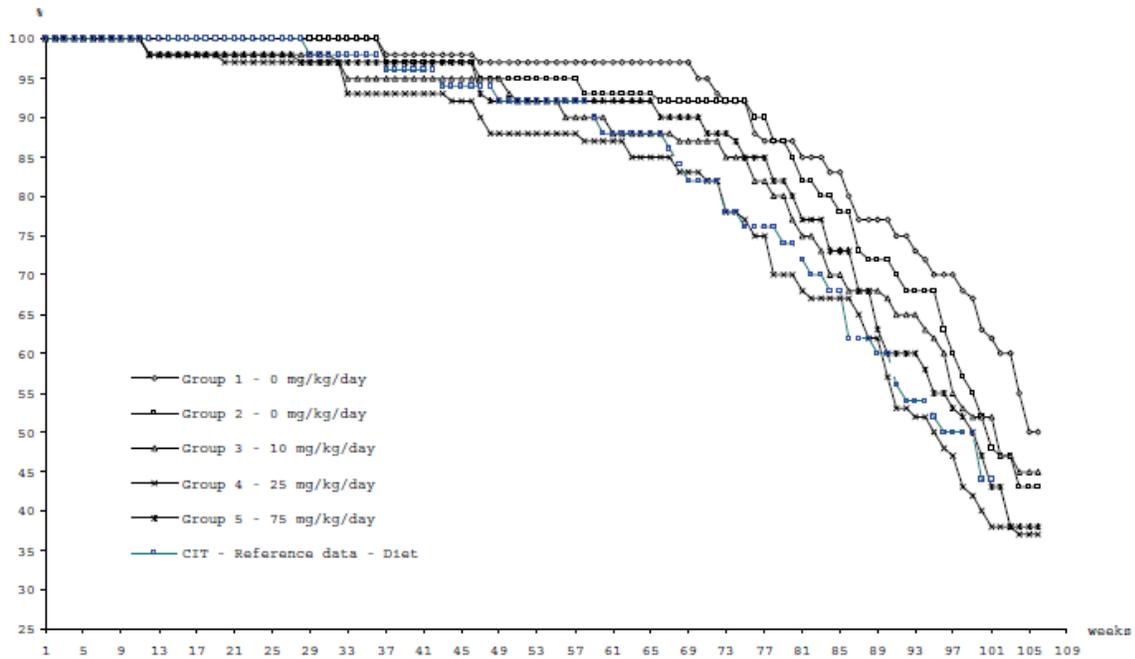
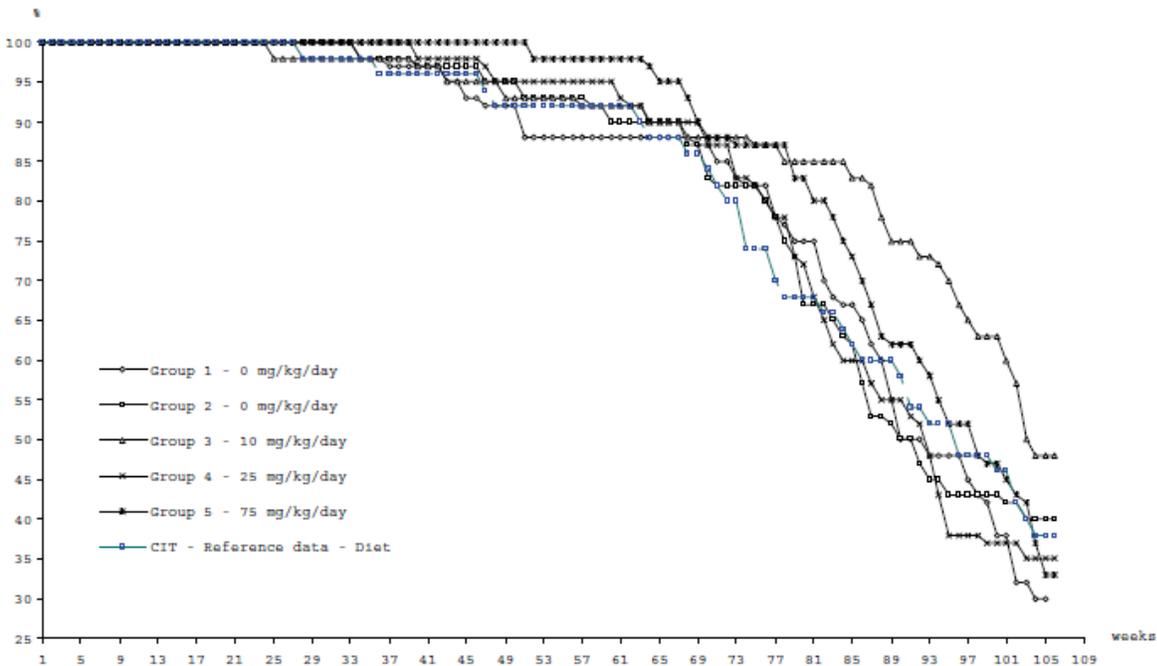


Figure 4: Kaplan-Meier plot of Survival in Female Mice



3.1.2. Tumor data analysis

Tumor data from mouse study were also analyzed by the sponsor using the same statistical methodologies that were used to analyze the tumor data from the rat study.

**Sponsor's findings:** Histopathological evaluation was performed to establish tumor incidences. Trend test statistics, using Peto's method did not show any statistically significant trends in neoplasm incidences in any organ. Trend test statistics, using the Poly-3 test (modified method of Bieler and Williams), revealed statistically significant trends to higher incidences for three tumor types:

- cortical adenoma in the adrenal cortex in males. The incidence in males treated at 75 mg/kg/day was 2/60 *versus* 0/120 in control mice,
- pheochromocytoma in the adrenal medulla in females. The incidence in females treated at 75 mg/kg/day was 2/60 *versus* 0/120 in control mice,
- skin fibrosarcoma in females. The incidence in females treated at 75 mg/kg/day was 2/58 *versus* 0/120 in controls.

The incidences of these neoplasms were within the range of incidences observed in <sup>(b) (4)</sup> control data and/or in the literature for Swiss CD-1 mice. In addition, no pre-neoplastic lesions were observed that would support a relationship of these tumors to treatment with the test item. A relationship to test item treatment was therefore ruled out for these three tumor types.

It was concluded that no treatment-related increases in tumor incidence were observed in any male or female groups of mice treated with Genz-112638.

### 3.2. Reviewer's analyses

This reviewer independently performed survival and tumor data analyses for mouse study. For the mouse data analyses this reviewer used similar methodologies that she used to analyze the data from the rat study. Data used in this reviewer's analyses were provided by the sponsor electronically. Analysis of comparing the combined vehicle controls with the treated groups was done in the reviewer's analysis.

#### 3.2.1. Survival analysis

The intercurrent mortality data are given in Tables 4A and 4B in the appendix for five treatment groups in males and females, respectively. The Kaplan-Meier curves for death rate are given in Figures 2A and 2B in the males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 5A and 5B in the appendix for the data of the combined dual controls and three treated groups in males and females, respectively.

**Reviewer's findings:** The test showed no statistically significant dose-response in survivals across the combined controls and treated groups in both males and females. But the test showed a statistically significant pair-wise difference between low dose group and the combined vehicle controls in survivals in females. Also the test results showed no statistically significant difference in mortality in both females and males when compared between the dual controls. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

#### 3.2.2. Tumor data analysis

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of control and treated groups are given in Table 6A and 6B in the appendix for data in males and females, respectively. As suggested by the reviewing pharmacologist Dr. King,

**Reviewer’s findings:** Following tumor types showed p-values less than or equal to 0.05 either tests for dose response relationship or pair-wise comparisons between the combined vehicle controls and each of individual treated groups, respectively.

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons (Combined controls, low, medium and high dose groups)**

		0 mg	10 mg	25 mg	75 mg				
		Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
Organ Name	Tumor Name	N=120	N=60	N=62	N=60	Dos Resp	C vs. L	C vs. M	C vs. H
<b>Male</b>									
ADRENAL GLANDS	ADENOMA; CORTEX	0 [67]	1 [29]	0 [26]	2 [29]	0.046 .	0.314 .	. .	0.097 .
LIVER	HEMANGIOSARCOMA	1 [67]	1 [28]	1 [27]	3 [29]	0.037 .	0.531 .	0.511 .	0.092 .
LUNGS	ADENOCARCINOMA	14 [69]	9 [29]	13 [32]	11 [30]	0.057 .	0.264 .	0.035 .	0.107 .
	ADENOCARCINOMA+ADENO	35 [72]	17 [30]	24 [33]	23 [35]	0.046 .	0.464 .	0.043 .	0.121 .
<b>Female</b>									
ADRENAL GLANDS	PHAEOCHROMOCYTOMA	0 [57]	0 [36]	0 [31]	2 [35]	0.047 .	. .	. .	0.126 .
SKIN	FIBROSARCOMA	0 [57]	0 [36]	0 [31]	2 [35]	0.047 .	. .	. .	0.126 .
UTERUS	SARCOMA; ENDOMETRIAL	1 [58]	5 [37]	2 [31]	2 [35]	0.415 .	0.028 .	0.254 .	0.290 .

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, none of the incidence of any tested tumor types in either sex was considered to have statistically significant positive dose relationship. Also based on the same proposed level of significance, none of the pair-wise comparisons of treated groups with the combined controls was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

**4. Evaluation of validity of the designs of rat and mouse studies**

As having been noted, the tumor data analyses from both rat and mouse studies including the combined vehicle controls and three treated groups showed no statistically significant dose-response relationship in any tested single

tumor type. Before drawing any conclusion regarding the carcinogenic or non-carcinogenic potential of the drug in rats and mice, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

- (i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
- (ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that "to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

- (i) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- (ii) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- (iii) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the GENZ-112638 rat and mouse studies, in the light of the above guidelines

#### 4.1. Rat Study

The following is the summary of survival data of rats in the high dose groups:

**Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91**

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	92%	82%	61%
Female	93%	74%	54%

Based on the survival criterion Haseman proposed, it could be concluded that enough rats were exposed to the high dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain from the concurrent combined control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

**Percent Difference in Mean body Weight Gain From combined controls**

Male			Female		
10mg	25mg	75mg	5mg	15mg	50mg
-4.55	-4.75	-22.8	-4.32	8.95	-8.95

Therefore, relative to the combined controls, there had been more than 22% loss in body weight gain in high dose group in males, around 8% in body weight gain in medium dose group in females and up to 10% loss in body weight gain in the rest dose group in both males and females.

The mortality rates at the end of the experiment were as follows:

**Mortality Rates at the End of the Experiment**

	Combined			
	Cont.	Low	Medium	High
Male	58%	60%	62%	51%
Female	56%	72%	71%	56%

This shows that the mortality rate of in the high dose groups in males is 7% lower than the combined controls but the high dose group in females has the same mortality rate as the combined controls. Thus, from the body weight gain and mortality data, it can be concluded that for males that the used high dose level might not have reached or exceeded the MTD. For females, the high dose group might be close to MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

**4.2. Mouse Study**

The following is the summary of survival data of rats in the high dose groups:

**Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91**

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	92%	82%	60%
Female	98%	87%	60%

Based on the survival criterion Haseman proposed, it could be concluded that enough mice were exposed to the high dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain from the concurrent combined control, defined as

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

**Percent Difference in Mean body Weight Gain From combined controls**

Male			Female		
10mg	25mg	75mg	10mg	25mg	75mg
4.09	-1.17	2.93	11.73	-9.26	2.47

Therefore, relative to the combined controls, there had been less than 10% loss in body weight gain in 25mg treated groups in both males and females, but increases weight gain in 10 mg and 75 mg groups in both males and females.

The mortality rates at the end of the experiment were as follows:

**Mortality Rates at the End of the Experiment**

	Combined			
	Cont.	Low	Medium	High
Male	51%	55%	65%	62%
Female	65%	54%	66%	63%

This shows that the mortality rate of in the high dose group in males is 11% higher than the combined controls but 2% lower than the combined controls in the high dose group and 9% lower than the combined controls in low dose group in females. Thus, from the mortality data it can be concluded that for both males and females the used high dose level might have not reached MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

## 5. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were intended to further assess the carcinogenic potential of GENZ-112638 in rats and mice, when administered daily via oral gavage to mice and rats for at least 103 weeks.

**Rat Study:** Three groups of 50 male and 50 female Sprague-Dawley rats received the test item, Genz-112638 (batch No. T1136) at the dose-levels of 10, 25 or 75 mg/kg/day in males for 105 weeks, or 5, 15 or 50 mg/kg/day in females for 103 weeks, by gavage, under a dosage-volume of 5 ml/kg.

The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared with the combined control groups. Also the test results showed no statistically significant difference in mortality in both females and males when compared between the dual controls.

For combined controls vs. three treated groups:

Based on the criteria of adjustment for multiple testing of trends proposed by Lin and Rahman, none of the incidence of any tested tumor types in either sex was considered to have statistically significant positive dose relationship. Also based on the same proposed level of significance, none of the pair-wise comparisons of treated groups with the combined controls was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

As having been noted, the tumor data analyses from rat study including combined controls with three treated groups showed no statistically significant dose-response relationship in any tested single tumor type.

From the body weight gain and mortality data, it can be concluded that for males that the used high dose level might not have reached or exceeded the MTD. For females, the high dose might be close to MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

**Mouse Study:** Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups and two control groups. Three groups of 60 male and 60 female CD1 mice received the test item, Genz-112638 (batch No. T1136), at dose-levels of 10, 25 or 75 mg/kg/day by dietary admixture for 105/106 weeks. In addition, two control groups of 60 males and 60 females received untreated diet under the same experimental conditions.

The test showed no statistically significant dose-response in survivals across the combined controls and treated groups in both males and females, and a statistically significant pair-wise difference between low dose group and the combined vehicle controls in survivals in females. Also the test results showed no statistically significant difference in mortality in both females and males when compared between the dual controls.

For combined vehicle controls vs. three treated groups:

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, none of the incidence of any tested tumor types in either sex was considered to have statistically significant positive dose relationship. Also based on the same proposed level of significance, none of the pair-wise comparisons of treated groups with the combined controls was considered to be statistically significant in either sex for increased tumor incidence in the treated group.

As having been noted, the tumor data analyses from mouse study including combined controls with three treated groups showed no statistically significant dose-response relationship in any tested single tumor type.

From the mortality data it can be concluded that for both males and females the used high dose level might have not reached MTD. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Min Min, Ph.D.  
Mathematical Statistician

Concur: Karl Lin, Ph.D.  
Team Leader, Biometrics-6

cc:  
Archival NDA 20-5494  
Dr. King  
Dr. Tiwari  
Dr. Nevius  
Lillian Patrician

Dr. Tsong  
Dr. Lin  
Dr. Min

**6. Appendix**

**Table 1A: Intercurrent Mortality Rate  
Male Rats**

Week	CONTROL1		CONTROL2		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT								
0-52	2	3.9%	3	6.0%	5	9.1%	5	9.4%	4	7.8%
53-78	9	21.2%	6	18.0%	8	23.6%	13	34.0%	5	17.7%
79-92	10	40.4%	5	28.0%	7	36.4%	5	43.4%	11	39.2%
93-104	12	63.5%	12	52.0%	13	60.0%	10	62.3%	6	51.0%
Term. Sac.	19	100.0%	24	100.0%	22	100.0%	20	100.0%	25	100.0%

**Table 1B: Intercurrent Mortality Rate  
Female Rats**

Week	CONTROL1		CONTROL2		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT								
0-52	1	1.9%	1	2.0%	1	1.7%	1	1.8%	4	7.0%
53-78	9	19.2%	7	16.0%	16	29.3%	12	23.6%	11	26.3%
79-92	7	32.7%	12	40.0%	13	51.7%	13	47.3%	11	45.6%
93-102	11	53.9%	9	58.0%	12	72.4%	13	70.9%	6	56.1%
Term. Sac.	24	100.0%	21	100.0%	16	100.0%	16	100.0%	25	100.0%

**Table 2A: Intercurrent Mortality Comparison  
Male Rats**

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	0.7335	0.7945	0.4459	0.7499
Homogeneity	0.6534	0.7883	0.3508	0.5987

**Table 2B: Intercurrent Mortality Comparison  
Female Rats**

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	0.9528	0.0826	0.1584	0.7448
Homogeneity	0.0636	0.0714	0.0489	0.6578

**Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=55	Med N=53	High N=51	Dos Resp	C vs. L	C vs. M	C vs. H
ADRENAL CORTICE		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; CORTICAL CELL	7 [69]	5 [30]	2 [30]	0 [31]	0.985	0.381	0.842	1.000
ADRENAL MEDULLA		(99)	(50)	(50)	(50)	.	.	.	.
	PHEOCHROMOCYTOMA; BENIGN	10 [70]	2 [30]	3 [31]	4 [32]	0.528	0.957	0.851	0.747
	PHEOCHROMOCYTOMA; MALIGNANT	4 [69]	0 [30]	0 [30]	1 [31]	0.694	1.000	1.000	0.868
ADRENAL_MEDULLA		(102)	(55)	(53)	(51)	.	.	.	.
	PHEOCHROMOCYTOMA_BENIGN+MALIGN	14 [70]	2 [30]	3 [31]	5 [32]	0.623	0.991	0.956	0.828
BRAIN		(100)	(50)	(50)	(50)	.	.	.	.
	ASTROCYTOMA; BENIGN	0 [68]	0 [30]	0 [30]	1 [31]	0.195	.	.	0.328
	ASTROCYTOMA; MALIGNANT	2 [69]	0 [30]	3 [30]	1 [31]	0.365	1.000	0.180	0.700
	MENINGIOMA; BENIGN	0 [68]	0 [30]	1 [31]	0 [31]	0.388	.	0.316	.
FORESTOMACH		(100)	(50)	(50)	(50)	.	.	.	.
	HEMANGIOMA	1 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
	TUMOR; BASAL CELL; BENIGN	1 [69]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
HEART		(100)	(50)	(50)	(50)	.	.	.	.
	SCHWANNOMA; ENDOCARDIAL; BENIG	1 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
HEMOLYMPHORET.		(100)	(50)	(50)	(50)	.	.	.	.
	LEUKEMIA; GRANULOCYTIC	0 [68]	2 [32]	1 [30]	0 [31]	0.567	0.121	0.316	.
	LYMPHOMA; MALIGNANT	0 [68]	0 [30]	1 [30]	0 [31]	0.384	.	0.316	.
	SARCOMA; HISTIOCYTIC	2 [69]	1 [30]	1 [30]	1 [32]	0.475	0.715	0.684	0.700
KIDNEY		(102)	(55)	(53)	(51)	.	.	.	.
	TUBULE_ADENOMA+CARCINOMA	1 [68]	1 [30]	0 [30]	0 [31]	0.819	0.565	1.000	1.000

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=55	Med N=53	High N=51	Dos Resp	C vs. L	C vs. M	C vs. H
KIDNEYS		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; TUBULE	0	1	0	0	0.572	0.339	.	.
		[68]	[30]	[30]	[31]	.	.	.	.
	CARCINOMA; TUBULE	1	0	0	0	1.000	1.000	1.000	1.000
		[68]	[30]	[30]	[31]	.	.	.	.
	HEMANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
	[68]	[30]	[30]	[31]	.	.	.	.	
	PAPILLOMA; TRANSITIONAL CELL	0	0	1	0	0.384	.	0.316	.
		[68]	[30]	[30]	[31]	.	.	.	.
LIVER		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; HEPATOCELLULAR	1	3	0	3	0.086	0.118	1.000	0.102
		[68]	[31]	[30]	[31]	.	.	.	.
	CARCINOMA; HEPATOCELLULAR	3	3	1	1	0.688	0.328	0.786	0.801
	[69]	[30]	[30]	[32]	.	.	.	.	
	HEPATOCELLULAR_ADENOMA+CARCINO	4	6	1	4	0.267	0.079	0.856	0.241
		[69]	[31]	[30]	[32]	.	.	.	.
LUNG		(102)	(55)	(53)	(51)	.	.	.	.
	BRONCHIO_ADENOMA+CARCINOMA	0	1	1	0	0.459	0.339	0.316	.
		[68]	[30]	[30]	[31]	.	.	.	.
LUNGS		(100)	(50)	(50)	(49)	.	.	.	.
	ADENOMA; BRONCHIO-ALVEOLAR	0	0	1	0	0.384	.	0.316	.
		[68]	[30]	[30]	[31]	.	.	.	.
	CARCINOMA; BRONCHIO-ALVEOLAR	0	1	0	0	0.572	0.339	.	.
	[68]	[30]	[30]	[31]	.	.	.	.	
MESENT. LYMPH N		(99)	(50)	(50)	(50)	.	.	.	.
	HEMANGIOMA	2	0	1	0	0.772	1.000	0.684	1.000
		[69]	[30]	[30]	[31]	.	.	.	.
	LYMPHANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
	[69]	[30]	[30]	[31]	.	.	.	.	
PANCREAS		(100)	(50)	(50)	(50)	.	.	.	.
	ACINAR_CELL_ADENOMA+ADENOCARCI	7	0	4	2	0.584	1.000	0.497	0.859
		[69]	[30]	[31]	[31]	.	.	.	.
	ADENOCARCINOMA; ACINAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[69]	[30]	[30]	[31]	.	.	.	.
	ADENOMA; ACINAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
	[68]	[30]	[30]	[31]	.	.	.	.	
	ADENOMA; ISLET CELL	5	0	4	2	0.408	1.000	0.317	0.734
		[69]	[30]	[31]	[31]	.	.	.	.

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=55	Med N=53	High N=51	Dos Resp	C vs. L	C vs. M	C vs. H
PITUITARY GLAND		(99)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; PARS DISTALIS	49 [81]	23 [37]	25 [37]	17 [34]	0.851	0.766	0.391	0.917
	ADENOMA; PARS INTERMEDIA	0 [68]	0 [30]	0 [30]	1 [31]	0.195	.	.	0.328
	PAR_DISTALIS+INTERMEDIA_ADENOM	49 [81]	23 [37]	25 [37]	17 [34]	0.851	0.766	0.391	0.917
PROSTATE		(99)	(50)	(50)	(50)	.	.	.	.
	ADENOCARCINOMA	1 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
	ADENOCARCINOMA+ADENOMA	2 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
	ADENOMA	1 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
	FIBROSARCOMA	1 [69]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
SALIVARY GLANDS		(98)	(49)	(50)	(49)	.	.	.	.
	ADENOCARCINOMA	0 [68]	1 [31]	0 [30]	0 [31]	0.575	0.345	.	.
SKIN		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; SEBACEOUS CELL	1 [68]	0 [30]	0 [30]	1 [31]	0.353	1.000	1.000	0.550
	BASAL CELL TUMOR; BENIGN	1 [68]	1 [30]	0 [30]	0 [31]	0.819	0.565	1.000	1.000
	BASAL CELL TUMOR; MALIGNANT	0 [68]	1 [30]	1 [31]	0 [31]	0.461	0.339	0.316	.
	BASAL_CELL_TUMOR_BENIIGN+MALIG	1 [68]	2 [30]	1 [31]	0 [31]	0.723	0.265	0.534	1.000
	CARCINOMA+KEROTOACANTHOMA+PAPI	7 [70]	0 [30]	6 [31]	3 [32]	0.369	1.000	0.194	0.705
	CARCINOMA; SQUAMOUS CELL	0 [68]	0 [30]	1 [31]	0 [31]	0.388	.	0.322	.
	FIBROMA	2 [69]	1 [30]	2 [30]	4 [31]	0.029	0.711	0.371	0.086
	HAIR FOLLICLE TUMOR; BENIGN	2 [68]	1 [30]	1 [30]	2 [32]	0.227	0.715	0.684	0.397
	HEMANGIOMA	1 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
	KERATOACANTHOMA	6 [70]	0 [30]	5 [30]	3 [32]	0.300	1.000	0.230	0.623
PAPILLOMA; SQUAMOUS CELL	1 [69]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000	

**Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=55	Med N=53	High N=51	Dos Resp	C vs. L	C vs. M	C vs. H
SPLEEN		(100)	(50)	(50)	(50)	.	.	.	.
	FIBROSARCOMA	1 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
	HEMANGIOSARCOMA	0 [68]	1 [30]	0 [30]	0 [31]	0.572	0.339	.	.
						.	.	.	.
TESTES		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; LEYDIG CELL	3 [69]	0 [30]	2 [30]	3 [31]	0.098	1.000	0.506	0.305
THYMUS		(99)	(50)	(50)	(50)	.	.	.	.
	MALIGNANT THYMOMA	0 [68]	0 [30]	0 [30]	1 [31]	0.195	.	.	0.328
THYROID GLANDS		(98)	(50)	(49)	(49)	.	.	.	.
	ADENOMA; C CELL	7 [68]	5 [31]	2 [30]	0 [31]	0.986	0.398	0.842	1.000
	ADENOMA; FOLLICULAR CELL	4 [68]	1 [30]	0 [30]	0 [31]	0.987	0.879	1.000	1.000
	CARCINOMA; C CELL	1 [68]	0 [30]	0 [30]	0 [31]	1.000	1.000	1.000	1.000
	CARCINOMA; FOLLICULAR CELL	2 [68]	2 [30]	0 [30]	1 [31]	0.583	0.418	1.000	0.700
	C_CELL_ADENOMA+CARCINOMA	8 [68]	5 [31]	2 [30]	0 [31]	0.991	0.485	0.885	1.000
	FOLLICULAR_CELL_ADENOMA+CARCIN	6 [68]	3 [30]	0 [30]	1 [31]	0.908	0.644	1.000	0.943
						.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

**Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	5 mg	15 mg	50 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=58	Med N=55	High N=57	Dos Resp	C vs. L	C vs. M	C vs. H
ADRENAL CORTICE		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; CORTICAL CELL	4	4	3	1	0.759	0.265	0.429	0.879
		[77]	[35]	[35]	[34]	.	.	.	.
ADRENAL MEDULLA		(99)	(50)	(49)	(49)	.	.	.	.
	PHEOCHROMOCYTOMA; BENIGN	3	1	0	0	0.968	0.808	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
	PHEOCHROMOCYTOMA; COMPLEX; BEN	0	1	0	0	0.573	0.333	.	.
		[76]	[34]	[34]	[34]	.	.	.	.
ADRENAL_MEDULLA		(102)	(58)	(55)	(57)	.	.	.	.
	PHEOCHROMOCYTOMA_BENIGN+COMPLE	3	2	0	0	0.956	0.542	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
BRAIN		(100)	(50)	(50)	(50)	.	.	.	.
	ASTROCYTOMA; BENIGN	1	0	0	0	1.000	1.000	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
	ASTROCYTOMA; MALIGNANT	1	0	0	0	1.000	1.000	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
	MENINGIOMA; MALIGNANT	0	0	1	0	0.386	.	0.333	.
		[76]	[34]	[35]	[34]	.	.	.	.
CLITORAL GLANDS		(97)	(48)	(48)	(49)	.	.	.	.
	ADENOMA	0	0	1	0	0.386	.	0.333	.
		[76]	[34]	[35]	[34]	.	.	.	.
DUODENUM		(100)	(50)	(50)	(50)	.	.	.	.
	LEIOMYOSARCOMA	0	0	0	1	0.191	.	.	0.339
		[76]	[34]	[34]	[34]	.	.	.	.
EYES		(100)	(50)	(50)	(50)	.	.	.	.
	MELANOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
FORESTOMACH		(100)	(50)	(50)	(50)	.	.	.	.
	TUMOR; BASAL CELL; BENIGN	0	1	0	0	0.573	0.333	.	.
		[76]	[34]	[34]	[34]	.	.	.	.
HEMOLYMPHORET.		(100)	(50)	(50)	(50)	.	.	.	.
	SARCOMA; HISTIOCYTIC	2	1	0	0	0.924	0.708	1.000	1.000
		[77]	[35]	[34]	[34]	.	.	.	.
LARYNX		(100)	(50)	(50)	(50)	.	.	.	.
	CARCINOMA; SQUAMOUS CELL	0	0	1	0	0.386	.	0.333	.
		[76]	[34]	[35]	[34]	.	.	.	.

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	5 mg	15 mg	50 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=58	Med N=55	High N=57	Dos Resp	C vs. L	C vs. M	C vs. H
LIVER		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; HEPATOCELLULAR	8	3	5	1	0.891	0.779	0.448	0.980
		[77]	[34]	[35]	[34]	.	.	.	.
	CARCINOMA; HEPATOCELLULAR	0	0	0	1	0.191	.	.	0.339
		[76]	[34]	[34]	[34]	.	.	.	.
	HEPATOCELLULAR_ADENOMA+CARCINO	8	3	5	2	0.746	0.779	0.448	0.912
		[77]	[34]	[35]	[34]	.	.	.	.
MAMMARY GLANDS		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOCARCINOMA	16	15	11	9	0.473	0.066	0.264	0.513
		[81]	[40]	[38]	[37]	.	.	.	.
MAMMARY GLANDS	ADENOCARCINOMA ARISING IN FIBR	5	4	1	1	0.854	0.367	0.916	0.920
		[77]	[36]	[34]	[34]	.	.	.	.
	ADENOMA	0	1	2	2	0.062	0.333	0.109	0.117
		[76]	[34]	[34]	[35]	.	.	.	.
	FIBROADENOMA	38	20	20	20	0.325	0.450	0.498	0.587
		[82]	[36]	[37]	[38]	.	.	.	.
	FIBROMA	2	0	0	1	0.473	1.000	1.000	0.715
		[76]	[34]	[34]	[34]	.	.	.	.
	TUMOR; MIXED; MALIGNANT	2	0	0	0	1.000	1.000	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
	ADENOCARCINOMA+ARISING_IN_FIBR	19	16	12	10	0.509	0.100	0.327	0.579
		[81]	[40]	[38]	[37]	.	.	.	.
	FIBROADENOMA+ADENOMA+FIBROMA	39	20	22	23	0.148	0.501	0.352	0.397
		[82]	[36]	[37]	[39]	.	.	.	.
MESENT. LYMPH N		(99)	(49)	(50)	(50)	.	.	.	.
	LYMPHANGIOMA	0	0	1	0	0.382	.	0.333	.
		[76]	[34]	[34]	[34]	.	.	.	.
OVARIES		(100)	(50)	(50)	(50)	.	.	.	.
	TUMOR; GRANULOSA CELL; MALIGNA	0	0	0	1	0.191	.	.	0.339
		[76]	[34]	[34]	[34]	.	.	.	.
	TUMOR; SERTOLI CELL; BENIGN	1	0	0	0	1.000	1.000	1.000	1.000
		[77]	[34]	[34]	[34]	.	.	.	.
	TUMOR; SERTOLI CELL; MALIGNANT	0	1	0	0	0.573	0.333	.	.
		[76]	[34]	[34]	[34]	.	.	.	.
PANCREAS		(100)	(50)	(50)	(50)	.	.	.	.
	ACINAR+ISLET_CELL_ADENOMA	3	0	0	1	0.579	1.000	1.000	0.814
		[77]	[34]	[34]	[34]	.	.	.	.
	ADENOMA; ACINAR CELL	0	0	0	1	0.191	.	.	0.339
		[76]	[34]	[34]	[34]	.	.	.	.
	ADENOMA; ISLET CELL	3	0	0	0	1.000	1.000	1.000	1.000
		[77]	[34]	[34]	[34]	.	.	.	.

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	5 mg	15 mg	50 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=58	Med N=55	High N=57	Dos Resp	C vs. L	C vs. M	C vs. H
PITUITARY GLAND		(99)	(50)	(50)	(49)	.	.	.	.
	ADENOMA; PARS DISTALIS	72	40	42	33	0.687	0.523	0.243	0.925
		[94]	[47]	[46]	[44]	.	.	.	.
	CARCINOMA; PARS DISTALIS	1	0	1	0	0.624	1.000	0.558	1.000
		[76]	[34]	[35]	[34]	.	.	.	.
	PAR_DISTALIS_ADENOMA+CARCINOMA	73	40	43	33	0.729	0.581	0.199	0.944
		[94]	[47]	[47]	[44]	.	.	.	.
SALIVARY GLANDS		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOCARCINOMA	0	0	1	0	0.382	.	0.333	.
		[76]	[34]	[34]	[34]	.	.	.	.
SKIN		(100)	(50)	(50)	(50)	.	.	.	.
	BASAL CELL TUMOR; MALIGNANT	0	1	0	0	0.573	0.333	.	.
		[76]	[34]	[34]	[34]	.	.	.	.
	KERATOACANTHOMA	2	1	0	0	0.920	0.704	1.000	1.000
		[78]	[34]	[34]	[34]	.	.	.	.
	PAPILLOMA; SQUAMOUS CELL	2	1	1	0	0.802	0.708	0.708	1.000
SKIN	PAPILLOMA; SQUAMOUS CELL	[76]	[34]	[35]	[34]	.	.	.	.
SPINAL CORD		(99)	(50)	(50)	(49)	.	.	.	.
	GLIOMA; NOT OTHERWISE SPECIFIE	1	0	0	0	1.000	1.000	1.000	1.000
		[77]	[34]	[34]	[34]	.	.	.	.
THYMUS		(99)	(50)	(50)	(50)	.	.	.	.
	BENIGN THYMOMA	1	0	0	1	0.345	1.000	1.000	0.565
		[77]	[34]	[34]	[34]	.	.	.	.
	MALIGNANT THYMOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[77]	[34]	[34]	[34]	.	.	.	.
THYROID GLANDS		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOMA; C CELL	9	3	2	3	0.657	0.828	0.932	0.838
		[78]	[34]	[35]	[34]	.	.	.	.
	ADENOMA; FOLLICULAR CELL	0	0	1	0	0.386	.	0.333	.
		[76]	[34]	[35]	[34]	.	.	.	.
	CARCINOMA; C CELL	1	0	0	1	0.346	1.000	1.000	0.565
		[76]	[34]	[34]	[34]	.	.	.	.
	CARCINOMA; FOLLICULAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[77]	[34]	[34]	[34]	.	.	.	.
THYROID_GLAND		(102)	(58)	(55)	(57)	.	.	.	.
	C_CELL_ADENOMA+CARCINOMA	10	3	2	4	0.530	0.871	0.953	0.762
		[78]	[34]	[35]	[34]	.	.	.	.
	FOLLICULAR_CELL_ADENOMA+CARCIN	1	0	1	0	0.621	1.000	0.558	1.000
		[77]	[34]	[35]	[34]	.	.	.	.

**Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Rats (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	5 mg	15 mg	50 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=102	Low N=58	Med N=55	High N=57	Dos Resp	C vs. L	C vs. M	C vs. H
URINARY BLADDER		(100)	(50)	(50)	(50)	.	.	.	.
	LEIOMYOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
UTERUS		(100)	(50)	(50)	(50)	.	.	.	.
	ADENOCARCINOMA; ENDOMETRIAL	1	0	0	0	1.000	1.000	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
	CARCINOMA; ADENOSQUAMOUS	0	0	0	1	0.191	.	.	0.339
		[76]	[34]	[34]	[34]	.	.	.	.
	POLYP; ENDOMETRIAL STROMA	8	4	3	4	0.449	0.624	0.772	0.640
		[77]	[35]	[34]	[35]	.	.	.	.
SARCOMA; ENDOMETRIAL STROMAL	1	1	0	2	0.131	0.558	1.000	0.273	
	[76]	[34]	[34]	[35]	.	.	.	.	
TUMOR; GRANULAR CELL; BENIGN	2	0	0	0	1.000	1.000	1.000	1.000	
	[77]	[34]	[34]	[34]	.	.	.	.	
VAGINA		(100)	(50)	(50)	(49)	.	.	.	.
	PAPILLOMA; SQUAMOUS CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[76]	[34]	[34]	[34]	.	.	.	.
	POLYP; STROMAL	3	2	0	4	0.075	0.553	1.000	0.193
		[77]	[35]	[34]	[36]	.	.	.	.
TUMOR; GRANULAR CELL; BENIGN	10	7	1	2	0.943	0.297	0.990	0.958	
	[78]	[35]	[34]	[35]	.	.	.	.	

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

**Table 4A: Intercurrent Mortality Rate  
Male Mice**

Week	CONTROL1		CONTROL2		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT								
0-52	2	3.3%	3	5.0%	5	8.3%	8	12.9%	5	8.3%
53-78	6	13.3%	5	13.3%	7	20.0%	12	32.3%	6	18.3%
79-92	7	25.0%	11	31.7%	9	35.0%	10	48.4%	13	40.0%
93-104	12	45.0%	15	56.7%	12	55.0%	10	64.5%	13	61.7%
Term. Sac.	33	55.0%	26	43.3%	27	45.0%	22	35.5%	23	38.3%

**Table 4B: Intercurrent Mortality Rate  
Female Mice**

Week	CONTROL1		CONTROL2		LOW		MEDIUM		HIGH	
	NO.OF DEATH	PERCENT								
0-52	8	13.1%	4	6.7%	6	9.5%	3	4.9%	1	1.7%
53-78	7	24.6%	11	25.0%	6	19.1%	11	23.0%	7	13.3%
79-92	16	50.8%	17	53.3%	7	30.2%	16	49.2%	16	40.0%
93-104	12	70.5%	4	60.0%	15	54.0%	10	65.6%	14	63.3%
Term. Sac.	18	29.2%	24	40.0%	29	46.0%	21	34.4%	22	36.7%

**Table 5A: Intercurrent Mortality Comparison  
Male Mice**

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	0.2354	0.6587	0.0617	0.2454
Homogeneity	0.1329	0.4905	0.0223	0.1518

**Table 5B: Intercurrent Mortality Comparison  
Female Mice**

Test	P-Value (across four groups)	P-Value (combined controls vs low)	P-Value (combined controls vs medium)	P-Value (combined controls vs high)
Dose Response	0.8673	0.0433	0.9764	0.5010
Homogeneity	0.2302	0.0610	0.9183	0.5917

**Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Male Mice (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=120	Low N=60	Med N=62	High N=60				
ADRENAL GLANDS		(120)	(60)	(58)	(60)	.	.	.	.
	ADENOMA; CORTEX	0	1	0	2	0.046	0.314	.	0.097
		[67]	[29]	[26]	[29]	.	.	.	.
	ADENOMA; SUBCAPSULAR CELL	2	1	2	2	0.192	0.681	0.346	0.373
		[67]	[28]	[27]	[29]	.	.	.	.
ADRENAL GLANDS	PHAECHROMOCYTOMA	0	1	2	0	0.498	0.314	0.088	.
		[67]	[28]	[27]	[29]	.	.	.	.
BRAIN		(120)	(59)	(58)	(60)	.	.	.	.
	ASTROCYTOMA; MALIGNANT	0	0	0	1	0.193	.	.	0.314
		[67]	[28]	[26]	[29]	.	.	.	.
COLON		(119)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	1	1	0	2	0.123	0.531	1.000	0.233
		[67]	[29]	[26]	[29]	.	.	.	.
	ADENOCARCINOMA+ADENOMA	1	1	1	2	0.112	0.531	0.511	0.233
		[67]	[29]	[27]	[29]	.	.	.	.
COLON	ADENOMA	0	0	1	0	0.371	.	0.299	.
		[67]	[28]	[27]	[29]	.	.	.	.
DUODENUM		(118)	(60)	(58)	(60)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
	ADENOCARCINOMA+ADENOMA	1	0	0	1	0.350	1.000	1.000	0.531
		[67]	[28]	[26]	[29]	.	.	.	.
DUODENUM	ADENOMA	0	0	0	1	0.193	.	.	0.314
		[67]	[28]	[26]	[29]	.	.	.	.
EPIDIDYMIDES		(120)	(60)	(59)	(59)	.	.	.	.
	ADENOMA; LEYDIG CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
GALL BLADDER		(101)	(47)	(48)	(54)	.	.	.	.
	ADENOCARCINOMA	0	0	0	1	0.193	.	.	0.314
		[67]	[28]	[26]	[29]	.	.	.	.
	PAPILLOMA	3	0	0	1	0.591	1.000	1.000	0.780
		[68]	[28]	[26]	[29]	.	.	.	.
HARDERIAN GLAND		(120)	(60)	(57)	(60)	.	.	.	.
	ADENOCARCINOMA	1	1	1	0	0.644	0.531	0.503	1.000
		[67]	[29]	[26]	[29]	.	.	.	.
	ADENOMA	8	2	3	2	0.732	0.881	0.695	0.881
		[67]	[29]	[27]	[29]	.	.	.	.

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
		Cont N=120	Low N=60	Med N=62	High N=60				
HEMOLYMPHORET.		(120)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA; GRANULOCYTIC	0	0	1	0	0.371	.	0.299	.
		[67]	[28]	[27]	[29]	.	.	.	.
	LYMPHOMA; MALIGNANT	12	7	3	7	0.357	0.402	0.879	0.420
		[69]	[30]	[27]	[32]	.	.	.	.
	SARCOMA; HISTIOCYTIC	1	1	2	0	0.628	0.531	0.213	1.000
		[67]	[29]	[27]	[29]	.	.	.	.
HEMOLYMPHORET.	TUMOR; MAST CELL; MALIGNANT	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
KIDNEYS		(120)	(60)	(58)	(60)	.	.	.	.
	ADENOMA; TUBULE	2	0	1	2	0.156	1.000	0.652	0.373
		[67]	[28]	[26]	[29]	.	.	.	.
LIVER		(119)	(60)	(58)	(60)	.	.	.	.
	ADENOMA; HEPATOCELLULAR	21	9	7	7	0.743	0.621	0.783	0.833
		[70]	[29]	[27]	[29]	.	.	.	.
	CARCINOMA; HEPATOCELLULAR	11	5	8	7	0.187	0.617	0.171	0.326
		[68]	[29]	[28]	[30]	.	.	.	.
	HEMANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
	HEMANGIOSARCOMA	1	1	1	3	0.037	0.531	0.511	0.092
		[67]	[28]	[27]	[29]	.	.	.	.
	HEPATOBLASTOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
	HEPATOBLASTOMA+CARCINOMA+ADENO	33	14	15	14	0.553	0.659	0.486	0.689
		[71]	[29]	[29]	[31]	.	.	.	.
	TUMOR; ITO CELL; BENIGN	0	1	0	0	0.553	0.314	.	.
		[67]	[28]	[26]	[29]	.	.	.	.
LUNGS		(120)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	14	9	13	11	0.057	0.264	0.035	0.107
		[69]	[29]	[32]	[30]	.	.	.	.
	ADENOCARCINOMA+ADENOMA	35	17	24	23	0.046	0.464	0.043	0.121
		[72]	[30]	[33]	[35]	.	.	.	.
	ADENOMA; BRONCHIO-ALVEOLAR	21	8	12	13	0.166	0.755	0.232	0.300
		[70]	[30]	[29]	[34]	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
MESENT. LYMPH N		(120)	(60)	(57)	(59)	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.

**Table 6A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=120	Low N=60	Med N=62	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
PANCREAS		(120)	(59)	(58)	(59)	.	.	.	.
	ADENOCARCINOMA; ACINAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
		[68]	[28]	[26]	[29]	.	.	.	.
PROSTATE		(120)	(60)	(58)	(59)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
	ADENOCARCINOMA+ADENOMA	1	0	1	0	0.606	1.000	0.511	1.000
	[67]	[28]	[27]	[29]	.	.	.	.	
	ADENOMA	0	0	1	0	0.371	.	0.299	.
	[67]	[28]	[27]	[29]	.	.	.	.	
SEMINAL VESICLE		(120)	(60)	(58)	(59)	.	.	.	.
	TUMOR; GRANULAR CELL; MALIGNAN	0	0	1	0	0.371	.	0.294	.
	[67]	[28]	[27]	[29]	.	.	.	.	
SKIN		(117)	(60)	(59)	(59)	.	.	.	.
	HEMANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
	[67]	[28]	[26]	[29]	.	.	.	.	
SPLEEN		(120)	(60)	(58)	(60)	.	.	.	.
	HEMANGIOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[67]	[28]	[26]	[29]	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
	[67]	[28]	[26]	[29]	.	.	.	.	
	LEIOMYOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
	[67]	[28]	[26]	[29]	.	.	.	.	
TESTES		(120)	(60)	(59)	(59)	.	.	.	.
	ADENOMA; LEYDIG CELL	2	1	2	0	0.738	0.681	0.346	1.000
	[67]	[28]	[27]	[29]	.	.	.	.	
THYROID GLANDS		(120)	(60)	(58)	(59)	.	.	.	.
	CARCINOMA; FOLLICULAR CELL	1	0	0	0	1.000	1.000	1.000	1.000
	[67]	[28]	[26]	[29]	.	.	.	.	
TONGUE		(120)	(60)	(60)	(60)	.	.	.	.
	HEMANGIOSARCOMA	0	0	0	1	0.193	.	.	0.314
	[67]	[28]	[26]	[29]	.	.	.	.	
	LESION; MESENCHYMAL PROLIFERAT	1	0	0	0	1.000	1.000	1.000	1.000
	[67]	[28]	[26]	[29]	.	.	.	.	

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

**Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=121	Low N=63	Med N=61	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
ADRENAL GLANDS		(120)	(60)	(60)	(60)	.	.	.	.
	ADENOMA; CORTEX	0	1	0	0	0.644	0.377	.	.
		[57]	[37]	[31]	[35]	.	.	.	.
	PHAECHROMOCYTOMA	0	0	0	2	0.047	.	.	0.126
		[57]	[36]	[31]	[35]	.	.	.	.
AORTA		(120)	(60)	(59)	(60)	.	.	.	.
	METASTATIC SARCOMA, site of pr	1	0	0	0	1.000	1.000	1.000	1.000
		[58]	[36]	[31]	[35]	.	.	.	.
BONE MARROW		(119)	(59)	(60)	(59)	.	.	.	.
	HEMANGIOSARCOMA	0	0	1	0	0.415	.	0.331	.
		[57]	[36]	[31]	[35]	.	.	.	.
BRAIN		(120)	(60)	(60)	(60)	.	.	.	.
	MENINGIOMA; MALIGNANT	1	0	0	0	1.000	1.000	1.000	1.000
		[58]	[36]	[31]	[35]	.	.	.	.
COLON		(120)	(59)	(59)	(60)	.	.	.	.
	ADENOCARCINOMA	0	1	0	0	0.644	0.377	.	.
		[57]	[37]	[31]	[35]	.	.	.	.
DUODENUM		(119)	(59)	(58)	(60)	.	.	.	.
	ADENOMA	0	1	0	0	0.642	0.372	.	.
		[57]	[36]	[31]	[35]	.	.	.	.
FORESTOMACH		(120)	(60)	(60)	(60)	.	.	.	.
	MAST CELL TUMOR; BENIGN	0	0	0	1	0.220	.	.	0.357
		[57]	[36]	[31]	[35]	.	.	.	.
HARDERIAN GLAND		(118)	(60)	(60)	(59)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
	ADENOMA	7	1	1	4	0.376	0.978	0.963	0.593
		[58]	[36]	[31]	[35]	.	.	.	.
HEMOLYMPHRET.		(120)	(60)	(60)	(60)	.	.	.	.
	LEUKEMIA; GRANULOCYTIC	1	0	0	0	1.000	1.000	1.000	1.000
		[58]	[36]	[31]	[35]	.	.	.	.
	LYMPHOMA; MALIGNANT	37	23	16	19	0.871	0.371	0.829	0.722
		[65]	[38]	[36]	[40]	.	.	.	.
	SARCOMA; HISTIOCYTIC	9	3	5	4	0.616	0.889	0.529	0.744
	[60]	[37]	[33]	[36]	.	.	.	.	

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=121	Low N=63	Med N=61	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
ILEUM		(120)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
LIVER		(120)	(60)	(59)	(57)	.	.	.	.
	ADENOMA; HEPATOCELLULAR	3	2	2	1	0.697	0.617	0.536	0.834
		[58]	[36]	[31]	[35]	.	.	.	.
LIVER	CARCINOMA+ADENOMA	4	2	3	1	0.768	0.727	0.436	0.895
		[58]	[36]	[31]	[35]	.	.	.	.
	CARCINOMA; HEPATOCELLULAR	1	0	1	0	0.659	1.000	0.561	1.000
LIVER		[57]	[36]	[31]	[35]	.	.	.	.
	HEMANGIOSARCOMA	2	0	0	0	1.000	1.000	1.000	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
LUNGS		(120)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	5	3	5	4	0.325	0.634	0.204	0.413
		[58]	[37]	[32]	[36]	.	.	.	.
LUNGS	ADENOMA; BRONCHIO-ALVEOLAR	9	2	4	6	0.273	0.958	0.682	0.440
		[59]	[37]	[32]	[36]	.	.	.	.
MAMMARY GLAND		(121)	(63)	(61)	(60)	.	.	.	.
	ADENOCARCINOMA+CARCINOMA+ADENO	3	1	1	2	0.403	0.849	0.811	0.589
		[58]	[36]	[32]	[35]	.	.	.	.
MAMMARY GLANDS		(119)	(60)	(60)	(58)	.	.	.	.
	ADENOCARCINOMA	2	0	1	2	0.210	1.000	0.711	0.450
		[58]	[36]	[32]	[35]	.	.	.	.
MAMMARY GLANDS	ADENOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
	CARCINOMA; SQUAMOUS CELL	0	1	0	0	0.642	0.372	.	.
MAMMARY GLANDS		[57]	[36]	[31]	[35]	.	.	.	.
MESENT. LYMPH N		(118)	(57)	(58)	(55)	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[58]	[36]	[31]	[35]	.	.	.	.
OVARIES		(117)	(60)	(60)	(58)	.	.	.	.
	ADENOMA; TUBULOSTROMAL	0	1	0	0	0.644	0.377	.	.
		[57]	[37]	[31]	[35]	.	.	.	.
OVARIES	CYSTADENOMA	3	2	1	0	0.936	0.617	0.804	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
	HEMANGIOMA	1	1	0	1	0.443	0.608	1.000	0.589
OVARIES		[57]	[36]	[31]	[35]	.	.	.	.
	LUTEOMA; BENIGN	1	1	1	2	0.169	0.608	0.554	0.290

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Combined controls, low, medium and high dose groups)**

Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=121	Low N=63	Med N=61	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
		[57]	[36]	[31]	[35]	.	.	.	.
	TUMOR; GRANULOSA CELL; BENIGN	1	0	0	0	1.000	1.000	1.000	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
	TUMOR; SEX CORD STROMAL; MIXED	1	0	2	1	0.276	1.000	0.254	0.589
		[57]	[36]	[31]	[35]	.	.	.	.
	TUMOR GRANULOSA+SEX_CORD&STROM	2	1	2	1	0.513	0.762	0.402	0.738
		[57]	[37]	[31]	[35]	.	.	.	.
PITUITARY GLAND		(119)	(60)	(60)	(59)	.	.	.	.
	ADENOMA; PARS DISTALIS	2	0	2	0	0.738	1.000	0.412	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
SKELETAL MUSCLE		(120)	(60)	(60)	(60)	.	.	.	.
	FIBROSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[58]	[36]	[31]	[35]	.	.	.	.
SKIN		(120)	(60)	(60)	(58)	.	.	.	.
	BASAL CELL TUMOR; BENIGN	0	0	0	1	0.220	.	.	0.357
		[57]	[36]	[31]	[35]	.	.	.	.
	CARCINOMA; SQUAMOUS CELL	0	0	0	1	0.220	.	.	0.357
		[57]	[36]	[31]	[35]	.	.	.	.
	FIBROSARCOMA	0	0	0	2	0.047	.	.	0.126
		[57]	[36]	[31]	[35]	.	.	.	.
	HAIR FOLLICLE TUMOR; BENIGN	1	0	0	0	1.000	1.000	1.000	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
	HISTIOCYTOMA; FIBROUS; MALIGNA	0	0	1	0	0.415	.	0.336	.
		[57]	[36]	[31]	[35]	.	.	.	.
	OSTEOSARCOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[58]	[36]	[31]	[35]	.	.	.	.
	PAPILLOMA+CARCINOMA+HAIR_FOLLI	1	1	0	1	0.443	0.608	1.000	0.589
		[57]	[36]	[31]	[35]	.	.	.	.
	PAPILLOMA; SQUAMOUS CELL	0	1	0	0	0.642	0.372	.	.
		[57]	[36]	[31]	[35]	.	.	.	.
	SARCOMA; Not Otherwise Specifi	0	1	0	0	0.644	0.377	.	.
		[57]	[37]	[31]	[35]	.	.	.	.
SPLEEN		(119)	(60)	(59)	(57)	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	1	0.393	1.000	1.000	0.589
		[57]	[36]	[31]	[35]	.	.	.	.
STOMACH		(120)	(60)	(60)	(60)	.	.	.	.
	ADENOCARCINOMA	1	0	0	0	1.000	1.000	1.000	1.000
		[58]	[36]	[31]	[35]	.	.	.	.
	ADENOMA	0	0	0	1	0.220	.	.	0.357
		[57]	[36]	[31]	[35]	.	.	.	.

**Table 6B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons  
Female Mice (Combined controls, low, medium and high dose groups)**

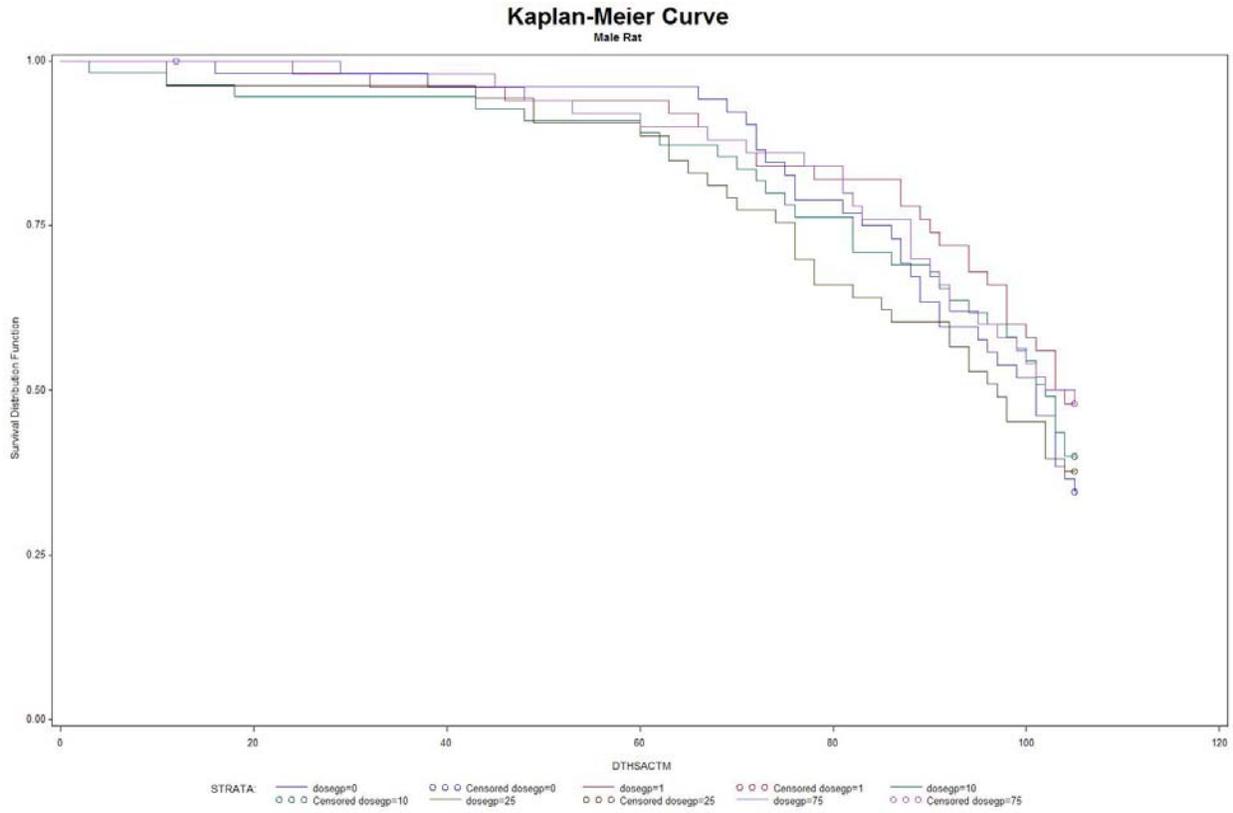
Organ Name	Tumor Name	0 mg	10 mg	25 mg	75 mg	P_Value	P_Value	P_Value	P_Value
		Cont N=121	Low N=63	Med N=61	High N=60	Dos Resp	C vs. L	C vs. M	C vs. H
URINARY BLADDER		(116)	(58)	(60)	(57)	.	.	.	.
	CARCINOMA; TRANSITIONAL CELL	0	0	1	0	0.415	.	0.331	.
		[57]	[36]	[31]	[35]	.	.	.	.
UTERUS		(120)	(60)	(60)	(59)	.	.	.	.
	ADENOCARCINOMA; ENDOMETRIAL	2	0	3	1	0.435	1.000	0.210	0.738
		[58]	[36]	[31]	[35]	.	.	.	.
	FIBROMA	0	0	1	0	0.419	.	0.336	.
		[57]	[36]	[32]	[35]	.	.	.	.
	HEMANGIOMA	2	1	1	0	0.853	0.756	0.704	1.000
		[57]	[36]	[31]	[35]	.	.	.	.
	HEMANGIOSARCOMA	1	0	0	1	0.393	1.000	1.000	0.589
		[57]	[36]	[31]	[35]	.	.	.	.
	LEIOMYOMA	5	3	3	2	0.692	0.623	0.549	0.781
		[58]	[36]	[32]	[35]	.	.	.	.
	LEIOMYOSARCOMA	1	2	0	0	0.865	0.318	1.000	1.000
		[58]	[37]	[31]	[35]	.	.	.	.
POLYP+SARCOMA	7	8	3	7	0.259	0.142	0.698	0.192	
	[58]	[37]	[31]	[36]	.	.	.	.	
POLYP; ENDOMETRIAL STROMAL	6	3	1	5	0.239	0.721	0.945	0.346	
	[58]	[36]	[31]	[35]	.	.	.	.	
SARCOMA; ENDOMETRIAL STROMAL	1	5	2	2	0.415	0.028	0.254	0.290	
	[58]	[37]	[31]	[35]	.	.	.	.	
SCHWANNOMA; BENIGN	0	0	1	0	0.415	.	0.331	.	
	[57]	[36]	[31]	[35]	.	.	.	.	
VAGINA		(120)	(59)	(60)	(57)	.	.	.	.
	CARCINOMA; SQUAMOUS CELL	0	1	0	0	0.642	0.372	.	.
		[57]	[36]	[31]	[35]	.	.	.	.
VAGINA	LEIOMYOMA	1	1	0	0	0.870	0.608	1.000	1.000
	[58]	[36]	[31]	[35]	.	.	.	.	

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

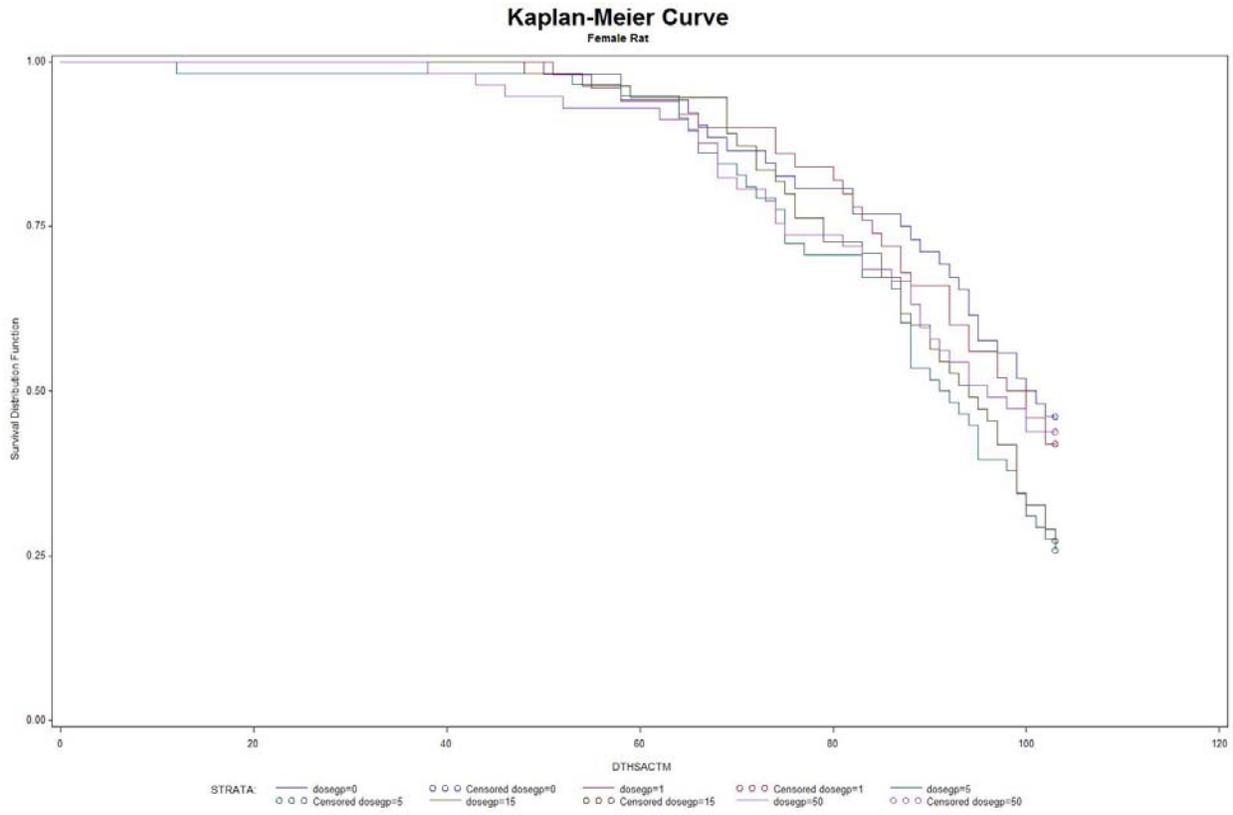
Numbers are the tumor bearing animals

**Figure 1A: Kaplan-Meier Survival Functions for Male Rats**  
Male Rats (two controls, low, medium and high dose groups)



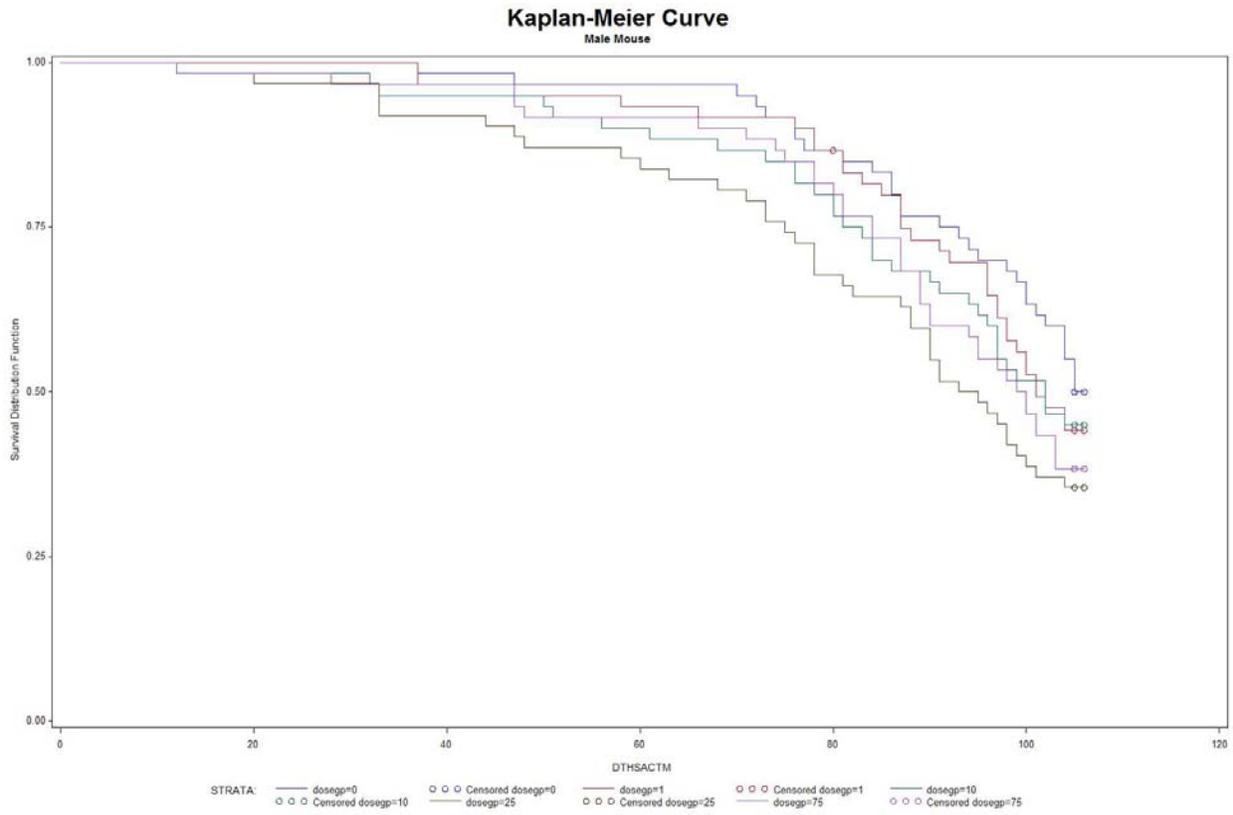
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 1B: Kaplan-Meier Survival Functions for Female Rats**  
Female Rats (two controls, low, medium and high dose groups)



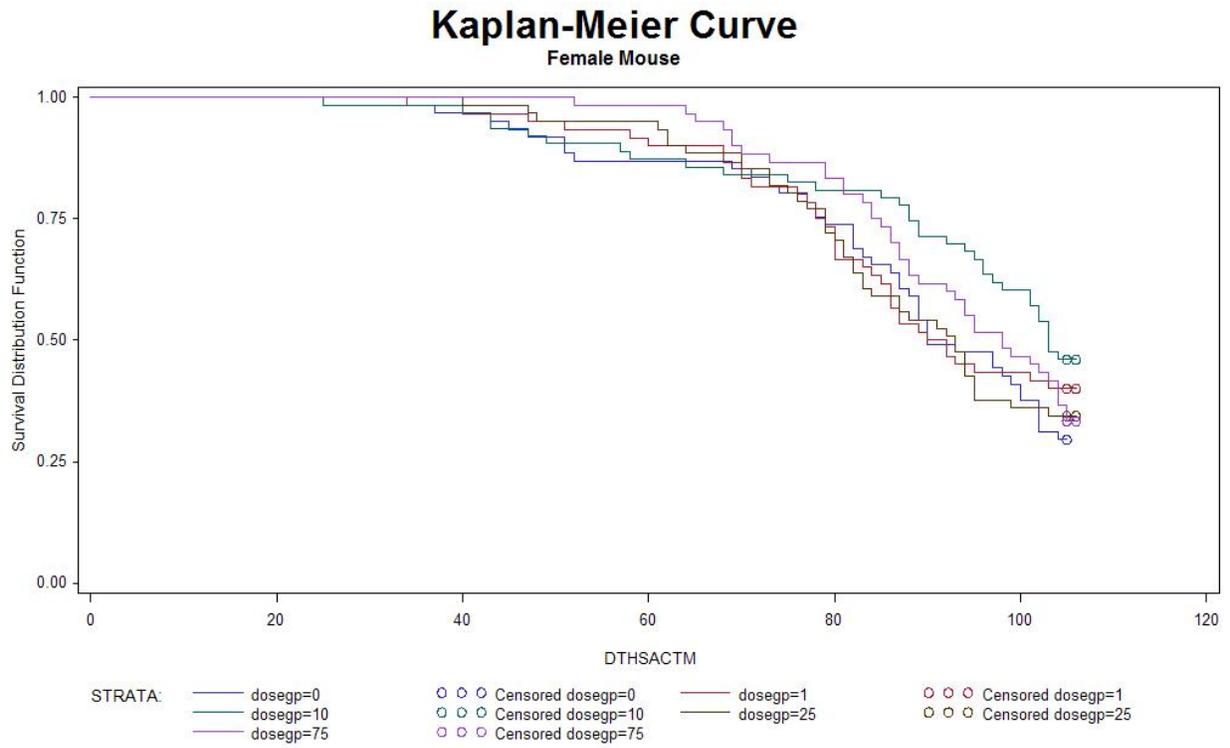
X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2A: Kaplan-Meier Survival Functions for Male Mice**  
Male Mice (two controls, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

**Figure 2B: Kaplan-Meier Survival Functions for Female Mice**  
Female Mice (two controls, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

## 7. References:

1. Bailer AJ, Portier CJ (1988). "Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples." *Biometrics*, 44, 417-431.
2. Bieler, G. S. and Williams, R. L. (1993). "Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity". *Biometrics* 49, 793-801.
3. Cox D. R. (1972) "Regression models and life tables", *Journal of the Royal Statistical Society*, B, 34, 187-220.
4. Gehan (1965) "A generalized Wilcoxon test for comparing arbitrarily singly censored samples", *Biometrika*, 52, 203-223.
5. Haseman, J (1983), "A re-examination of false-positive rates for carcinogenesis studies", *Fundamental and Applied Toxicology*, 3: 334-339.
6. Lin, K.K. and Rahman, M.A. (1998), "Overall false positive rates in tests for linear trend in tumor incidence in animal carcinogenicity studies of new drugs", *Journal of Biopharmaceutical Statistics*, 8(1), 1-15.
7. Rahman, M.A. and Lin, K.K. (2008), "A comparison of False Positive Rates of Peto and Poly-3 Methods for Long-Term Carcinogenicity Data Analysis Using Multiple Comparison Adjustment Method Suggested by Lin and Rahman", *Journal of Biopharmaceutical Statistics*, 18:5, 849-858.
8. Peto, R., M.C. Pike, N.E. Day, R.G. Gray, P.N. Lee, S. Parish, J. Peto, Richards, and J. Wahrendorf (1980), "Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments", Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, *Annex to supplement, World Health Organization, Geneva*, 311-426.
9. Tarone RE (1975), "Test for trend in life table analysis", *Biometrika*, 62: 679-82.
10. U.S. Department of Health and Human Services, "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals", Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, 2001.

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

/s/  
-----

MIN MIN  
04/11/2014

KARL K LIN  
04/14/2014  
Concur with review

## STATISTICS FILING CHECKLIST FOR A NEW NDA

<b>NDA Number:</b> 205494	<b>Applicant:</b> Genzyme Corporation	<b>Stamp Date:</b> SEP 20, 2013
<b>Drug Name:</b> CERDELGA™ (eliglustat)	<b>NDA Type:</b> 505(b)(1) New Molecular Entity (NME) Priority	<b>Indication:</b> The long-term treatment of adult patients with Gaucher Disease Type 1

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

	<b>Content Parameter for RTF</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1	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.	<b>X</b>			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.)		<b>X</b>		There were adequate and complete clinical study reports (CSRs), which were ICH E3 compliant, along with the ISS submitted. There was no full ISE report submitted in Module 5; however a sufficient summary of efficacy is submitted within Module 2.7.3.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).		<b>X</b>		Subgroup analyses for Gender, Race, and Age were not presented for either Phase 3 pivotal/confirmatory clinical studies (i.e. the ENGAGE and ENCORE trials) in this submission. Almost all of the patients in both pivotal trials were white and between the ages of 18 and 65 (i.e., adults), and so subgroup analyses for race and age may provide little information. An information request for a gender subgroup analysis in both trials will be issued (see below).
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	<b>X</b>			All data sets provided were of satisfactory quality and were compliant with CDISC data standards (i.e. SDTM and ADaM). Appropriate data definition files in Define.XML format were included.

## STATISTICS FILING CHECKLIST FOR A NEW NDA

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE?       YES      

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	<b>X</b>			The designs utilized for the ENGAGE and ENCORE trials appeared appropriate.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	<b>X</b>			For the ENGAGE and ENCORE trials, the endpoints and corresponding methods of analysis were pre-specified in the protocols and Statistical Analysis Plans (SAP).
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			<b>X</b>	There was no formal interim analysis planned for either the ENGAGE or ENCORE trials.
Appropriate references for novel statistical methodology (if present) are included.			<b>X</b>	The statistical methodology in the ENGAGE and ENCORE trials did not appear novel hence no references were presented.
Safety data organized to permit analyses across clinical trials in the NDA.	<b>X</b>			Safety datasets were submitted for each study individually. In addition, ISS datasets were also submitted.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	<b>X</b>			The sponsor's investigation of the effect of dropouts on the statistical analyses appeared adequate for the ENGAGE and ENCORE studies.

### Background

On September 20, 2013, the Genzyme Corporation submitted this New Drug Application (NDA) for CERDELGA™ (eliglustat) in accordance with Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and Title 21 of the Code of Federal Regulations, Part 314.50. The active pharmaceutical ingredient (API) of eliglustat (84 mg in capsule form to be administered orally twice per day with or without food) is Genz-112638 which is a water soluble, white to off-white powder. Effective on January 2, 2004, the applicant had initiated clinical development of eliglustat under IND 67,589 in adult patients with Gaucher Disease Type 1 (GD1), which is the proposed indication. Eliglustat has been developed to establish safety and efficacy in this patient population. The applicant obtained *Orphan Designation* from the Office of Orphan Products Development (OOPD) on September 17, 2008.

## STATISTICS FILING CHECKLIST FOR A NEW NDA

Gaucher Disease is a rare lysosomal storage disorder, with prevalence of 1 in 50,000 live births, caused by a deficiency of the enzyme acid- $\beta$ -glucosidase (also known as glucocerebrosidase). This deficiency results in the over-accumulation of glucosylceramide (GL-1), an important component in animal muscle and nerve cell membranes, in tissue macrophages that become engorged and are typically found in the liver, spleen, and bone marrow. As one of a group of inherited sphingolipidoses, Gaucher Disease is a multi-systemic and heterogeneous disorder that is a serious and chronically debilitating condition given the persistent and irreversible morbidity that will develop over time in the majority of patients. The classic manifestations of Gaucher Disease are organomegaly (i.e., organ enlargement), hematological abnormalities, and bone disease. Symptoms specifically for GD1 may begin in early childhood but typically onset later on in life, and they are non-neurological in nature.

Eliglustat is a novel substrate reduction therapy (SRT) and its mechanism of action differs from that of the enzyme replacement therapies (ERTs), which augment acid- $\beta$ -glucosidase activity and are commonly used to treat GD1. Eliglustat is a highly selective and potent inhibitor of glucosylceramide synthase, the enzyme which produces GL-1, and this mechanism of action is hypothesized to reverse the GD1 disease process.

This NDA was submitted electronically in eCTD format via the FDA Electronic Submissions Gateway (ESG). The content, including the electronic data sets and labeling information, is located in the Center for Drug Evaluation and Research (CDER) electronic document room (EDR) at the location: [\\CDSESUB1\evsprod\NDA205494\0000](#).

### **Brief Overview and Summary of Relevant Trials**

This application includes data from four clinical safety and efficacy studies. The clinical efficacy and safety of eliglustat has been primarily evaluated in two pivotal trials. Study GZGD02507 (ENGAGE) is a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study in treatment naïve GD1 patients. Study GZGD02607 (ENCORE) is a phase 3, multinational, multicenter, randomized, open-label, active-controlled, parallel group study in GD1 patients previously treated with Cerezyme ERT. A parallel dose group phase 3 study, GZGD03109 (EDGE), and an open-label proof-of-concept phase 2 study, GZGD00304 also provided supportive data.

For the ENGAGE and ENCORE studies, the clinical/tabulation datasets were compliant to the CDISC/SDTM v.3.1.2 implementation guide standard, and the analysis datasets were compliant to the CDISC/ADaM v.1.0 implementation guide standard. Adequate data definition files (in define.xml and define.pdf formats), a reviewer's guide and software code (.txt, .sas, and .pdf formats in triplicate) were also submitted for each pivotal study.

The following table presents some information on the two pivotal clinical trials ENGAGE and ENCORE contained in this submission.

## STATISTICS FILING CHECKLIST FOR A NEW NDA

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
Safety and Efficacy; Phase 3	GZGD02507 (ENGAGE)	To confirm the efficacy and safety of eliglustat after 39 weeks of treatment in treatment naïve patients with GD1	Multinational, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group	Eliglustat; 50 mg and 100 mg BID;  Capsules administered orally	Total: 40	GD1	39 weeks
Safety and Efficacy; Phase 3	GZGD02607 (ENCORE)	To demonstrate that, in patients with GD1 who have been stabilized with Cerezyme, the majority of patients who receive eliglustat remain stable after 39 weeks of treatment	Multinational, Multicenter, Randomized, Open-label, Active-controlled, Parallel group	Eliglustat; 50 mg, 100 mg, and 150 mg BID;  Capsules administered orally	Total: 160	GD1	52 weeks

### Review Issues

There are no review issues identified at this time. However, there is one statistical information request to the Applicant for the 74-day letter as follows: For both studies GZGD02507 (ENGAGE) and GZGD02607 (ENCORE), provide the subgroup efficacy analysis by gender for the primary and key secondary endpoints.

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

/s/  
-----

BEHRANG VALI  
11/06/2013

FREDA COONER  
11/06/2013