CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study
Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1

(ENGAGE)

Protocol Number: GZGD02507
EudraCT: 2008-005222-37
31 March 2009
Amendment 1: 21 May 2009
Amendment 2 (United Kingdom): 22 July 2009
Amendment 3: 25 February 2010
Amendment 4: 10 November 2010
Amendment 5: 12 July 2011
Amendment 6: 27 March 2012
Amendment 7: 05 February 2013

This protocol was designed and will be conducted, recorded, and reported in accordance with the principles of Good Clinical Practice (GCP) as stated in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national or international laws.

I have read and agree to abide by the requirements of this clinical trial as described in the study protocol.

Investigator Signature     Date
The following has reviewed and approved this protocol entitled: “A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1,” Protocol Number: GZGD02507; EudraCT: 2008-005222-37, Amendment 7 Final: 05 February 2013.
1. SYNOPSIS

NAME OF COMPANY
Genzyme Corporation
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Cambridge, MA 02142
USA
Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands

NAME OF FINISHED PRODUCT

NAME OF ACTIVE INGREDIENT
Genz-112638

SUMMARY TABLE
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TITLE:
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study Confirming the Efficacy and Safety of Genz-112638 in Patients with Gaucher Disease Type 1 (ENGAGE)

PROTOCOL NO.: GZGD02507

INVESTIGATOR STUDY CENTERS:
Approximately 30 study sites worldwide will participate in this study.

OBJECTIVES:
The primary objective of this study is to confirm the efficacy and safety of Genz-112638 (USAN: eliglustat tartrate) after 39 weeks of treatment in patients with Gaucher disease type 1.

The secondary objective of this study is to determine the long-term efficacy, safety, and pharmacokinetics (PK) of Genz-112638 in patients with Gaucher disease type 1.

METHODOLOGY:
This Phase 3 study, ENGAGE, will consist of 2 periods: The Double-Blind Primary Analysis Period (Day 1 to Week 39) and the Open-Label Period (post-Week 39 [Day 1 of the Open-Label Period] through study completion).

The Double-Blind Primary Analysis Period will include 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) provides informed consent, the patient will undergo Screening assessments and, if all eligibility criteria are met, the patient will be randomized to receive Genz-112638 or placebo for 39 weeks. After Week 39 assessments are completed, each patient will enter the Open-Label Period where all patients will receive Genz-112638 from post-Week 39 (Day 1 of the Open-Label Period) through study completion. The Open-Label Period will include a dose-adjustment period (post-Week 39 to Week 47), a long-term treatment period (Week 48 through study completion which includes a safety follow-up period [30 to 37 days after the patient’s last dose of treatment]).

In order to achieve balance between the treatment groups, all patients will be stratified based on their spleen volume (in multiples of normal [MN]) into 1 of 2 groups. The patients within a given group will then be randomized in a 1:1 ratio to receive either Genz-112638 or placebo.

The 2 groups are as follows:
- Group 1: Low severity spleen volume (≤ 20MN)
- Group 2: High severity spleen volume (> 20 MN)

NUMBER OF PATIENTS:
Allowing for a drop-out rate of 20%, approximately 36 male and female patients will be randomized in this study in a 1:1 ratio to receive Genz-112638 or placebo in order to yield at least 28 evaluable patients at the end of the Double-Blind Primary Analysis Period (39 weeks). This sample size assumes a 25% decrease in spleen volume in MN for Genz-112638 and a 5% decrease in spleen volume in MN for placebo at 39 weeks. This sample size
INCLUSION AND EXCLUSION CRITERIA:

Patients must meet all of the following inclusion criteria in order to participate in this study:

1. The patient (and/or their parent/legal guardian) is willing and able to provide signed informed consent prior to any study-related procedures to be performed.
2. The patient is at least 16 years old at the time of randomization.
3. The patient’s Tanner Stage should be ≥ 4 prior to randomization.
4. The patient has a diagnosis of Gaucher disease type 1 confirmed by a documented deficiency of acid β-glucosidase activity by enzyme assay.
5. The patient has the following symptoms of Gaucher disease during the Screening period:
   A. At least one of the following laboratory abnormalities:
      1. Hemoglobin level of 8.0 to 11.0 g/dL if female or 8.0 to 12.0 g/dL if male (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
      2. Platelet count of 50,000 to 130,000/mm³ (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
   B. Splenomegaly (spleen volume of 6 to 30MN).
   C. If hepatomegaly is present, the liver volume must be < 2.5MN.
6. The patient consents to provide a blood sample to Genzyme for genotyping for Gaucher disease, chitotriosidase, and cytochrome P450 2D6 (CYP2D6, to categorize the patient’s predicted rate of metabolism), unless the patient’s genotypes for Gaucher disease, chitotriosidase, and CYP2D6 are already available.
7. Female patients of childbearing potential must have a documented negative pregnancy test prior to randomization. In addition, all female patients of childbearing potential must use a medically accepted form of contraception throughout the study (either a barrier method or hormonal contraceptive with ethinyl estradiol and norethindrone or similar active components).
8. The patient is willing to abstain from consumption of grapefruit, grapefruit juice, or grapefruit products for 72 hours prior to administration of the first dose of study medication and throughout the duration of the Double-Blind Primary Analysis Period.

Patients will be excluded from participation in this study if they meet any of the following exclusion criteria:

1. The patient has had a partial or total splenectomy.
2. The patient has received substrate reduction therapies for Gaucher disease within 6 months prior to randomization.
3. The patient has received enzyme replacement therapy for Gaucher disease within 9 months prior to randomization.
4. The patient has any evidence of neurologic (e.g., peripheral neuropathy, tremor, seizures, Parkinsonism, or cognitive impairment) or pulmonary involvement (e.g., pulmonary hypertension) as related to Gaucher disease.
5. The patient has current symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathologic fracture, or has had a bone crisis in the 12 months prior to randomization.
6. The patient is transfusion-dependent.
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7. The patient has the following laboratory abnormalities during the Screening period:
   A. Hemoglobin level < 8 g/dL (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
   B. Platelet count of < 50,000/mm³ (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).

8. The patient has documented anemia due to causes other than Gaucher disease that requires treatment not yet initiated or not yet stable under treatment for at least 3 months (e.g., iron, vitamin B-12, and/or folate deficiency) prior to randomization.

9. The patient has documented thalassemia minor or sickle cell trait with a platelet count of < 50,000 or > 130,000/mm³.

10. The patient has ever had any radiation treatment in the abdominal region.

11. The patient has documented prior esophageal varices or liver infarction or current liver enzymes (alanine aminotransferase [ALT] / aspartate aminotransferase [AST]) or total bilirubin > 2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.

12. The patient has any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic (e.g. hypokalemia, hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses that may preclude participation in the study.

13. The patient is known to have any of the following: Clinically significant coronary artery disease including history of myocardial infarction [MI] or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2nd or 3rd degree atrioventricular (AV) block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia (VT).

14. The patient has tested positive for the human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen.

15. The patient has received an investigational product within 30 days prior to randomization.

16. The patient is scheduled for in-patient hospitalization, including elective surgery, during the study.

17. The patient has a history of cancer within 5 years of randomization, with the exception of basal cell carcinoma.

18. The patient is pregnant or lactating.

19. The patient has received any medication that may cause QTc interval prolongation within 30 days prior to randomization.

20. The patient has received (acute or chronic) treatment with a cytochrome P450 3A4 (CYP3A4) inducer within 30 days prior to randomization.

21. The patient is not a CYP2D6 poor metabolizer or is an indeterminate metabolizer with one allele identified as active, and has received any medication that is a strong inhibitor of CYP3A4 or CYP2D6 within 30 days prior to randomization, except where a patient has been receiving chronic treatment with either a strong inhibitor of CYP3A4 or a strong inhibitor of CYP2D6 (but not both medications) for at least 30 days prior to randomization and plans to continue on the same dosing regimen during the Double-Blind Primary Analysis Period.

22. The patient is a CYP2D6 poor metabolizer or an indeterminate metabolizer with neither allele known to be active and has received (acute or chronic) treatment with a strong inhibitor of CYP3A4 within 30 days prior to randomization.
### DOSE/ROUTE/REGIMEN:

Genz-112638 and placebo capsules will be supplied as 50, 100 mg, and 150 mg capsules. The 150 mg capsules will be made available to the sites only for dispensing to patients who have completed the Double-Blind Primary Analysis Period. All doses of Genz-112638 and placebo will be taken orally with water.

### DOUBLE-BLIND PRIMARY ANALYSIS PERIOD:

At Screening, during the Double-Blind Primary Analysis Period, patients will be randomized (once a patient meets all of eligibility criteria) in a 1:1 ratio to receive either Genz-112638 or placebo.

On Day 1 of the Double-Blind Primary Analysis Period, patients randomized to receive Genz-112638 will receive 50 mg of Genz-112638 (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule) at the study site. Patients randomized to receive placebo will receive matching placebo capsules (one 50 mg placebo capsule and one 100 mg placebo capsule) at the study site. Patients will only receive the morning dose of Genz-112638 or placebo on Day 1. The Investigator and the Genzyme Investigational Team will remain blinded to PK data.

Twice daily (BID) dosing will begin on Day 2. Patients randomized to receive placebo will receive matching placebo capsules BID (provided as one 50 mg placebo capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 39. Patients randomized to receive Genz-112638 will receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 4. For patients randomized to receive Genz-112638, dose-adjustments will occur based on plasma trough and 2-hour (peak) concentrations of Genz-99067 collected during the Week 2 PK. For patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL, the treatment dose will be increased at Week 4 to 100 mg of Genz-112638 BID (provided as one 100 mg Genz-112638 capsule and one 50 mg placebo capsule per dose) for the remainder of the Double-Blind Primary Analysis Period. Patients who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL will continue to receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule per dose) for the remainder of the Double-Blind Primary Analysis Period. For patients who have a peak Genz-99067 plasma concentration of ≥150 ng/mL at any time, follow the dosing scheme at the bottom of this section.

During the Double-Blind Primary Analysis Period, the patient, Investigator, and the Genzyme Investigational Team will be blinded to the identity of the placebo or Genz-112638 capsules; the Investigator and the Genzyme Investigational Team will also be blinded to the PK data. Genzyme Clinical Pharmacy Research Services will remain unblinded throughout the study in order to provide the appropriate investigational product to patients. A pharmacokineticist consultant outside the Genzyme Investigational Team will receive reports of Genz-99067 plasma concentrations. The appropriate drug kits will be assigned to each patient by Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) according to treatment randomization and dose-adjustment PK results provided by the Central Laboratory. **Note:** The Primary Analysis Period will not be unblinded until all patients have completed the Double-Blind Primary Analysis Period.

If at any time during the Double-Blind Primary Analysis Period, the patient has a Genz-99067 plasma peak concentration ≥150 ng/mL (as reported to the pharmacokineticist consultant), the patient will be asked to temporarily stop dosing and return to the study site. The patient will undergo end-of-blinded treatment assessments, and may be allowed to start the Open-Label Period.
The investigator will verify that the blinded treatment was taken appropriately, assess concomitant medications (defined as all prescription and non-prescription medications, including herbal supplements) for potential to interact with Genz-112638, and determine whether concomitant medications can be discontinued or non-interacting alternatives are available. Depending on conditions present with the peak concentration as described below, further actions taken will be as follows:

- A concurrent related adverse event (AE), cardiac concern, or medical event of interest (MEOI) or Genz-99067 peak concentration ≥250 ng/mL:
  - Conduct end-of-Blinded Period assessments. Patient may continue on open-label treatment in the Open-Label Period.
  - Collect a single electrocardiogram (ECG), conduct 24-hour Holter, and collect blood chemistry.
  - Reintroduce Genz-112638 open-label, at 50 mg once daily (QD).
  - At reintroduction, conduct ECGs at 0, 1, 2, 3, and 4 hours, and PK samples at pre-dose and 2 hours post-dose.
  - After 2 weeks, collect a 24-hour PK profile at the following timepoints: Pre-dose (a.m. at 0 hours) and at 1, 2, 3, 4, 6, 8, and 24 hours post-dose.
  - The lowest dose allowed in the study is 50 mg QD. If the peak concentration remains ≥150 ng/mL, the patients should be discontinued from treatment if no adjustments to concomitant medications or other factors can be made.

- No concurrent related AEs, cardiac concern, or MEOI, and concentration ≤250 ng/mL:
  - Conduct end-of-Blinded Period assessments. Patient may continue on open-label treatment in the Open-Label Period.
  - No cardiac assessments are required.
  - Reintroduce Genz-112638 open-label, at 50 mg BID if interacting concomitant medications can be changed. Otherwise, reintroduce open-label at 50 mg QD.
  - After 2 weeks, collect PK samples at pre-dose and 2 hours post-dose at a minimum (for patients on 50 mg QD, collect 24-hour PK as described for this dose level in Pharmacokinetics below).
  - Decrease dose as necessary, if the peak concentration remains ≥150 ng/mL. (The lowest dose allowed in the study is 50 mg QD.)

Note: Although the treatment assignment will at this time be assumed to be Genz-112638 and not placebo, the dose the patient took for the Double-Blind Primary Analysis Period will remain unknown. Therefore, all patients must, at least temporarily, receive doses as outlined above. A dose increase after these steps have been taken may be allowed, after examination of the patients’ data and in consultation with the Sponsor’s Medical Monitor and Global Safety Officer.

OPEN-LABEL PERIOD:
After all Week 39 study assessments have been completed, patients will enter the Open-Label Period. On Day 1 of the Open-Label Period, all patients will begin BID dosing and will receive their morning dose of 50 mg of
Genz-112638 (provided as one 50 mg Genz-112638 capsule) at the study site to allow for blood sample collection at the scheduled post-dose time points for 4-hour PK analysis. All patients will receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule per dose) until Week 43.

Dose-adjustments during the Open-Label Period will occur based on plasma trough and peak concentrations of Genz-99067 collected during the Week 41 and Week 45 PK. For patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL at Week 41, the treatment dose will be increased at Week 43 to 100 mg of Genz-112638 BID (provided as one 100 mg Genz-112638 capsule per dose). Patients who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL at Week 41 will continue to receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule per dose) until Week 47. Plasma trough and peak concentrations of Genz-99067 will be collected for all patients during Week 45. For patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL at Week 45, the Genz-112638 dose will be increased at Week 47 either from 50 mg to 100 mg of Genz-112638 BID or from 100 mg to 150 mg of Genz-112638 BID for the remainder of the Open-Label Period. Patients receiving 50 mg or 100 mg of Genz-112638 who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL at Week 45 will continue to receive 50 mg or 100 mg of Genz-112638 BID for the remainder of the Open-Label Period. During the Open-Label Period, patients will return to the study site at Weeks 41, 43, 45, 47, and 52, and every 3 months thereafter until study completion. For patients who have a peak Genz-99067 plasma concentration of ≥ 150 ng/mL at any time, follow the dosing scheme below.

If at any time during the Open-Label Period, the patient has a Genz-99067 plasma peak concentration ≥ 150 ng/mL, the patient will be asked to temporarily stop dosing and return to the study site. The investigator will verify that the study drug doses were taken appropriately, assess concomitant medications for potential to interact with Genz-112638, and determine whether concomitant medications can be discontinued or non-interacting alternatives are available. Depending on conditions present with the peak concentration as described below, further actions taken will be as follows:

- A concurrent related adverse event (AE), cardiac concern, or MEOI or Genz-99067 peak concentration > 250 ng/mL:
  - Collect a single ECG, conduct Holter analysis, and collect blood chemistry.
  - Reintroduce Genz-112638 at 50 mg BID (or 50 mg QD if the patient is already at 50 mg BID; if the patient is on 50 mg QD, temporarily stop dosing).
  - At reintroduction, conduct ECGs at 0, 1, 2, 3, and 4 hours, and PK samples at pre-dose and 2 hours post-dose.
  - After 2 weeks, collect PK samples at pre-dose and 2 hours post-dose at a minimum (for patients on 50 mg QD, collect 24-hour PK as described for this dose level in Pharmacokinetics below).
  - Decrease dose, as necessary, if the peak concentration remains ≥ 150 ng/mL. (The lowest dose allowed in the study is 50 mg QD.)

- No concurrent related AEs, cardiac concern, or MEOI, and concentration ≤ 250 ng/mL:
  - No cardiac assessments are required.
  - Reintroduce Genz-112638 at the current dose if interacting concomitant medications can be
A dose increase after these steps have been taken may be allowed, after examination of the patients’ data and in consultation with the Sponsor’s Medical Monitor and Global Safety Officer.

REFERENCE TREATMENT:
Placebo will be used as the reference treatment in this study. Matching placebo capsules will be identical to the Genz-112638 capsules in size and color.

STUDY DURATION:
Following a 45-day Screening period, each patient will be treated for 39 weeks. After the 39-week Double-Blind Primary Analysis Period, all patients will be treated with Genz-112638 during the Open-Label Period. Each patient’s total duration of participation in this study (including both the Double-Blind and Open-Label Periods) will be at least 130 weeks; each patient may continue participation for a total of up to 6 years.

CRITERIA FOR EVALUATION:
EFFICACY:
The primary efficacy endpoint is the percentage change in spleen volume (in MN) from Baseline to 39 weeks of treatment with Genz-112638 as compared to placebo.

Secondary efficacy endpoints include the following: Absolute changes from Baseline in hemoglobin level (in g/dL), percentage changes from Baseline in liver volume (in MN), and percentage changes from Baseline in platelet count. An additional secondary analysis for patients treated with Genz-112638 will include analyses of within-patient change from Baseline to 39 Weeks for the following: percentage change in spleen volume (MN); absolute change in hemoglobin level (in g/dL), percentage change in liver volume (in MN), and percentage change in platelet count.

Note: If an increase of > 30% in spleen or liver volume, in MN, is observed, the parameter will be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses.

Note: At Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion, 2 assessments of hemoglobin level and platelet count will be obtained and the average will be used in analyses involving the secondary efficacy endpoints. In the event that a patient is missing 1 of the 2 assessments at a particular timepoint, then the single assessment will be used in the analyses.

Tertiary efficacy endpoints include the following: Biomarkers (chemokine CC motif ligand 18 [CCL18] and chitotriosidase); bone disease assessments (X-ray, dual-energy X-ray absorptiometry [DXA], magnetic resonance imaging [MRI], and bone marrow burden score); Gaucher assessments (mobility, bone crisis, and bone pain); and Quality of Life (QOL) questionnaires (Brief Pain Inventory [BPI], Fatigue Severity Scale [FSS], and Short Form-36 [SF-36] Health Survey).
Exploratory efficacy endpoints include Gaucher disease severity score system (DS3) and investigational biomarkers including glucosylceramide (GL-1) assayed from dried blood spots [DBS] on filter paper and from plasma, as well as GM3 ganglioside [GM3], ceramide, sphingomyelin, macrophage inflammatory protein-1 beta (MIP1-β), and lyso-GL-1 (assayed from plasma), and serum biomarkers of bone formation (e.g., bone-specific alkaline phosphatase [BAP]) and bone resorption (e.g., cross-linked C-terminal telopeptide of type I collagen [CTx-I]).

SAFETY:
The safety of Genz-112638 will be assessed by evaluation of standard clinical parameters including adverse events (AEs), serious adverse events (SAEs), concomitant medications, vital signs, physical examinations, neurologic examinations, chest X-rays, bone disease assessments, electrophysiology assessments (including 24-hour Holter monitoring assessments and 12-Lead electrocardiograms [ECGs]), echocardiograms (ECHOs) with Doppler, routine clinical laboratory tests (chemistry, hematology, and urinalysis), and neuropsychological testing by Mini Mental Status Examination (MMSE), and pregnancy testing for female patients of childbearing potential.

Adverse events will be captured from the time the patient (and/or their parent/legal guardian) provides signed informed consent through the safety follow-up period (30 to 37 days after the patient’s last dose of treatment). An independent Data Monitoring Committee (DMC) will oversee safety monitoring in the study.

PHARMACOKINETICS:
All patients will have blood samples collected for PK analyses.

During the Double-Blind Primary Analysis Period, blood samples for PK analyses will be collected at the following timepoints:
- Day 1: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, and 4 hours post-dose.
- Week 2: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 4: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose.
- Week 13: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 26: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 39: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose.

During the dose-adjustment period in the Open-Label Period, blood samples for PK analyses will be collected at the following timepoints:
- Post-Week 39 (Day 1 of the Open-Label Period, blinded): Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, and 4 hours post-dose.
- Week 41: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 43: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose.
- Week 45: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 47: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose for all patients, and also at 0.5, 6, 12, 16, 22, and 24 hours post-dose for patients who qualify for a dose increase to 150 mg BID.
During the treatment period in the Open-Label Period, blood samples for PK analyses will be collected at the following timepoints:
- Weeks 52, 65, 91, 104, 117, and 130, and every 3 months thereafter until study completion: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 78: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose.

Patients receiving a 50-mg QD dose will have a PK profile at least 2 weeks after the start of this dose at the following timepoints: Pre-dose (a.m. at 0 hours) and at 1, 2, 3, 4, 6, 8, and 24 hours post-dose.

If a patient experiences a peak Genz-99067 plasma concentration ≥150 ng/mL, PK samples will be collected as follows:
- If the peak is accompanied by a related AE, a cardiac concern, or an MEOI, or is ≥250 ng/mL, samples will be taken at pre-dose and 2 hours post-dose upon reintroduction of Genz-112638 and at pre-dose and 2 hours post-dose 2 weeks later.
- Otherwise, PK samples will be taken at pre-dose and 2 hours post-dose 2 weeks after reintroduction of Genz-112638.

If a patient initiates chronic treatment with a strong or moderate inhibitor of CYP2D6 or CYP3A4 or chronic treatment with an inducer of CYP3A4, or changes current chronic treatment of these medications (including discontinuation of such medication), during the Open-Label Period (when permitted by protocol), a pre-dose and 1, 2, 3, 4, and 8 hours post dose PK blood samples will be collected at approximately 2 weeks after the start of or change in concomitant treatment.

After Day 1 of the double-blind primary analysis period, dose and time of administration of Genz-112638 will be collected for the 2 days prior to each PK sampling day.

In addition to analyzing the blood samples for Genz-99067, select samples from the serial sampling scheme at each dose level, along with a few trough samples, may be analyzed for metabolites of Genz-99067. This analysis is considered exploratory.

**PHARMACOGENETICS:**
If permitted according to local regulations, blood will be collected for DNA analysis from patients who consent to this component of the clinical study. Refusal to participate will not result in ineligibility for the main part of the clinical study. DNA samples may be used for analysis of candidate genes believed or hypothesized to influence the PK, safety, and/or efficacy of Genz-112638. DNA samples may also be stored for future testing of additional genes that, at a later date, are discovered or found to be associated with the PK or pharmacodynamics (PD) of Genz-112638 or Gaucher’s disease. Genotyping will only be performed if it is believed or hypothesized by Genzyme that such genetic analysis might help clarify issues with the clinical data.
STATISTICAL METHODS:

Note: A clinical study report (CSR) will be produced at the end of the Double-Blind Primary Analysis Period, which will include efficacy, safety, and PK analyses. A final CSR to summarize long-term efficacy, safety, and PK parameters will be produced at study completion, which will include data on all patients in the study for at least 130 weeks.

Efficacy Analyses will be performed on the Intent-to-Treat (ITT) population as well as on a Per Protocol (PP) population. The ITT population will include all patients who receive at least 1 dose of Genz-112638 or placebo. Any patient missing 20% or more of the doses during the Double-Blind Primary Analysis Period will not be included in the PP population. Likewise, ITT patients with major protocol deviations that would be expected to interfere with the assessment of efficacy will not be included the PP population. Major protocol deviations will be prospectively defined in the Statistical Analysis Plan (SAP). The PP population will be determined prior to database lock and unblinding of the study.

Primary Efficacy Analyses
The primary efficacy endpoint is the percentage change in spleen volume (in MN) from Baseline to 39 weeks of treatment with Genz-112638 as compared to placebo. Analysis of Covariance (ANCOVA) will be used to analyze the ITT population. If the percentage change in spleen volume data from Baseline to Week 39 is normally distributed, based on the Shapiro-Wilk test using a 5% level of significance, then ANCOVA will be used to analyze the primary efficacy endpoint. If the percentage change in spleen volume data from Baseline to Week 39 is not normally distributed then the change in spleen volume data will be ranked and the ANCOVA will be performed on the ranked data. In either case, the ANCOVA will include treatment (Genz-112638 vs. placebo) and Baseline spleen severity (the randomization stratification variable).

The statistical tests will be conducted at the 5% level of significance. The assessment of spleen volume prior to randomization will be used as the Baseline assessment. The spleen volume assessment obtained at Week 39 or the last available spleen volume assessment in the case of early withdrawal will be used as the Week 39 assessment. Note: If an increase of > 30% in spleen volume is observed, the parameter will be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses. The PP population analyses of the primary efficacy endpoint will also be conducted in a similar manner. Likewise, as a sensitivity analysis, the subset of the ITT population who complete 39 weeks of treatment and have the Baseline and Week 39 assessment for spleen volume will also be analyzed in a similar manner for the primary efficacy endpoint.

Secondary Efficacy Analyses
For the Double-Blind Primary Analysis Period, there will be 3 secondary efficacy endpoints in the study: (1) the absolute change in hemoglobin levels (in g/dL) from Baseline to Week 39, (2) the percentage change in liver volumes (in MN) from Baseline to Week 39, and (3) the percentage change in platelet counts from Baseline to Week 39. These secondary efficacy endpoints will be analyzed, using ANCOVA in the same manner as described for the primary efficacy endpoint, for the ITT population. Note: If an increase of > 30% in liver volume is observed, the parameter will be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses. When performing the analyses for these 3 secondary efficacy endpoints, a closed-testing procedure will be used. First, the absolute change in hemoglobin levels (in g/dL) from Baseline to
### Week 39 Analysis
Week 39 will be analyzed at the 5% level of significance. If there is a statistically significant Genz-112638 treatment effect for the change in hemoglobin levels, then the percentage change in liver volumes (in MN) from Baseline to Week 39 will be analyzed at the 5% level of significance. If there is a statistically significant Genz-112638 treatment effect for the percentage change in liver volumes (in MN), then the percentage change in platelet counts from Baseline to Week 39 will be analyzed at the 5% level of significance. The PP and ITT completer populations will also be analyzed in a similar manner for the secondary efficacy endpoints.

An additional secondary analysis for patients treated with Genz-112638 will look at the within-patient change from Baseline to Week 39 for these 4 endpoints: percentage change in spleen volume (MN); absolute change in hemoglobin level (in g/dL); percentage change in liver volume (in MN); and percentage change in platelet count. For this analysis, Baseline for the original placebo patients will be the start of the Open-Label Period (Day 1 of the Open-Label Period) and Baseline for the original Genz-112638 patients will be the start of the Double-Blind Primary Analysis Period (Day 1). This will provide a Baseline prior to the start of Genz-112638 treatment. The data from both treatment groups will be aligned based on time on Genz-112638 treatment and changes from Baseline will be summarized. If the within-patient changes on the mentioned endpoints are normally distributed then paired T-test procedure will be used to analyze the ITT population. If the within-patient changes are not normally distributed then Wilcoxon signed-ranks test will be used to analyze the ITT population. The PP population analysis will also be conducted in similar manner. The spleen volume assessment obtained at Week 39 or the last available spleen volume assessment in the case of early withdrawal will be used as the Week 39 assessment. Likewise, the subset of the ITT population who complete 39 weeks of treatment and have the Baseline and Week 39 assessment for spleen volume will also be analyzed in a similar manner. Note: For the original placebo patients, appropriate aligned week assessment will be used for analysis.

### Tertiary and Exploratory Efficacy Analyses
Tertiary efficacy endpoints include the following: Biomarkers (CCL18 and chitotriosidase); bone disease assessments (X-ray, DXA, MRI, and bone marrow burden score); Gaucher assessments (mobility, bone crisis, and bone pain); and QOL questionnaires (BPI, FSS, and SF-36). For the Double-Blind Primary Analysis Period, the continuous tertiary efficacy endpoint parameters and changes (absolute or percentage) in these endpoints will be summarized and analyzed by treatment group as detailed in the SAP. Likewise, any categorical tertiary efficacy endpoint parameters will be summarized and analyzed by treatment groups as detailed in the SAP. The biomarkers will be analyzed using ANCOVA in the same manner as described for the primary efficacy endpoint.

Exploratory efficacy endpoints include Gaucher disease severity score system (DS3) and investigational biomarkers including GL-1 assayed from DBS on filter paper and from plasma, as well as GM3, ceramide, sphingomyelin, MIP1-β, and lyso-GL-1 (assayed from plasma), and serum biomarkers of bone formation (e.g., BAP) and bone resorption (e.g., CTx-I). For the Double-Blind Primary Analysis Period, the continuous exploratory efficacy endpoint parameters and changes (absolute or percentage) in these endpoints will be summarized and analyzed by treatment group as detailed in the SAP. Likewise, any categorical exploratory efficacy endpoint parameters will be summarized and analyzed by treatment groups as detailed in the SAP. GL-1 will be analyzed using ANCOVA in the same manner as described for the primary efficacy endpoint.
Long-term efficacy will be summarized for the various parameters based on patients who remain in the study during the Open-Label Period and who have data at the particular timepoints. Long-term efficacy analysis in the primary, secondary, tertiary, and exploratory continuous parameters will be based upon absolute or percent changes from Baseline (as outlined in the SAP). In the Open-Label Period, Baseline for the original placebo patients will be the start of the Open-Label Period (Day 1 of the Open-Label Period) and Baseline for the original Genz-112638 patients will be the start of the Double-Blind Primary Analysis Period (Day 1). This will provide a Baseline prior to the start of Genz-112638 treatment. The data from both treatment groups will be aligned based on time on Genz-112638 treatment and changes from Baseline will be summarized. Any categorical endpoints will be summarized according to appropriate timepoints.

SAFETY:
Safety analyses will be performed on the safety population defined as all patients who receive at least 1 dose of Genz-112638 or placebo.

For the Double-Blind Primary Analysis Period, safety results will be reported by treatment group. For the Open-Label Period, safety results will also be reported by treatment group as changes from Baseline to study completion, where Baseline refers to start of Genz-112638 treatment.

For the Double-Blind Primary Analysis Period, AEs will be summarized by incidence, preferred term, system organ class (SOC), seriousness, severity and relationship to treatment overall and by treatment group. Concomitant medications will also be summarized by incidence/frequency overall and by treatment group. Both pre-treatment and treatment-emergent AEs will be summarized. Changes from Baseline (start of placebo or Genz-112638 treatment) in vital signs, laboratory assessments (chemistry, hematology, and urinalysis), and ECG assessments will be summarized by treatment group. Electrophysiological assessments will be summarized by treatment group. Neurologic examinations, chest X-rays, bone disease assessments, physical examinations, Holter monitoring, and MMSE, will also be summarized by treatment group for the different timepoints. Likewise, analysis of clinical laboratory tests will be based upon changes from Baseline (mean, median, SD, and range) and shift tables (low [L], normal [N], high [H]) will be summarized by treatment group.

For the Open-Label Period, data from both treatment groups will be aligned based on time on Genz-112638 treatment for all safety parameters. Adverse events will be summarized by incidence, preferred term, SOC, seriousness, severity, and relationship to Genz-112638 and to underlying disease. Concomitant medications will also be summarized by incidence/frequency. Changes from Baseline (start of Genz-112638 treatment) in vital signs, laboratory assessments (chemistry, hematology, and urinalysis), ECG assessments, and ECHOs with Doppler will be summarized. Neurologic examinations, chest X-rays, bone disease assessments, physical examinations, and Holter monitoring will also be summarized for all treated patients for the different timepoints. Likewise, analysis of clinical laboratory tests will be based upon changes from Baseline (mean, median, SD, and range) and shift tables (L, N, H) for all treated patients will be produced.

PHARMACOKINETICS:
Serial plasma concentration time data collected for Genz-99067 will be analyzed using non-compartmental methods for all patients with evaluable data. Actual sample and dosing times will be used for pharmacokinetic analyses. Pharmacokinetic parameters, as data permit, will be reported for individual patients and summarized.
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using descriptive statistics by dose and visit. Trough concentrations will be summarized separately, along with other single time-point plasma concentration data by dose and visit. Exploratory PK-PD analyses may be performed as deemed necessary.

Exploratory metabolite analysis will be performed on select plasma samples. If data permit, pharmacokinetic parameters will be estimated for metabolites using non-compartmental methods. These will be reported for individual subjects and summarized using descriptive statistics.

In addition to non-compartmental analyses or when the data do not lend to a non-compartmental approach, pharmacokinetic data will be analyzed using non-linear mixed-effects modeling approach for population pharmacokinetic analyses. For population PK analyses, data from this clinical study will be pooled with data from other clinical studies with extensive and/or sparse sampling. The population PK analyses will characterize the inter- and intra- subject variability in pharmacokinetic parameters and evaluate the effect of covariates such as, but not limited to, demographics (e.g. age, gender, body weight, race), disease status and CYP2D6 status on oral clearance and volume. Exploratory population PK-PD analyses may also be performed to evaluate and characterize exposure-response relationships.

Raw and derived data will be summarized using descriptive statistics and presented graphically, as appropriate.

PHARMACOGENETICS:
The pharmacogenomics analysis is considered exploratory. The relationship of pharmacogenetic variability of known absorption, distribution, metabolism, excretion (ADME), and transporter, efficacy and/or safety genes will be examined graphically with respect to pharmacokinetics and pharmacodynamics, respectively. If any relationships are apparent, these will be described in the final clinical study report.
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3. ABBREVIATIONS AND TERMS

- β: beta
- AE: adverse event
- ACE: angiotensin-converting enzyme
- ADME: absorption, distribution, metabolism, excretion
- ALP: alkaline phosphatase
- ALT: alanine aminotransferase
- ANCOVA: analysis of covariance
- AST: aspartate aminotransferase
- AV: atrioventricular
- BAP: bone-specific alkaline phosphatase
- BID: twice daily
- BMD: bone mineral density
- BPI: Brief Pain Inventory
- BUN: blood urea nitrogen
- CCL18: chemokine CC motif ligand 18
- CK: creatine kinase
- Cmax: maximum observed concentration
- CSR: clinical study report
- CTx-I: cross-linked C-terminal telopeptide of type I collagen
- CYP2D6: cytochrome P450 2D6
- CYP3A4: cytochrome P450 3A4
- DBS: dried blood spots
- DMC: Data Monitoring Committee
- DS3: Disease Severity Score System
- DXA: dual-energy X-ray absorptiometry
- eCRF: electronic case report form
- ECG: electrocardiogram
- ECHO: echocardiogram
- EDC: electronic data capture
- ERT: enzyme replacement therapy
- FSS: Fatigue Severity Scale
- GI: gastrointestinal
- GCP: Good Clinical Practice
- GGT: gamma glutamyl transpeptidase
- GL-1: glucosylceramide
- H: high
- HCG: human chorionic gonadotropin
- HDL: high-density lipoprotein
- HEENT: head, eyes, ears, nose, and throat
- HIV: human immunodeficiency virus
- HPLC: high-performance liquid chromatography
- IB: Investigator’s Brochure
- ICH: International Conference on Harmonisation
IEC             Independent Ethics Committee  
INR             International Normalized Ratio  
IVRS/IWRS       Interactive Voice Response System/ Interactive Web Response System  
IRB             Institutional Review Board  
ITT             intent-to-treat  
L               low  
LDH             lactate dehydrogenase  
LDL             low-density lipoprotein  
MCH             mean corpuscular hemoglobin  
MCHC            mean corpuscular hemoglobin concentration  
MCV             mean corpuscular volume  
MedDRA          Medical Dictionary for Regulatory Activities  
MEOI            Medical Event of Interest  
MI              myocardial infarction  
MIP1-β          macrophage inflammatory protein-1 beta  
MMA             methylmalonic acid  
MMSE            Mini Mental Status Examination  
MN              multiples of normal  
MRI             magnetic resonance imaging  
N               normal  
PCR             polymerase chain reaction  
P-gp            P-glycoprotein  
PK              pharmacokinetic  
PM              poor metabolizer  
POR             Proof of Receipt  
PP              per protocol  
PT              prothrombin time  
PTT             partial thromboplastin time  
QD              once daily  
QOL             quality of life  
RBC             red blood cell  
SAE             serious adverse event  
SAP             Statistical Analysis Plan  
SD              standard deviation  
SF-36           Short Form-36 Health Survey  
SOC             system organ class  
SOM             Study Operations Manual  
SUSAR           suspected unexpected serious adverse reaction  
TRAP            tartrate-resistant acid phosphatase  
ULN             upper limit of normal  
US              United States  
WBC             white blood cell
4.  INTRODUCTION

Genzyme is developing Genz-112638 (USAN: eliglustat tartrate) as an oral therapy for Gaucher disease type 1. Genz-112638 is a member of a class of glucosylceramide (GL-1) synthase inhibitors that resembles the substrate (ceramide).

Gaucher disease is an autosomal recessive lysosomal glycolipid storage disease that results from a deficiency of acid β-glucosidase. The major natural substrate for this enzyme is GL-1, an intermediate metabolite in the synthesis and catabolism of more complex glycosphingolipids. Gaucher disease is characterized by lysosomal accumulation of GL-1 due to impaired GL-1 hydrolysis secondary to the deficiency of the enzyme acid β-glucosidase. In patients with Gaucher disease, different tissues show increases in GL-1 concentration, leading to the main manifestations of the disease: Anemia, thrombocytopenia, hepatosplenomegaly, skeletal disease, and neurological disease (Beutler, 2001, The Metabolic and Molecular Bases of Inherited Disease; Brady, 1997, Baillieres Clin Haematol.; Charrow, 2000, Arch Intern Med.; Cox, 2001, J Inherit Metab Dis.; Elstein, 2002, Paediatr Drugs.).

The hallmark of Gaucher disease is the presence of lipid-engorged cells derived from the monocyte/macrophage system (Gaucher cell), which show a characteristic histological appearance and are distributed in tissues where macrophages reside (i.e., liver, spleen, lung, and bone marrow). It is believed that the storage material within these Gaucher cells of visceral tissues originates from phagocytosis of the blood cells, while in neurons of the brain, the storage material is believed to originate from endogenous synthesis (Beutler, 2001, The Metabolic and Molecular Bases of Inherited Disease).

Gaucher disease type 1 is rare, with an estimated frequency of 1 in 60,000 births in the general population (Grabowski, 1997, Genet Test.). Although it is panethnic, it is most commonly seen in the Ashkenazi Jewish population. Based on results of gene frequency for the two most common Ashkenazi Jewish mutations, the incidence of Gaucher disease in this population has been estimated to be 1 in 855 births (Beutler, 2001, The Metabolic and Molecular Bases of Inherited Disease).

Gaucher disease type 1 has a broad spectrum of severity (Beutler, 2001, The Metabolic and Molecular Bases of Inherited Disease). Thrombocytopenia is the most common hematological abnormality. Anemia is frequently mild, but occasionally may be quite severe. Some patients with severe visceral enlargement of the spleen and liver have minimal skeletal involvement, while some with severe bone disease have minimal visceral disease. In other patients, visceral involvement and skeletal involvement are approximately equal in severity. The degree and type
of bone involvement is markedly variable; however, loss of bone mass is very common, irrespective of the disease severity.

The accumulation of GL-1 and the more common clinical manifestations of the disease including anemia, thrombocytopenia, hepatosplenomegaly, and bone disease, can be treated by enzyme replacement therapy (ERT) with recombinant acid β-glucosidase (Cerezyme®, Genzyme and VPRIV™, Shire) (Altarescu, 2000, Blood Cells Mol Dis.; Barranger, 2001, J. Inherit. Metab. Dis.; Pastores, 2004, Semin Hematol.; Vellodi, 2001, J Inhert Metab Dis.; Weinreb, 2002, Am J Med; Aerts 2010, Nat Rev Drug Discov.). Taliglucerase (ELELYSOTM, 2012, Protalix Biotherapeutics and Pfizer, Inc.) was approved in the United States on 1 May 2012 as an ERT for the treatment of GD1. An alternative approach under development is the use of substrate reduction using Genz-112638, which acts by partially inhibiting the enzyme GL-1 synthase. The goal of this approach is to reduce the synthesis of the accumulated GL-1 (substrate reduction therapy) to a level where the residual enzyme activity of the mutant acid β-glucosidase, the enzyme deficient in Gaucher disease, can degrade GL-1, thus preventing storage of GL-1.

4.1 Summary of Benefits and Risks

A Phase 2 study (GZGD00304) is ongoing to evaluate the 1 year and long-term (>1 year) efficacy, safety, and pharmacokinetics (PK) of Genz-112638 administered as an oral dose of 50 mg twice daily (BID) or 100 mg BID to patients with Gaucher disease type 1. Data from this study indicate that patients with Gaucher disease type 1 manifest notable improvement in the major clinical manifestations of the disease (i.e., anemia, thrombocytopenia, hepatosplenomegaly, and skeletal manifestations) by 52 weeks and as early as 26 weeks for some clinical endpoints (Lukina, 2010a, Blood). These improvements continued through 2 years of treatment (Lukina, 2010b, Blood). Biomarkers of the disease such as chitotriosidase, chemokine CC motif ligand 18 (CCL18), angiotensin-converting enzyme (ACE), and tartrate-resistant acid phosphatase (TRAP) have also shown improvement during the same time period. Among the exploratory biomarkers, plasma GL-1 normalized after 4 weeks of treatment with Genz-112638.

The most commonly observed drug-related adverse events (AEs) in healthy, normal volunteers exposed to Genz-112638 in Phase 1 clinical trials were abdominal pain, diarrhea or loose stools, nausea and/or vomiting, dizziness or presyncope, and headache. During the multiple-dose Phase 1b trial (GZGD00204), doses of 350 mg BID of Genz-112638 (≥ 3.5 times the maximum Genz-112638 dose used in the Phase 2 study) resulted in more frequent subject withdrawals (5 out of 8 subjects) mainly due to gastrointestinal (GI) drug-related AEs. The maximum
tolerated single dose of Genz-112638 was 20 mg/kg (GZGD00103) and the maximum tolerated repeat dose of Genz-112638 was 200 mg BID (GZGD00204).

Phase 2 study data received to date shows that the doses of 50 mg or 100 mg of Genz-112638 BID were generally well tolerated in the Gaucher disease type 1 patient population. Drug-related AEs have been infrequent, and most commonly involve GI symptoms. All drug-related AEs have been mild.

Based on signals seen in preclinical data, cardiac electrophysiology in humans was monitored closely in Phase 1 and 2 studies. A few subjects and patients had asymptomatic cardiac rhythm changes observed by telemetry that were transient and were assessed as unlikely or possibly related to Genz-112638. The rhythm changes seen in patients were reviewed by independent external electrophysiologists and deemed unlikely related to study drug.

Although not assessed as AEs, concentration-dependent, mild prolongation of the QRS, PR, and QTc intervals on electrocardiograms (ECGs) was observed after high single-dose (≥10 mg/kg) and repeat dose (≥200 mg BID) administration of Genz-112638 in healthy volunteers (GZGD00103 and GZGD00204). Modeling from the single-dose thorough QT/QTc study (GZGD01707) predicts that a concentration of 250 ng/mL Genz-99067 (the free base of the L-tartaric acid salt Genz-112638) would produce a 10 msec increase in QTcF interval. Trends of prolongation of QTc were not observed with repeat dosing of 50 mg Genz-112638 BID in healthy subjects in the multiple-dose Phase 1b trial (GZGD00204) or with repeat dosing of 50 mg or 100 mg Genz-112638 BID in Gaucher type 1 patients in the Phase 2 study (GZGD00304). A small increase in PR interval duration (mean time-averaged increase of up to +7 msec) and an approximately 2-msec increase in QRS interval duration (by timepoint analysis) were detected at doses of 50 mg and 100 mg BID in the Phase 2 study. Caution must be used in administering Genz-112638 to patients with structural heart disease, coronary artery disease, or a predisposition to syncope due to atrioventricular (AV) block. Use of Genz-112638 is contraindicated in patients with predisposition to arrhythmias such as long QT syndrome and second or third degree AV block.
In vitro data indicate that Genz-112638 is metabolized predominantly by cytochrome P450 2D6 (CYP2D6) and cytochrome P450 3A4 (CYP3A4), is an inhibitor of CYP2D6 and is also a substrate for and inhibitor of the p-glycoprotein (P-gp) transporter system.

Regarding the effect of other drugs on Genz-112638, in Phase 1 drug interaction studies, systemic exposure to Genz-99067 increased by 7- to 9-fold following co-administration of Genz-112638 with paroxetine (a strong inhibitor of CYP2D6) and by approximately 4-fold following co-administration of Genz-112638 with ketoconazole (a strong inhibitor of CYP3A4 and P-gp). These increases in Genz-99067 plasma concentrations may be associated with an increased risk of certain drug-related AEs (e.g., GI events). In addition, pharmacokinetic simulations were performed to evaluate the drug-drug interaction with Genz-112638 and moderate CYP inhibitors, fluconazole (CYP3A4) and terbinafine (CYP2D6). The observed effects on systemic exposure to Genz-99067 were qualitatively similar to strong inhibitors however, the magnitude of the effect was smaller. In a Phase 1 drug interaction study with rifampin (a strong inducer of CYP3A4), Genz-99067 systemic exposure was decreased by approximately 90% following repeat oral administration of Genz-112638 with rifampin. This decrease in Genz-112638 exposure may lead to reduced efficacy, and a dose increase of Genz-112638 may be required. Therefore, precautions should be taken if Genz-112638 is co-administered with drugs or substances (e.g., grapefruit, grapefruit juice, or grapefruit products) that share a common metabolic pathway (e.g., CYP2D6 or CYP3A4), or modulate the activity of these enzymes.
Regarding the effect of Genz-112638 on other drugs, a Phase 1 study evaluating the potential for a drug-drug interaction between Genz-112638 and metoprolol, a CYP2D6 substrate, showed increases in metoprolol mean total exposure (AUC_{last}) and mean peak exposure (C_{max}) of approximately 2-fold and 1.5-fold, respectively, compared to the corresponding values after a single dose of metoprolol 50 mg administered alone. Based on these results, Genz-112638 is considered a moderate inhibitor of CYP2D6 and thus may decrease the metabolism of drugs that rely on this enzyme for their clearance. Caution is recommended when Genz-112638 is co-administered with drugs that are mainly metabolized by this enzyme, and that have a narrow therapeutic index, e.g., flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting drugs that are mainly metabolized by CYP2D6, e.g., antidepressants such as desipramine, clomipramine and nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol; refer to the study operations manual (SOM) for a list of additional medications. Consideration should be given to decreasing the dose of CYP2D6 substrates with narrow therapeutic indices when co-administered with Genz-112638. A Phase 1 study evaluating the potential for a drug-drug interaction between Genz-112638 and digoxin, a P-gp substrate, showed increases in digoxin mean total exposure (AUC_{last}) and mean peak exposure (C_{max}) of approximately 49% and 70%, respectively, following co-administration of a single dose of digoxin with BID Genz-112638 compared with a single dose of digoxin administered alone. Based on these results, caution should be used when administering Genz-112638 in combination with P-gp substrates that have narrow therapeutic indices (e.g., digoxin, phenytoin) or drugs that require titration when administered with P-gp inhibitors (e.g., tolvaptan, colchicine); refer to the SOM for a list of additional medications. When co-administering Genz-112638 with such drugs, close monitoring of levels of the P-gp substrate drug (e.g., digoxin) is recommended, and additional monitoring of the patient and reduction of the dose of the P-gp substrate drug may be required.

The reproductive risks of Genz-112638 in humans have not been studied. Studies in rats showed a transient decrease in the amount of viable sperm as well as transient degeneration necrosis of germ cells when Genz-112638 was administered at very high doses (at approximately 100 times higher than the human equivalent received in the ongoing Phase 2 study). Results from the long-term study in non-human primates showed no statistically significant effects on spermatogenesis, sperm motility, morphology, or concentration, or total live sperm. Based on these findings in rats and non-human primates, there is no evidence of a likely significant risk to subjects or patients at the therapeutic doses of Genz-112638 in humans. The safety of Genz-112638 during pregnancy, embryonic or fetal development, and breast-feeding has not been established. As with any new product, Genz-112638 may involve risks to the unborn child that are currently unknown.
The clinical improvements and good tolerability observed in patients with Gaucher disease treated with Genz-112638 to date may not be seen in all treated Gaucher patients.

Refer to the current Investigator’s Brochure (IB) for additional information.

5. **STUDY OBJECTIVES**

The primary objective of this study is to confirm the efficacy and safety of Genz-112638 after 39 weeks of treatment in patients with Gaucher disease type 1.

The secondary objective of this study is to determine the long-term efficacy, safety, and PK of Genz-112638 in patients with Gaucher disease type 1.

6. **INVESTIGATIONAL PLAN**

6.1 **Study Design**

This Phase 3 study, ENGAGE, will consist of 2 periods: The Double-Blind Primary Analysis Period (Day 1 to Week 39) and the Open-Label Period (post-Week 39 [Day 1 of the Open-Label Period] through study completion).

The Double Blind Primary Analysis Period will include 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) provides informed consent, the patient will undergo Screening assessments and, if all of the eligibility criteria are met, the patient will be randomized to receive Genz-112638 or placebo for 39 weeks. After Week 39 assessments are completed, each patient will enter the Open-Label Period where all patients will receive Genz-112638 from post-Week 39 (Day 1 of the Open-Label Period) through study completion. The Open-Label Period will include a dose-adjustment period (post-Week 39 to Week 47), a long-term treatment period (Week 48 through study completion which includes a safety follow-up period [30 to 37 days after the patient’s last dose of treatment]).

In order to achieve balance between the treatment groups, all patients will be stratified into 1 of 2 groups based on their spleen volume (in multiples of normal [MN]). The patients within a given group will then be randomized in a 1:1 ratio to receive either Genz-112638 or placebo.

The 2 groups are as follows:

- **Group 1**: Low severity spleen volume (≤ 20MN)
- **Group 2**: High severity spleen volume (> 20MN)
On Day 1 of the Double-Blind Primary Analysis Period, patients randomized to receive Genz-112638 will receive 50 mg of Genz-112638 (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule) at the study site. Patients randomized to receive placebo will receive matching placebo capsules (one 50 mg placebo capsule and one 100 mg placebo capsule) at the study site. Patients will only receive the morning dose of Genz-112638 or placebo on Day 1. The Investigator and the Genzyme Investigational Team will remain blinded to PK data.

Twice daily (BID) dosing will begin on Day 2. Patients randomized to receive placebo will receive matching placebo capsules BID (provided as one 50 mg placebo capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 39. Patients randomized to receive Genz-112638 will receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 4. For patients randomized to receive Genz-112638, dose-adjustments will occur based on plasma trough and 2-hour (peak) concentrations of Genz-99067 (the free base of the L-tartaric acid salt Genz-112638) collected during the Week 2 PK. For patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL, the treatment dose will be increased at Week 4 to 100 mg of Genz-112638 BID (provided as one 100 mg Genz-112638 capsule and one 50 mg placebo capsule per dose) for the remainder of the Double-Blind Primary Analysis Period. Patients who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL will continue to receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule per dose) for the remainder of the Double-Blind Primary Analysis Period. During the Double-Blind Primary Analysis Period, patients will return to the study site at Weeks 2, 4, 13, 26, and 39.

During the Double-Blind Primary Analysis Period, the patient, Investigator, and the Genzyme Investigational Team will be blinded to the identity of the placebo or Genz-112638 capsules; the Investigator and the Genzyme Investigational Team will also be blinded to the PK data. Genzyme Clinical Pharmacy Research Services will remain unblinded throughout the study in order to provide the appropriate investigational product to patients. A pharmacokineticist consultant outside the Genzyme Investigational Team will receive reports of Genz-99067 plasma concentrations. The appropriate drug kits will be assigned to each patient by Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) according to treatment randomization and dose-adjustment PK results provided by the central laboratory. Note: The Primary Analysis Period will not be unblinded until all patients have completed the Double-Blind Primary Analysis Period.

If at any time during the Double-Blind Primary Analysis Period, a patient has a peak PK of ≥150 ng/mL (as reported to the pharmacokineticist consultant), the patient will stop dosing, will
return to the site for end-of-blinded treatment assessments and other evaluations and a possible
dose decrease (Section 8.1.1), and will be allowed to start the Open-Label Period.

After all Week 39 study assessments have been completed, patients will enter the Open-Label
Period. On Day 1 of the Open-Label Period, all patients will begin BID dosing and will receive
their morning dose of 50 mg of Genz-112638 (provided as one 50 mg Genz-112638 capsule) at
the study site to allow for blood sample collection at the scheduled post-dose time points for
4-hour PK analysis. All patients will receive 50 mg of Genz-112638 BID (provided as one
50 mg Genz-112638 capsule per dose) until Week 43.

Dose-adjustments during the Open-Label Period will occur based on plasma trough and peak
concentrations of Genz-99067 collected during Week 41 and Week 45 PK. For patients who
have a Genz-99067 plasma trough concentration of <5 ng/mL at Week 41, the treatment dose
will be increased at Week 43 to 100 mg of Genz-112638 BID (provided as one 100 mg
Genz-112638 capsule per dose). Patients who have a Genz-99067 plasma trough concentration
of ≥5 ng/mL at Week 41 will continue to receive 50 mg of Genz-112638 BID (provided as one
50 mg Genz-112638 capsule per dose) until Week 47. Plasma trough and peak concentrations of
Genz-99067 will be collected for all patients during Week 45. For patients who have a
Genz-99067 plasma trough concentration of <5 ng/mL at Week 45, the Genz-112638 dose will
be increased at Week 47 either from 50 mg to 100 mg of Genz-112638 BID or from 100 mg to
150 mg of Genz-112638 BID for the remainder of the Open-Label Period. Patients receiving
50 mg or 100 mg of Genz-112638 who have a Genz-99067 plasma trough concentration of
≥5 ng/mL at Week 45 will continue to receive 50 mg or 100 mg of Genz-112638 BID for the
remainder of the Open-Label Period. During the Open-Label Period, patients will return to the
study site at Weeks 41, 43, 45, 47, and 52, and every 3 months thereafter until study completion.
If at any time during the Open-Label Period, the patient has a Genz-99067 plasma peak
concentration of ≥150 ng/mL, the patient will be asked to temporarily stop dosing and return to
the study site for further evaluations and a possible dose decrease (Section 8.1.2).

Following a 45-day Screening period, each patient will be treated for 39 weeks. After the
39-week Double-Blind Primary Analysis Period all patients will be treated with Genz-112638
during the Open-Label Period. Each patient’s total duration of participation in this study
(including both the Double-Blind and Open-Label Periods) will be at least 130 weeks; each
patient may continue participation for a total of up to 6 years.

The primary efficacy endpoint is the percentage change in spleen volume (in MN) from Baseline
to 39 weeks of treatment with Genz-112638 as compared to placebo. Secondary efficacy
endpoints include the following: Absolute changes from Baseline in hemoglobin levels (in g/dL),
percentage changes from Baseline in liver volumes (in MN), and percentage changes from
Baseline in platelet counts. An additional secondary analysis for patients treated with Genz-112638 will include analyses of within-patient change from Baseline to 39 Weeks for the following: percentage change in spleen volume (MN); absolute change in hemoglobin level (in g/dL), percentage change in liver volume (in MN), and percentage change in platelet count.

*Note:* If an increase of > 30% in spleen or liver volume is observed, in MN, the parameter will be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses.

*Note:* At Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion, 2 assessments of hemoglobin level and platelet count will be obtained and the average will be used in analyses involving the secondary efficacy endpoints. In the event that a patient is missing 1 of the 2 assessments at a particular timepoint, then the single assessment will be used in the analyses.

Tertiary efficacy endpoints include the following: Biomarkers (chemokine CC motif ligand 18 [CCL18] and chitotriosidase); bone disease assessments (X-ray, dual-energy X-ray absorptiometry [DXA], magnetic resonance imaging [MRI], and bone marrow burden score); Gaucher assessments (mobility, bone crisis, and bone pain); and Quality of Life (QOL) questionnaires (Brief Pain Inventory [BPI], Fatigue Severity Scale [FSS], and Short Form-36 (SF-36) Health Survey).

Exploratory efficacy endpoints include Gaucher disease severity score system (DS3) and investigational biomarkers including GL-1 assayed from dried blood spots [DBS] on filter paper and from plasma, as well as GM3 ganglioside (GM3), ceramide, sphingomyelin, macrophage inflammatory protein-1 beta (MIP1-β), and lyso-GL-1 (assayed from plasma), and serum biomarkers of bone formation (e.g., bone-specific alkaline phosphatase [BAP]) and bone resorption (e.g., cross-linked C-terminal telopeptide of type I collagen [CTx-I]).

The safety of Genz-112638 will be assessed by evaluation of standard clinical parameters including AEs, serious adverse events (SAEs), concomitant medications, vital signs, physical examinations, neurologic examinations, chest X-rays, bone disease assessments, electrophysiology assessments (including 24-hour Holter monitoring assessments and 12-Lead ECGs), echocardiograms (ECHOs) with Doppler, routine clinical laboratory tests (chemistry, hematology, and urinalysis), neuropsychological testing by Mini Mental Status Examination (MMSE), and pregnancy testing for female patients of childbearing potential.
Figure 6-1: Study Dosing and Pharmacokinetic Timeline

- Day 1: Genz-112638 50 mg BID
  - 4-hour PK

- Wk 2: Genz-112638 50 mg BID
  - Trough and peak

- Wk 4: Genz-112638 50 or 100 mg BID
  - Trough and peak

- Wk 13: Genz-112638 50 mg BID
  - 8-hour PK

- Wk 26: Genz-112638 50 or 100 mg BID
  - 8-hour PK

- Wk 39: Genz-112638 50 mg BID
  - Double-Blind Dose-Adjustment

- Wk 41: Open-Label Dose Adjustment

- Wk 43: Genz-112638 50 mg BID
  - Placebo

- Wk 45: Genz-112638 50 or 100 mg BID
  - Double-Blind Treatment Period**

- Wk 47: Genz-112638 50 or 150 mg BID

- Wk 52: Genz-112638 50 or 100 mg BID

- Wk 54: Genz-112638 50 or 100 mg BID

- Wk 56: Genz-112638 50 or 100 mg BID

- Wk 58: Genz-112638 50 or 100 mg BID

- Wk 60: Genz-112638 50 or 100 mg BID

- Wk 62: Genz-112638 50 or 100 mg BID

- Wk 64: Genz-112638 50 or 100 mg BID

- Wk 66: Genz-112638 50 or 100 mg BID

- Wk 68: Genz-112638 50 or 100 mg BID

- Wk 70: Genz-112638 50 or 100 mg BID

- Wk 72: Genz-112638 50 or 100 mg BID

- Wk 74: Genz-112638 50 or 100 mg BID

- Wk 76: Genz-112638 50 or 100 mg BID

- Wk 78: Genz-112638 50 or 100 mg BID

- Wk 80: Genz-112638 50 or 100 mg BID

- Wk 82: Genz-112638 50 or 100 mg BID

- Wk 84: Genz-112638 50 or 100 mg BID

- Wk 86: Genz-112638 50 or 100 mg BID

- Wk 88: Genz-112638 50 or 100 mg BID

- Wk 90: Genz-112638 50 or 100 mg BID

- Wk 92: Genz-112638 50 or 100 mg BID

- Wk 94: Genz-112638 50 or 100 mg BID

- Wk 96: Genz-112638 50 or 100 mg BID

- Wk 98: Genz-112638 50 or 100 mg BID

- Wk 100: Genz-112638 50 or 100 mg BID

- Wk 102: Genz-112638 50 or 100 mg BID

- Wk 104: Genz-112638 50 or 100 mg BID

- Wk 106: Genz-112638 50 or 100 mg BID

- Wk 108: Genz-112638 50 or 100 mg BID

- Wk 110: Genz-112638 50 or 100 mg BID

- Wk 112: Genz-112638 50 or 100 mg BID

- Wk 114: Genz-112638 50 or 100 mg BID

- Wk 116: Genz-112638 50 or 100 mg BID

- Wk 118: Genz-112638 50 or 100 mg BID

- Every 3 Months§:

** The PK assessments on Day 1 of the Open-Label Period will be blinded. Week 39 +1 Day refers to the first dosing day in the Open-Label Period after all Week 39 assessments have been completed.

** Refer to Section 8.1 for details of Genz—112638 dosing instructions and Section 9.5 for details of the PK timeline.

† If the patient’s trough plasma concentration of Genz-99067 (the free base of the L tartaric acid salt Genz-112638) is < 5 ng/mL at Week 2 during the double-blind treatment period (or Week 41 during the open-label treatment period), then the dose will be increased from 50 mg BID to 100 mg BID; if trough plasma concentration of Genz-99067 is ≥ 5 ng/mL at Week 2 or Week 41, then the dose will not be increased. Peak plasma concentration must be <150 ng/mL.

‡ If the patient’s trough plasma concentration of Genz-99067 is < 5 ng/mL at Week 45 during the open-label treatment period, then the dose will be increased either from 50 mg BID to 100 mg BID or from 100 mg BID to 150 mg BID; if trough plasma concentration of Genz-99067 is ≥ 5 ng/mL at Week 45, then the dose will not be increased. Peak plasma concentration must be <150 ng/mL.

§ Or upon patient discontinuation or withdrawal from the study.
6.2 Discussion of Study Design

The primary objective of this Phase 3 study is to confirm the efficacy and safety of Genz-112638 after 39 weeks of treatment in patients with Gaucher disease type 1. The secondary objective is to determine the long-term efficacy, safety, and PK of Genz-112638 in patients with Gaucher disease type 1.

To effectively achieve the primary objective, a randomized, double-blind, placebo-controlled study design was employed, and the following study design parameters were considered:

1. A randomized, double-blind, placebo-controlled study design was employed in order to confirm the efficacy and safety of Genz-112638 and to minimize the potential for subjective bias. In order to provide meaningful statistical comparisons between treatment and placebo arms, patients will be randomized into these 2 groups.

2. Allowing for a drop-out rate of 20%, approximately 36 male and female patients will be randomized in this study in a 1:1 ratio to receive Genz-112638 or placebo in order to yield at least 28 evaluable patients at the end of the Double-Blind Primary Analysis Period (39 weeks). This sample size assumes a 25% decrease in spleen volume in MN for Genz-112638 and a 5% decrease in spleen volume in MN for placebo at 39 weeks. This sample size also assumes a standard deviation of 15%, a two-sided, two-sample t-test with a 5% level of significance and power of 92%.

3. Genz-112638 exhibits highly variable pharmacokinetics. In this study, all patients will receive a starting dose of 50 mg BID and the dose of Genz-112638 will be escalated to achieve a target trough concentration of at least 5 ng/mL Genz-99067, which is considered to be safe and efficacious based on previous preclinical data and findings from Phase 1 studies and the ongoing Phase 2 study. As in the Phase 2 study, in the Double-Blind Primary Analysis Period of this study the dose may be adjusted to 100 mg BID. In the Open-Label Period, patients may also have an additional dose adjustment to 150 mg BID of Genz-112638 if their trough plasma concentration is < 5 ng/mL at a dose of 100 mg BID. These doses are less than the maximum tolerated repeat dose of 200 mg BID from Phase 1 testing (GZGD00204). Recent data from Phase 3 studies indicate a higher-than-expected level of exposure in certain patients; these patients may benefit from lower doses of Genz-112638; therefore, if a post-dose plasma level of Genz-99067 ≥150 ng/mL is seen, a provision is included for a 50 mg once daily (QD) dose (Section 8.1). Refer to Section 8.5 for further details.

4. Data on the efficacy endpoints chosen in this clinical study will enable Genzyme to confirm the effect of Genz-112638 to reduce GL-1 synthesis, and characterize its efficacious changes
in hematological parameters, organomegaly, and key biomarkers in patients with Gaucher disease type 1. Safety and PK measures (Sections 9.4 and 9.5) were chosen to characterize the exposure/response relationship and any potential toxicity issues. The ECG and PK timepoints chosen for this study are based on data from the Phase 1 studies and a Phase 2 study where maximum observed concentration ($C_{\text{max}}$) was observed from 1 to 4 hours post-dose.

5. Since bone maturation is nearly complete, patients will be allowed to participate in this study if they have reached a Tanner Stage of $\geq 4$ prior to randomization.

6. Medications that are inducers of CYP3A4 or strong inhibitors of CYP2D6 or CYP3A4 are prohibited (with a few exceptions) during the Double-Blind Primary Analysis Period. Medications that are inducers of CYP3A4 or strong or moderate inhibitors of CYP2D6 or CYP3A4 are prohibited (with a few exceptions) during dose adjustment in the Open-Label Treatment Period because these medications have the potential to alter the metabolism of Genz-112638 with resultant effects on either safety or efficacy. After completion of dose adjustment during the Open-Label Treatment Period, strong or moderate inhibitors of CYP2D6 or CYP3A4 may be used chronically in the CYP2D6 non-poor metabolizer patient (a strong or a moderate inhibitor may be used alone but not simultaneously), and strong or moderate inhibitors of CYP2D6 (but not CYP3A4) may be used in CYP2D6 poor metabolizer patients. Refer to Section 8.3 for further details.

7. **PATIENT POPULATION AND SELECTION**

Approximately 30 study sites worldwide will participate in this study.

7.1 **Inclusion Criteria**

Patients must meet all of the following inclusion criteria in order to participate in this study:

1. The patient (and/or their parent/legal guardian) is willing and able to provide signed informed consent prior to any study-related procedures to be performed.

2. The patient is at least 16 years old at the time of randomization.

3. The patient’s Tanner Stage should be $\geq 4$ prior to randomization.

4. The patient has a diagnosis of Gaucher disease type 1 confirmed by a documented deficiency of acid β-glucosidase activity by enzyme assay.
5. The patient has the following symptoms of Gaucher disease during the Screening period:

   A. At least one of the following laboratory abnormalities:

      1. Hemoglobin level of 8.0 to 11.0 g/dL if female or 8.0 to 12.0 g/dL if male
         (the mean of 2 measurements from separate blood samples collected at least
         24 hours apart during Screening).

      2. Platelet count of 50,000 to 130,000/mm³ (the mean of 2 measurements from
         separate blood samples collected at least 24 hours apart during Screening).

   B. Splenomegaly (spleen volume of 6 to 30 MN).

   C. If hepatomegaly is present, the liver volume must be < 2.5MN.

6. The patient consents to provide a blood sample to Genzyme for genotyping for Gaucher
   disease, chitotriosidase, and CYP2D6 (to categorize the patient’s predicted rate of
   metabolism), unless the patient’s genotypes for Gaucher disease, chitotriosidase, and
   CYP2D6 are already available.

7. Female patients of childbearing potential must have a documented negative pregnancy test
   prior to randomization. In addition, all female patients of childbearing potential must use a
   medically accepted form of contraception throughout the study (either a barrier method or
   hormonal contraceptive with ethinyl estradiol and norethindrone or similar active
   components).

8. The patient is willing to abstain from consumption of grapefruit, grapefruit juice, or
   grapefruit products for 72 hours prior to administration of the first dose of study medication
   and throughout the duration of the Double-Blind Primary Analysis Period.

Procedures for the evaluation of study inclusion criteria are described in the SOM.

7.2 Exclusion Criteria

Patients will be excluded from participation in this study if they meet any of the following
exclusion criteria:

   1. The patient has had a partial or total splenectomy.

   2. The patient has received substrate reduction therapies for Gaucher disease within 6
      months prior to randomization.

   3. The patient has received enzyme replacement therapy for Gaucher disease within
      9 months prior to randomization.
4. The patient has any evidence of neurologic (e.g., peripheral neuropathy, tremor, seizures, Parkinsonism, or cognitive impairment) or pulmonary involvement (e.g., pulmonary hypertension) as related to Gaucher disease.

5. The patient has current symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathologic fracture, or has had a bone crisis in the 12 months prior to randomization.

6. The patient is transfusion-dependent.

7. The patient has the following laboratory abnormalities during the Screening period:
   A. Hemoglobin level < 8 g/dL (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).
   B. Platelet count of < 50,000/mm$^3$ (the mean of 2 measurements from separate blood samples collected at least 24 hours apart during Screening).

8. The patient has documented anemia due to causes other than Gaucher disease that requires treatment not yet initiated or not yet stable under treatment for at least 3 months (e.g., iron, vitamin B-12, and/or folate deficiency) prior to randomization.

9. The patient has documented thalassemia minor or sickle cell trait with a platelet count of < 50,000 or >130,000/mm$^3$.

10. The patient has ever had any radiation treatment in the abdominal region.

11. The patient has documented prior esophageal varices or liver infarction or current liver enzymes (alanine aminotransferase [ALT]/ aspartate aminotransferase [AST]) or total bilirubin >2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.

12. The patient has any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, GI, pulmonary, neurologic, endocrine, metabolic (e.g., hypokalemia, hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses that may preclude participation in the study.

13. The patient is known to have any of the following: Clinically significant coronary artery disease including history of myocardial infarction [MI] or ongoing signs or symptoms consistent with cardiac ischemia or heart failure; or clinically significant arrhythmias or conduction defect such as 2nd or 3rd degree AV block, complete bundle branch block, prolonged QTc interval, or sustained ventricular tachycardia (VT).
14. The patient has tested positive for the human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen.

15. The patient has received an investigational product within 30 days prior to randomization.

16. The patient is scheduled for in-patient hospitalization, including elective surgery, during the study.

17. The patient has a history of cancer within 5 years of randomization, with the exception of basal cell carcinoma.

18. The patient is pregnant or lactating.

19. The patient has received any medication that may cause QTc interval prolongation within 30 days prior to randomization.

20. The patient has received (acute or chronic) treatment with a CYP3A4 inducer within 30 days prior to randomization.

21. The patient is not a CYP2D6 poor metabolizer or is an indeterminate metabolizer with one allele identified as active, and has received any medication that is a strong inhibitor of CYP3A4 or CYP2D6 within 30 days prior to randomization, except where a patient has been receiving chronic treatment with either a strong inhibitor of CYP3A4 or a strong inhibitor of CYP2D6 (but not both medications) for at least 30 days prior to randomization and plans to continue on the same dosing regimen during the Double-Blind Primary Analysis Period.

22. The patient is a CYP2D6 poor metabolizer or an indeterminate metabolizer with neither allele known to be active and has received (acute or chronic) treatment with a strong inhibitor of CYP3A4 within 30 days prior to randomization.

Procedures for the evaluation of study exclusion criteria are described in the SOM.
7.3 Patient Discontinuation/Withdrawal Criteria

Patients are free to discontinue participation or withdraw consent from the study at any time, for any reason, and without prejudice to further treatment. Patients who discontinue/withdraw from this study will receive treatment as deemed appropriate by their treating physician.

A patient's participation in the study also may be discontinued at any time at the discretion of the Investigator or Genzyme. The Investigator will contact Genzyme’s Medical Monitor if a patient meets any of the withdrawal criteria. The following may be justifiable reasons for the Investigator or Genzyme to remove a patient from the study:

- The patient was erroneously included in the study.
- The patient is uncooperative, including failure to appear at one or more study visits, or is not compliant with taking study medication.
- The patient develops an exclusion criterion or concurrent disease.
- The patient receives other investigational product(s) during the course of this study.
- The patient experiences an AE that is considered intolerable by the patient or investigator.
- Genzyme terminates the study.
- A patient must be withdrawn from the study if she becomes pregnant at any point during the study.

If a patient meets at least 1 of the following criteria, the Investigator must notify the Genzyme Medical Monitor. The Investigator, Genzyme, and a Data Monitoring Committee (DMC) will review the clinical status of the patient and will determine if the patient will be withdrawn from the study.

- The patient’s hemoglobin level falls below 7 g/dL and remains below 7 g/dL when hematology laboratory testing is repeated within approximately 2 weeks.
- The patient’s platelet count falls below 30,000/mm³ and remains below 30,000/mm³ when hematology laboratory testing is repeated within approximately 2 weeks, or if the patient experiences a clinically significant bleeding episode assessed by the Investigator as related to a low platelet count.
- A decline in the patient’s Gaucher disease status which, in the opinion of the Investigator, warrants discontinuation from the study (e.g., repeated bone crises).
If a patient discontinues or withdraws from participation in the study, they will be contacted in order to obtain information about the reason(s) for discontinuation/withdrawal and for collection of any potential AEs. The patient will be asked to return to the clinic as an attempt to complete all study discontinuation/withdrawal assessments. The Investigator will provide a written report on the Completion/Discontinuation section of the patient’s electronic case report form (eCRF) describing the reason for discontinuation. Patients who discontinue/withdraw participation from the study will not be replaced.

For further details regarding reporting AEs, refer to Section 9.4.11.

7.4 Patient Screening Log

Each study site will be instructed to maintain a log of each patient considered for the study, including patients who are not randomized in the study. For all patients screened, the following will be recorded:

- The dates of Screening,
- Patient initials,
- The reason for not randomizing the patient into the study, if applicable,
- The date of consent, and
- The patient identification number.

8. TREATMENTS

8.1 Treatments Administered

There are 2 treatment phases for this study: The Double-Blind Primary Analysis Period and the Open-Label Period.

During the Double-Blind Primary Analysis Period, the patient, Investigator, and the Genzyme Investigational Team will be blinded to the identity of the placebo or Genz-112638 capsules; the Investigator and the Genzyme Investigational Team will also be blinded to the PK data. Genzyme Clinical Pharmacy Research Services will remain unblinded throughout the study in order to provide the appropriate investigational product to patients. A pharmacokineticist consultant outside the Genzyme Investigational Team will receive reports of Genz-99067 plasma concentrations. The appropriate drug kits will be assigned to each patient by IVRS/IWRS according to treatment randomization and dose-adjustment PK results provided by the central
laboratory. *Note:* The Primary Analysis Period will not be unblinded until all patients have completed the Double-Blind Primary Analysis Period.

All doses of study medication (Genz-112638 or placebo) will be taken orally with water.

### 8.1.1 Double-Blind Primary Analysis Period

At Screening, during the Double-Blind Primary Analysis Period, patients will be randomized (once a patient meets all of eligibility criteria) in a 1:1 ratio to receive either Genz-112638 or placebo.

On Day 1 of the Double-Blind Primary Analysis Period, patients randomized to receive Genz-112638 will receive 50 mg of Genz-112638 (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule) at the study site. Patients randomized to receive placebo will receive matching placebo capsules (one 50 mg placebo capsule and one 100 mg placebo capsule) at the study site. Patients will only receive the morning dose of Genz-112638 or placebo on Day 1. The Investigator and the Genzyme Investigational Team will remain blinded to PK data.

Twice daily (BID) dosing will begin on Day 2. Patients randomized to receive placebo will receive matching placebo capsules BID (provided as one 50 mg placebo capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 39. Patients randomized to receive Genz-112638 will receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule per dose) from the morning of Day 2 until Week 4. For patients randomized to receive Genz-112638, dose-adjustments will occur based on plasma trough and 2-hour (peak) concentrations of Genz-99067 collected during the Week 2 PK. For patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL, the treatment dose will be increased at Week 4 to 100 mg of Genz-112638 BID (provided as one 100 mg Genz-112638 capsule and one 50 mg placebo capsule per dose) for the remainder of the Double-Blind Primary Analysis Period. Patients who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL will continue to receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule and one 100 mg placebo capsule per dose) for the remainder of the Double-Blind Primary Analysis Period. For patients who have a peak Genz-99067 plasma concentration of ≥150 ng/mL at any time, follow the dosing scheme below.

If at any time during the Double-Blind Primary Analysis Period, the patient has a Genz-99067 plasma peak concentration ≥150 ng/mL, the patient will be asked to temporarily stop dosing and return to the study site. The patient will undergo end-of-blinded treatment assessments, and may be allowed to start the Open-Label Period. The investigator will verify that the blinded treatment was taken appropriately, assess concomitant medications for potential to interact with Genz-112638, and determine whether concomitant medications can be discontinued or non-interacting
alternatives are available. Depending on conditions present with the peak concentration as described below, further actions taken will be as follows:

- A concurrent related adverse event (AE), cardiac concern, or medical event of interest (MEOI) or Genz-99067 peak concentration >250 ng/mL:
  - Conduct end-of-Blinded Period analyses. Patient may continue on open-label treatment in the Open-Label Period.
  - Collect a single ECG, conduct 24-hour Holter, and collect blood chemistry.
  - Reintroduce Genz-112638 open-label, at 50 mg QD.
  - At reintroduction, conduct ECGs at 0, 1, 2, 3, and 4 hours, and PK samples at pre-dose and 2 hours post-dose.
  - After 2 weeks, collect a 24-hour PK profile at the following timepoints: Pre-dose (a.m. at 0 hours) and at 1, 2, 3, 4, 6, 8, and 24 hours post-dose.
  - The lowest dose allowed in the study is 50 mg QD. If the peak concentration remains ≥150 ng/mL, the patients should be discontinued from treatment if no adjustments to concomitant medications or other factors can be made.

- No concurrent related AEs, cardiac concern, or MEOI, and concentration ≤250 ng/mL:
  - Conduct end-of-Blinded Period analyses. Patient may continue on open-label treatment in the Open-Label Period.
  - No cardiac assessments are required.
  - Reintroduce Genz-112638 open-label, at 50 mg BID if interacting concomitant medications can be changed. Otherwise, reintroduce open-label at 50 mg QD.
  - After 2 weeks, collect PK samples at pre-dose and 2 hours post-dose at a minimum (for patients on 50 mg QD, collect 24-hour PK as described for this dose level in Section 9.5).
  - Decrease dose as necessary, if the peak concentration remains ≥150 ng/mL. (The lowest dose allowed in the study is 50 mg QD.)

Note: Although the treatment assignment will at this time be assumed to be Genz-112638 and not placebo, the dose the patient took for the Double-Blind Primary Analysis Period will remain
unknown. Therefore all patients must, at least temporarily, receive doses as outlined above. A dose increase after these steps have been taken may be allowed, after examination of the patients’ data and in consultation with the Sponsor’s Medical Monitor and Global Safety Officer.

### 8.1.2 Open-Label Period

After all Week 39 study assessments have been completed, patients will enter the Open-Label Period. On Day 1 of the Open-Label Period, all patients will begin BID dosing and will receive their morning dose of 50 mg of Genz-112638 (provided as one 50 mg Genz-112638 capsule) at the study site to allow for blood sample collection at the scheduled post-dose time points for 4-hour PK analysis. All patients will receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule per dose) until Week 43.

Dose-adjustments during the Open-Label Period will occur based on plasma trough and peak concentrations of Genz-99067 collected during the Week 41 PK. For patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL, the treatment dose will be increased at Week 43 to 100 mg of Genz-112638 BID (provided as one 100 mg Genz-112638 capsule per dose). Patients who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL will continue to receive 50 mg of Genz-112638 BID (provided as one 50 mg Genz-112638 capsule per dose) until Week 43.

Plasma trough and peak concentrations of Genz-99067 will be collected for all patients during Week 45. For patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL at Week 45, the Genz-112638 dose will be increased at Week 47. For patients on 50 mg of Genz-112638 BID whose plasma trough concentration is < 5 ng/mL, the dose will be increased to 100 mg BID. For patients receiving 100 mg of Genz-112638 who have a Genz-99067 plasma trough concentration of < 5 ng/mL, the Genz-112638 dose will be increased to 150 mg of Genz-112638 BID. Patients receiving 50 mg or 100 mg of Genz-112638 who have a Genz-99067 plasma trough concentration of ≥5 ng/mL will continue to receive 50 mg or 100 mg of Genz-112638 BID. For patients who have a peak Genz-99067 plasma concentration of ≥150 ng/mL at any time, follow the dosing scheme below.

If the patient does not tolerate the increase in the dose, the investigator will contact the Genzyme Medical Monitor and Global Safety Officer to discuss a possible dose decrease. The DMC may be consulted as appropriate.

If at any time during the Open-Label Period, the patient has a Genz-99067 plasma peak concentration ≥150 ng/mL, the patient will be asked to temporarily stop dosing and return to the study site. The investigator will verify that the study drug doses were taken appropriately, assess concomitant medications for potential to interact with Genz-112638, and determine whether concomitant medications can be discontinued or non-interacting alternatives are available.
Depending on conditions present with the peak concentration as described below, further actions taken will be as follows:

- A concurrent related adverse event (AE), cardiac concern, or MEOI or Genz-99067 peak concentration >250 ng/mL:
  - Collect a single ECG, conduct 24-hour Holter, and collect blood chemistry.
  - Reintroduce Genz-112638 at 50 mg BID (or 50 mg QD if the patient is already at 50 mg BID; if the patient is on 50 mg QD, temporarily stop dosing).
  - At reintroduction, conduct ECGs at 0, 1, 2, 3, and 4 hours, and PK samples at pre-dose and 2 hours post-dose.
  - After 2 weeks, collect PK samples at pre-dose and 2 hours post-dose at a minimum (for patients on 50 mg QD, collect 24-hour PK as described for this dose level in Section 9.5).
  - Decrease dose as necessary, if the peak concentration remains ≥150 ng/mL. (The lowest dose allowed in the study is 50 mg QD.)

- No concurrent related AEs, cardiac concern, or MEOI, and concentration ≤250 ng/mL:
  - No cardiac assessments are required.
  - Reintroduce Genz-112638 at the current dose if interacting concomitant medications can be changed. Otherwise, reintroduce at the next lower dose.
  - After 2 weeks, collect PK samples at pre-dose and 2 hours post-dose at a minimum (for patients on 50 mg QD, collect 24-hour PK as described for this dose level in Section 9.5).
  - Decrease dose as necessary, if the peak concentration remains ≥150 ng/mL. (The lowest dose allowed in the study is 50 mg QD.)

A dose increase after these steps have been taken may be allowed, after examination of the patients’ data and in consultation with the Sponsor’s Medical Monitor and Global Safety Officer.
8.2 Investigational Product

Genz-112638 is a water soluble, white to off-white powder. The chemical name of Genz-112638 is \((1R,2R)\)-Octanoic acid \([2-(2',3'-dihydro-benzo [1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt. The molecular formula of Genz-112638 is \(C_{23}H_{36}N_2O_4+\frac{1}{2}(C_4H_6O_6)\). The molecular weight of Genz-112638 is 479.60 g/mole, and the molecular weight of Genz-99067 (the free base of the L-tartaric acid salt Genz-112638) is 404.5 g/mole.

The molecular structure of Genz-112638 is presented in Figure 8-1.

![Figure 8-1: Molecular Structure of Genz-112638](image)

8.2.1 Packaging and Labeling

Genzyme will supply both Genz-112638 and placebo. Genz-112638 will consist of 50 mg, 100 mg, and 150 mg hard gelatin capsules. The 150 mg capsules will be made available to the sites only for dispensing to patients who have completed the Double-Blind Primary Analysis Period (refer to the Investigational Product Handling Manual for detailed descriptions of each capsule strength). Placebo capsules will be identical in appearance to the 50 mg and 100 mg Genz-112638 capsules and will contain 50% Avicel PH101 and 50% Lactose Monohydrate USP/Ph-Eur.

During the Double-Blind Primary Analysis period, kits will be assembled according to Genz-112638 or placebo treatment, and will contain blister packs of Genz-112638 50 mg or 100 mg capsules and the appropriate strength matching placebos.
During the Open-Label Period, only Genz-112638 will be supplied. Genz-112638 50 mg, 100 mg, and 150 mg capsules will be provided in induction-sealed, high density polyethylene bottles with child resistant closure caps. The labels for the investigational product will include the study protocol number, storage conditions, and Genzyme’s name and address. Also included on the label will be any required cautionary statements, in accordance with regulations specific to each country where this study is being conducted.

8.2.2 Drug Storage and Accountability

8.2.2.1 Drug Storage

Blister packs of investigational product (Genz-112638 or placebo) and bottles of Genz-112638 will be stored in an area with access limited to only the Investigator or designee. The storage area will be a secure location that has a controlled room temperature of approximately 25°C (77°F), with excursions permitted from 15°C to 40°C (59°F to 104°F). The investigational product must be protected from heat, moisture, and light. For additional information, refer to the Investigational Product Handling Manual.

Patients are to store their blister packs and bottles of investigational product at room temperature (excursions are permitted from 15°C to 40°C [59°F to 104°F]) and away from heat, moisture, and light. Investigational product should not be stored in a bathroom. For additional information, refer to the Investigational Product Handling Manual.

8.2.2.2 Drug Accountability

The Investigator or designee is responsible for maintaining accountability records for all inventory transactions (i.e., receipt and return). For additional information, refer to the Investigational Product Handling Manual.

The investigational product may only be used in accordance with this approved protocol and must not be used for any other purpose. The investigational product may only be used for patients who are randomized in this study.
Patients will be instructed to bring all used and unused blister packs and bottles of investigational product with them to the study site at each study visit for purposes of accountability and reconciliation. Investigational product will be distributed at regular study visits according to the investigational product handling manual. Patient compliance with the treatment regimen will be determined at each study site visit through counting and recording the number of remaining capsules. Acceptable drug compliance is defined as a calculated drug compliance within a range of 90% to 105% between each study visit.

On visits in which a new supply of medication is being dispensed to the patient, the morning dose should be taken from the new supply of medication dispensed. For all visits, the old supply is to be returned to the site for accountability.

For further details regarding disposition of unused investigational product, refer to Section 12.3.6.2 and the Investigational Product Handling Manual.

### 8.3 Medications and Therapies

Genz-112638 is a substrate for CYP2D6 resulting in highly variable metabolism partly dependent upon the CYP2D6 genotype of the individual. Genz-112638 is metabolized to a lesser extent by CYP3A4, is an inhibitor of CYP2D6, and is also a substrate for and inhibitor of the P-gp transporter.

Refer to Section 4.1 for results of Phase 1 drug-drug interaction studies and simulations, which indicate a potential for Genz-112638 exposure and effects to be altered by strong or moderate inhibitors of CYP3A4 or CYP2D6 and inducers of CYP3A4, and for Genz-112638 to increase the exposure of CYP2D6 and P-gp substrate drugs. Examples of the above-mentioned medications are provided in the SOM.

### 8.3.1 Prior Medications and Therapies

Information regarding prior medications and therapies taken by the patient within the 30 days prior to the patient providing written, informed consent will be recorded on the patient’s eCRF. Additionally, information regarding the patient’s use of ERT for Gaucher disease including last administration of ERT and use of pharmacological chaperone or substrate reduction therapies, if applicable, will be collected regardless of the time of treatment prior to randomization and will be recorded on the patient’s eCRF.

Patients must abstain from ingestion of grapefruit, grapefruit juice, and grapefruit products within 72 hours prior to the first dose of study medication and for the duration of the study.
Information on prohibited prior medications is provided in Section 7.2 (see exclusion criteria 2, 15, 19, 20, 21, and 22).

8.3.2 Concomitant Medications and Therapies

Information on all concomitant medications (defined as all prescription and non-prescription medications, including herbal supplements) taken by the patient from the time of informed consent through the final follow-up assessment will be recorded on the patient’s eCRF.

Grapefruit, grapefruit juice, and grapefruit products are not permitted at any time during the study. Information on concomitant medications prohibited during the Double-Blind Primary Analysis Period and the Open-Label Period is provided in Section 8.3.2.1 and Section 8.3.2.2, respectively.

Guidance regarding the use of concomitant medications has been revised during the course of the study based on information from concurrent clinical drug-drug interaction studies with Genz-112638. Section 8.3.2.2 provides the guidance on the use of concomitant medications as of the date of this amendment. In some instances, this guidance may restrict the use of medications that a patient was previously permitted to receive under an earlier amendment to this protocol. In such cases, if continued use of the restricted concomitant medication is clinically indicated, and the patient is deemed to be clinically stable and is not being considered for a further Genz-112638 dose increase, then the patient may be allowed to continue on his/her current dosing regimen of the restricted concomitant medication.

The Sponsor’s Medical Monitor must be contacted if a subject requires the use of any medication that may alter the metabolism of Genz-112638, as described below. The Sponsor’s Medical Monitor must also be contacted if a patient on chronic therapy discontinues that medication at any time.

8.3.2.1 During the Double-Blind Primary Analysis Period

Table 8-1 summarizes medications that are prohibited during the primary analysis period, and the specific circumstances under which exceptions may be granted for temporary or chronic use of such medications. Collectively, temporary use of these medications should not occur on more than 2 occasions. In the event that an interruption of study drug dosing is required, as noted in the table, every attempt will be made to ensure that the patient does not miss more than 20% of the scheduled doses of study drug during the Double-Blind Primary Analysis Period so that the patient is not excluded from the PP population (see Section 11.3).
### Table 8-1 Prohibited Medications During the Double-Blind Primary Analysis Period

<table>
<thead>
<tr>
<th>Medication</th>
<th>When Is it Prohibited?</th>
<th>In Which Patients?</th>
<th>Exceptions for Temporary Use</th>
<th>Exceptions for Chronic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc Interval Prolonging Medications</td>
<td>Entire period</td>
<td>All Patients</td>
<td>Medication for the treatment of acute illness is allowed after completion of dose adjustment.</td>
<td>Chronic use is not permitted.</td>
</tr>
<tr>
<td>CYP3A4 Inducers¹</td>
<td>Entire period</td>
<td>All Patients</td>
<td>≤2 weeks on each occurrence</td>
<td>Chronic use is not permitted.</td>
</tr>
<tr>
<td>Strong CYP3A4 Inhibitors¹</td>
<td>Entire period</td>
<td>CYP2D6 PMs³</td>
<td>≤2 weeks on each occurrence</td>
<td>Chronic use is not permitted.</td>
</tr>
<tr>
<td>Strong CYP3A4 Inhibitors¹</td>
<td>Entire period</td>
<td>CYP2D6 non-PMs⁴</td>
<td>≤2 weeks on each occurrence</td>
<td>Chronic use is permitted in patients who are receiving these medications at the time of randomization and will continue on the same dosing regimen throughout the primary analysis period.⁵</td>
</tr>
<tr>
<td>Strong CYP2D6 Inhibitors¹</td>
<td>Entire period</td>
<td>CYP2D6 non-PMs⁴</td>
<td>≤2 weeks on each occurrence</td>
<td>Chronic use is permitted in patients who are receiving these medications at the time of randomization and will continue on the same dosing regimen throughout the primary analysis period.⁵</td>
</tr>
</tbody>
</table>
PM = poor metabolizer

1 - Examples of these medications are provided in the SOM.

2 - Temporary use is permitted after completion of dose adjustment (i.e., at least 4 weeks after the dose adjustment at Week 4). Collectively, temporary use of these medications should not occur on more than 2 occasions.

3 - Includes CYP2D6 poor metabolizers and patients who are indeterminate metabolizers with neither allele identified as active.

4 - Includes CYP2D6 intermediate, extensive, and/or ultra-rapid metabolizers and patients who are indeterminate metabolizers with one allele identified as active.

5 - Patients may not chronically receive both a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor during the Double-Blind Primary Analysis Period.
### 8.3.2.2 During the Open-Label Period

Table 8-2 provides an overview of allowed and prohibited inhibitors and inducers, for chronic use, as determined by the patient's CYP2D6 metabolizer status. Genz-112638 is considered a moderate inhibitor of CYP2D6 and thus may decrease the metabolism of drugs that rely on this enzyme for their clearance; there is no change in the recommended dosing for Genz-112638.

#### Table 8-2 Potential Concomitant Medications for Chronic Use with Genz-112638 (during the open-label period)

<table>
<thead>
<tr>
<th>CYP2D6 Metabolizer Status</th>
<th>Category of Metabolic Inducer / Inhibitor</th>
<th>CYP3A4 Inducer&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Moderate CYP3A4 Inhibitor&lt;sup&gt;1&lt;/sup&gt; ALONE</th>
<th>Strong CYP3A4 Inhibitor&lt;sup&gt;1&lt;/sup&gt; ALONE</th>
<th>Moderate CYP2D6 Inhibitor&lt;sup&gt;1&lt;/sup&gt; ALONE</th>
<th>Strong CYP2D6 Inhibitor&lt;sup&gt;1&lt;/sup&gt; ALONE</th>
<th>Moderate or Strong CYP3A4 Inhibitor and Moderate or Strong CYP2D6 Inhibitor COMBINED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor Metabolizer (PM)&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Non-Poor Metabolizer (non-PM)&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>No&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;5&lt;/sup&gt;</td>
<td>No</td>
</tr>
</tbody>
</table>

1 Refer to the study-specific Study Operations Manual for examples of these medications.
2 Includes CYP2D6 poor metabolizers and patients who are indeterminate metabolizers with neither allele identified as active.
3 Includes CYP2D6 intermediate, extensive, and/or ultra-rapid metabolizers and patients who are indeterminate metabolizers with one allele identified as active.
4 Some patients may require a chronic inducer of CYP3A4 and may need a dose adjustment (an increased dose of Genz-112638 up to a maximum dose of 150 mg BID is permitted).
5 The dose of Genz-112638 should be reduced upon introduction of the inhibitor (regardless of initial dose) and a pre-dose and 1, 2, 3, 4, and 8 hours post-dose pharmacokinetic blood samples will be collected at approximately 2 weeks after the introduction of drug.

#### 8.3.2.2.1 During Dose Adjustment

During the dose adjustment period, inclusive of Week 39 +1 day through at least 4 weeks after the last dose adjustment at Week 47, patients are prohibited from initiating treatment (acute or chronic) with any of the following medications:

- Medications that cause QTc interval prolongation
- CYP3A4 inducers
- Strong or moderate CYP3A4 inhibitors
• Strong or moderate CYP2D6 inhibitors (prohibited only in CYP2D6 non-poor metabolizers (non-PMs), i.e., patients who are CYP2D6 extensive, intermediate, or ultra-rapid metabolizers or indeterminate metabolizers with one allele known to be active)

Patients who are CYP2D6 non-PMs and received chronic therapy with a strong or moderate inhibitor of CYP3A4 or CYP2D6 prior to randomization and throughout the Double-Blind Primary Analysis Period are permitted to continue that medication on the same dosing regimen during dose adjustment in the open-label extension period. Such patients may not continue to chronically receive both a strong or moderate CYP3A4 inhibitor and a strong or moderate CYP2D6 inhibitor.

8.3.2.2.2 After Completion of Dose Adjustment

After completion of the dose adjustment period, i.e., at least 4 weeks after the last dose adjustment at Week 47, patients are permitted to initiate treatment with strong or moderate inhibitors of CYP2D6 or CYP3A4 or inducers of CYP3A4, or to receive temporary treatment with medications that may cause QTc interval prolongation, as described below.

Temporary use of the following medications is permitted in any patient (regardless of CYP2D6 metabolizer status) and will be managed with respect to the duration of temporary use and actions taken (including a dose interruption of Genz-112638, where applicable):

• Medications that cause QTc interval prolongation
• CYP3A4 inducers
• Strong or moderate CYP2D6 inhibitors
• Strong or moderate CYP3A4 inhibitors

New chronic use (>2 weeks) of the following medications is permitted and will be managed as described below:

• CYP3A4 inducers
• Strong or moderate CYP2D6 inhibitors
• Strong or moderate CYP3A4 inhibitors (permitted only in patients who are CYP2D6 non-PMs, i.e., extensive, intermediate, or ultra-rapid metabolizers or indeterminate metabolizers with one allele known to be active; such patients may not chronically receive both a strong or moderate CYP3A4 inhibitor and a strong or moderate CYP2D6 inhibitor).

Patients initiating new chronic therapy with a strong or moderate inhibitor of CYP2D6 or CYP3A4 will require a dose reduction of Genz-112638 at the start of co-administration as follows:

• A patient on 150 mg BID of Genz-112638 will receive 100 mg BID;
• A patient on 100 mg BID of Genz-112638 will receive 50 mg BID;
• A patient on 50 mg BID of Genz-112638 will receive 50 mg once daily (QD);
• A patient on 50 mg QD will interrupt the dose.

After 2 weeks at the lower dose, plasma levels of Genz-99067 will be assessed pre-dose and 1, 2, 3, 4, and 8 hours post-dose or, for patients on 50 mg QD, a 24-hour profile will be obtained (see Section 9.5 and Table 9-4). The results will be discussed with the Sponsor’s Medical Monitor and, depending on plasma levels, the dose of Genz-112638 may be further decreased. The lowest dose allowed on the study is 50 mg QD. A patient receiving this dose who must begin new chronic use of a strong or moderate inhibitor of CYP3A4 or CYP2D6 should be discontinued from the study.

Patients initiating new chronic therapy with an inducer of CYP3A4 will require collection of samples for PK analysis and dose adjustment decisions (see Section 9.5 and Table 9-4). A dose increase up to a maximum dose of 150 mg BID is permitted.

Pharmacokinetic sampling will also be performed for patients with changes in chronic use of strong or moderate CYP3A4 or CYP2D6 inhibitors or CYP3A4 inducers (including discontinuation of such medication), as described in Section 9.5.

8.4 Method of Assigning Patients to Treatment

Upon confirmation by the medical monitor that the patient meets all eligibility criteria and completion of the Screening assessments, eligible patients will be randomized as described in the SOM.

Approximately 36 male and female patients will be randomized in this study. In order to achieve balance between the treatment groups, all patients will be stratified into 1 of 2 groups based on their spleen volume (in MN). The patients within a given group will then be randomized in a 1:1 ratio to receive either Genz-112638 or placebo. Due to the rare nature of the disease under investigation, no specific number of patients per study site could be established. Patients who discontinue/withdraw participation from the study will not be replaced.

The 2 groups are as follows:
• **Group 1:** Low severity spleen volume (≤ 20MN)
• **Group 2:** High severity spleen volume (> 20MN)

Each patient will be assigned an identification number when they provide informed consent for screening, as described in the SOM. Once randomized, the patient’s identification number will not change during the entire study. A patient who is not randomized in the study because of a deficiency in folate, iron, or vitamin B-12, or symptomatic bone disease, or other transient conditions observed at Screening (see Section 9.3.6 and Section 9.3.10 for further details) may
be allowed to return for re-screening and will be identified by the identification number they initially received.

8.5 Dose Selection

Based on the estimated efficacious dose in humans as determined from preclinical data and findings from Phase 1 studies and the ongoing Phase 2 study, the 3 doses of Genz-112638 selected for this study (50 mg, 100 mg, and 150 mg BID) should result in plasma exposures that are effective and well tolerated.

The 50 mg and 100 mg BID doses of Genz-112638 were selected for this study based on the promising efficacy and safety results seen in the ongoing Phase 2 clinical trial in Gaucher disease type 1 patients. Results of the primary analysis period from this ongoing study have shown notable improvement in hemoglobin level, platelet count, hepatosplenomegaly, and skeletal manifestations by 52 weeks (and as early as 26 weeks for some clinical endpoints), improvement in the biomarkers chitotriosidase, ACE, and TRAP in the same time period, and normalization of the exploratory biomarker plasma GL-1 after 4 weeks of treatment. The dose regimen was well tolerated and produced plasma levels at or above the predicted efficacious range of 6 ng/mL to 14 ng/mL in a majority of patients (refer to the current Genz-112638 IB for details).

The dose and dosing frequency for the Phase 2 study were derived from results obtained from non-clinical studies and three Phase 1 trials. From preclinical studies, an IC50 of 6 ng/mL to 14 ng/mL was established for glucosylceramide synthase inhibition in intact cells.

BID dosing was selected based upon the 6-hour half-life determined in the Phase 1a single dose study. In the Phase 1b multi-dose study, a dose of 50 mg of Genz-112638 BID (equivalent to 0.7 mg/kg for a 70 kg patient) was shown to be safe and well tolerated, and produced a mean C_max of 7 ng/mL at steady state (range 3.9 ng/mL to 14 ng/mL). At this dose, all subjects showed a reduction in the plasma GL-1 level. In the Phase 2 study, all patients received a starting dose of 50 mg of Genz-112638 BID, with the possibility of a dose adjustment to 100 mg of Genz-112638 BID if the trough plasma concentration of Genz-99067 was < 5 ng/mL.

Each patient’s final dose in this study will be a function of their metabolic activity. As in the Phase 2 study design, all patients who are randomized to the Genz-112638 treatment group in this study will initially be dosed with 50 mg of Genz-112638 BID so that patients who are slow metabolizers will not have excessively high plasma levels of the drug. After receiving 50 mg of Genz-112638 BID for 2 weeks, patients who have a trough plasma concentration of Genz-99067 of < 5 ng/mL will undergo a dose increase to 100 mg BID.
The decision to allow an additional dose adjustment up to 150 mg BID during the Open-Label Period is based on analysis of 52-week data from this Phase 2 study, which show a strong correlation between reduction in spleen volume (in MN) and all Genz-99067 PK parameters, e.g., patients with a trough plasma concentration $\geq$ 5 ng/mL are predicted to show greater reduction in spleen volume than patients with a trough plasma concentration $<$ 5 ng/mL. Specifically, patients with trough plasma concentration $\geq$ 5 ng/mL are predicted to show a reduction in spleen volume of at least 5.6 MN (or a 28% reduction based on an average Baseline value of 20 MN) after 1 year of treatment with Genz-112638. Therefore, patients who have trough plasma concentrations $<$ 5 ng/mL at a dose of 100 mg BID, likely due to rapid metabolizer status, may benefit from a higher plasma level, which can be achieved by a further dose increase to 150 mg BID. A mechanism has also been put into place to ensure that patients avoid a level of Genz-99067 that does not allow an adequate safety margin in the case of an unexpected concomitant medication that interacts with Genz-112638. If a patient’s 2-hour (peak) concentration of Genz-99067 is $\geq$150 ng/mL, a thorough evaluation of the patient’s concomitant medications and other factors, plus additional assessments and a possible dose adjustment will take place (Section 8.1).

In summary, the selected doses of 50, 100, or 150 mg of Genz-112638 BID, which will be assigned based on trough plasma concentrations, are expected to be safe and efficacious in this study.
8.6 Blinding and Randomization

8.6.1 Blinding

During the Double-Blind Primary Analysis Period, the patient, Investigator, and the Genzyme Investigational Team will be blinded to the identity of the placebo or Genz-112638 capsules; the Investigator and the Genzyme Investigational Team will also be blinded to the PK data. Genzyme Clinical Pharmacy Research Services will remain unblinded throughout the study in order to provide the appropriate investigational product to patients. A pharmacokineticist consultant outside the Genzyme Investigational Team will receive reports of Genz-99067 plasma concentrations. The appropriate drug kits will be assigned to each patient by IVRS/IWRS according to treatment randomization and dose-adjustment PK results provided by the central laboratory. Note: The Primary Analysis Period will not be unblinded until all patients have completed the Double-Blind Primary Analysis Period.

8.6.2 Randomization

Refer to the SOM for further details regarding randomization.

9. PROCEDURES AND CONSIDERATIONS

9.1 Study Flowchart and Assessments

The study will be conducted as outlined in the following sections. Table 9-1 and Table 9-2 summarize the schedule of study assessments.

Written informed consent for the study must be obtained prior to any protocol-required procedures. Screening assessments will be completed within 2 Screening periods prior to Day 1. Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized in the study after all required procedures are completed (refer to the SOM for further details). Study visits for the double-blind period will be based on calendar days from Day 1. Study visits for the open-label period will be based on calendar days from Week 39 + 1 Day.
### Table 9-1  Schedule of Study Assessments: Screening through Week 130

<table>
<thead>
<tr>
<th></th>
<th>Screening Period Days -45 to Day -1</th>
<th>Double-Blind Primary Analysis Period (Day 1 to Week 39)</th>
<th>Open-Label Period (Post-Week 39 [Day 1 of the Open-Label Period] to Week 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4-week Dose-Adjustment</td>
<td>8-week Dose-Adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(± 3 days)</td>
<td>(± 14 days)</td>
</tr>
<tr>
<td>Day 1 Wk 2</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wk 4 (-3/+7 days)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wk 13 Wk 26 Wk 39</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wk 39 +1 Day A (+7 days)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wks 41, 43, 45, 47 (-3/+7 days)**</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Wk 52 Wk 65 Wk 78 Wk 91 Wk 104 Wk 117 Wk 130</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- **Assign Identification Number**
- **Medical History**
- **Demographics and Baseline Characteristics**
- **Inclusion/Exclusion Criteria Review**
- **Complete Physical Examination (including weight)**
- **Height**
- **Vital Signs (BP, HR, respiratory rate, temperature)**
- **AE Assessment**
- **Concomitant Medications**
- **Genotyping of Gaucher Disease Mutation**, **Chitotriosidase**, **Cytochrome P450 2D6**
- **Gaucher Disease Enzyme Assay**
<table>
<thead>
<tr>
<th></th>
<th>Screening Period</th>
<th>Double-Blind Primary Analysis Period (Day 1 to Week 39)</th>
<th>Open-Label Period (Post-Week 39 [Day 1 of the Open-Label Period] to Week 130)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days -45 to Day -1</td>
<td>4-week Dose-Adjustment (± 3 days)</td>
<td>8-week Dose-Adjustment (± 14 days)</td>
<td>Treatment Period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(± 14 days)</td>
<td>Wk 39 +1 Day A (± 7 days)</td>
<td>Treatment Period</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wks 41, 43, 45, 47 (-3/+7 days)**</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wk 52  Wk 65  Wk 78  Wk 91  Wk 104  Wk 117  Wk 130</td>
<td></td>
</tr>
<tr>
<td>Hemoglobinopathies 1</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>HIV, Hepatitis B and C</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Randomization to Placebo or Genz-112638</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine or Serum Pregnancy Test 2</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Investigational Product Administration</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hematology (including hemoglobin level and platelet count) and Serum Chemistry 3</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Level and Platelet Count 4</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Iron, RBC Folate, and Vitamin B-12</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Total Iron Binding Capacity, Ferritin, MMA and Homocysteine</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Biomarkers (CCL18 and Chitotriosidase)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Exploratory Biomarkers: GL-1 (Plasma and DBS on filter paper), and MIP1-β (Plasma)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
## Screening Period

Days -45 to Day -1

### Double-Blind Primary Analysis Period

(Day 1 to Week 39)

<table>
<thead>
<tr>
<th></th>
<th>4-week Dose-Adjustment</th>
<th>8-week Dose-Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(± 3 days)</td>
<td>(± 14 days)</td>
</tr>
<tr>
<td></td>
<td>Wk 39</td>
<td>Wks 41, 43, 47</td>
</tr>
<tr>
<td></td>
<td>+1 Day A (+7 days)</td>
<td>(-3/+7 days)*</td>
</tr>
<tr>
<td></td>
<td>Wk 52</td>
<td>Wk 65</td>
</tr>
<tr>
<td></td>
<td>Wk 65</td>
<td>Wk 78</td>
</tr>
<tr>
<td></td>
<td>Wk 78</td>
<td>Wk 91</td>
</tr>
<tr>
<td></td>
<td>Wk 91</td>
<td>Wk 104</td>
</tr>
<tr>
<td></td>
<td>Wk 104</td>
<td>Wk 117</td>
</tr>
<tr>
<td></td>
<td>Wk 117</td>
<td>Wk 130</td>
</tr>
</tbody>
</table>

### Treatment Period

(Day 1 of the Open-Label Period) to Week 130

### Open-Label Period

(Post-Week 39 [Day 1 of the Open-Label Period] to Week 130)

### Treatment Period

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Exploratory Biomarkers:

- GM3, Ceramide, Sphingomyelin
- Lyso-GL-1
- Gaucher Disease Severity Score System
- Exploratory Bone Biomarkers
- Coagulation study (PT, PTT, and INR)
- PK Sample Collection
- Complete Neurological Examination (by neurologist)
- MMSE
- ECHO with Doppler
- 12-Lead ECG
- Holter Monitoring
- Spleen Volume (by MRI)
- Liver Volume (by MRI)

**Notes:**

- X: Data collected
- †: Data collected and analyzed
- §: Data collected and reviewed
- #: Data collected and reviewed and analyzed
<table>
<thead>
<tr>
<th>Screening Period</th>
<th>Double-Blind Primary Analysis Period (Day 1 to Week 39)</th>
<th>Open-Label Period (Post-Week 39 [Day 1 of the Open-Label Period] to Week 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days -45 to Day -1</td>
<td>Treatment Period</td>
<td>Treatment Period</td>
</tr>
<tr>
<td></td>
<td>4-week Dose-Adjustment</td>
<td>8-week Dose-Adjustment</td>
</tr>
<tr>
<td></td>
<td>(± 3 days)</td>
<td>(± 14 days)</td>
</tr>
<tr>
<td></td>
<td>(± 14 days)</td>
<td>(± 14 days)</td>
</tr>
<tr>
<td></td>
<td>Day 1 Wk 2 Wk 4 +1 Day A Wk 13 Wk 26 Wk 39 +7 days</td>
<td>Wks 41, 43, 45, 47 +7 days A Wk 52 Wk 65 Wk 78 Wk 91 Wk 104 Wk 117 Wk 130</td>
</tr>
<tr>
<td>1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest X-ray (posterior-anterior and lateral views) †</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MRI entire bilateral femur and lumbar spine †</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DXA (spine and bilateral femur) †</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>X-ray (lateral view of spine) †</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Gaucher Assessments (mobility, bone crisis, and bone pain)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>QOL Questionnaires (BPI, FSS, SF-36) ‡</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacogenetic Blood Sample (Optional)</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

For patients who are re-screened, genotyping of CYP2D6, chitotriosidase, and Gaucher disease mutation, Gaucher Disease enzyme assay, and hemoglobinopathies do not need to be repeated, if performed previously. Genotyping may be performed at either Screening 1 or Screening 2.

Spleen/liver volume assessments (by MRI), chest X-ray, and bone disease assessments (MRI, DXA, and X-ray) performed within 15 weeks prior to randomization may serve as Baseline assessments provided they are performed according to protocol specifications (refer to the SOM for further details). Additionally, patients are required to fast at least 6 hours before the organ volume MRI is performed to reduce the meal effect; however water and juice (excluding grapefruit juice) are allowed.

The MRI of the spleen/liver will be performed 2 times at Week 26 for a subset of patients (up to 20 patients) who complete 6 months of treatment (Week 26) to test/re-test variability of volumetric MRIs. The Week 26 MRI can be performed on the same day, after a short break, without food or drink (water is allowed) between the test/re-test MRIs or up to 3 days after the 26 week timepoint MRI. The MRI should be performed at the same time of day. Additionally, patients are required to fast at least 6 hours prior to the MRI being performed to reduce the meal effect; however water and juice (excluding grapefruit juice) are allowed.

During the Open-Label Period of the study, only the post-Week 39 +1 Day visit will be blinded. Week 39 +1 Day refers to the first dosing day in the Open-Label Period after all Week 39 study assessments have been completed. This is the day that determines the timing of subsequent visits.
A complete physical examination (including the measurement of weight) will be performed, including but not limited to examination of the skin; head, eyes, ears, nose, and throat (HEENT); lymph nodes; heart, lungs, and abdomen; extremities and joints; and neurological and mental status. Whenever possible, the same physician will perform the examination at each designated study visit.

Vital signs will be measured pre-dose (at 0 hours) and as needed.

A blood sample will be collected for genotyping of Gaucher disease mutation, chitotriosidase, and CYP2D6, unless the patient’s genotypes for Gaucher disease, chitotriosidase, and CYP2D6 are already available.

Pregnancy testing is for women of childbearing potential only and will be performed monthly either at home or at the study site. The site’s clinical staff will contact the patient to confirm the negative pregnancy test results during their biweekly assessment of the patient. At each study visit, the investigator or designee must review the pregnancy test results. Prior to performing any radiologic study assessment, the radiologist/technician must review the patient’s pregnancy test results and document that the female patient of childbearing potential has a negative pregnancy test result. When going to the radiology laboratory for a radiological assessment, the patient must bring her pregnancy test results with her, or results must be immediately delivered from the clinic directly to the radiologist/technician for review prior to any study assessments being performed. The radiologist/technician is required to sign, date, and note the time of their review on the pregnancy result report.

During the Double-Blind Period, only the morning dose of Genz-112638 or placebo will be given on Day 1; BID dosing will begin on Day 2. During the Double-Blind Primary Analysis Period, patients will receive either Genz-112638 (50 or 100 mg) or placebo.

On Day 1 of the Open-Label Period, all patients will begin BID dosing and receive their morning dose of 50 mg of Genz-112638 at the study site. All patients will receive 50 mg of Genz-112638 BID until Week 43. At Week 43, patients who have a Genz-99067 plasma trough concentration of < 5 ng/mL at Week 41 will receive a dose increase to 100 mg of Genz-112638 BID, while patients who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL at Week 41 will continue to receive 50 mg of Genz-112638 BID. At Week 47, patients receiving 50 or 100 mg BID who have a Genz-99067 plasma trough concentration of < 5 ng/mL at Week 45 will receive a dose increase to 100 mg or 150 mg BID, respectively, while patients who have a Genz-99067 plasma trough concentration of ≥ 5 ng/mL at Week 45 will continue to receive the same dose for the remainder of the Open-Label Period.

Patients should fast approximately 8 hours prior to the blood sample collection for serum chemistry. Note: The blood sample for serum chemistry will be assessed at the central laboratory; the blood sample for hematology will be assessed at the local laboratory (platelet count will be assessed using automated counts).

The blood sample collected for the second hemoglobin level and platelet count (for efficacy) will be collected at least 24 hours after the first sample (and may be collected on Week 39 + 1 Day, before study drug dosing). The blood samples for hemoglobin level and platelet count will be assessed at the local laboratory (platelet count will be assessed using automated counts).

Refer to Section 9.5 and Table 9-4 for timepoints for collection of blood samples for PK analyses. Pharmacokinetic samples may be collected for patients receiving concomitant medications (see Section 9.5 for further details).

To be performed at Week 45 only.

Refer to Table 9-3 for timepoints for performance of 12-lead ECGs.

Holter monitoring will be performed prior to Day -7.

If the patient’s spleen or liver volume increases > 30% above the patient’s Baseline value, a measurement (by MRI) must be repeated in approximately 4 weeks. Additionally, patients are required to fast at least 6 hours prior to the MRI being performed to reduce the meal effect; however water and juice (excluding grapefruit juice) are allowed.

May be performed on the same day as the MRIs to assess spleen and liver volumes.

QOL questionnaires must be administered before any blood is collected from the patient.

Additional 24-hour Holter monitoring and ECGs are required if the patient has a Genz-99067 peak plasma concentration ≥150 ng/mL that is accompanied by a related AE, a cardiac concern, or an MEOI, or is >250 ng/mL.

Excess stored serum samples from the analysis of chitotriosidase will be used for bone biomarker analysis; a separate sample will NOT be collected. See Section 9.3.9.3 for further details.

Patients will be contacted approximately every 2 weeks for safety monitoring and will be asked if they have had any significant experiences or begun taking any new medications.

** The Week 41 and Week 45 visits cannot be less than 11 days from the prior visit.
Table 9-2  Schedule of Study Assessments: After Week 130 through Study Completion

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Every 3 Months (± 14 days)</th>
<th>Every 6 Months (± 14 days)</th>
<th>Every 12 Months after Week 104 (± 14 days)</th>
<th>Every 24 Months after Week 78 (± 14 days)</th>
<th>Study Completion or Patient Discontinuation/Withdrawal</th>
<th>Follow-Up A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Physical Examination (including weight)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital Signs (BP, HR, respiratory rate, temperature)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>AE Assessment</td>
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<tr>
<td>Concomitant Medications</td>
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<td></td>
<td>CONTINUOUS MONITORING</td>
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</tr>
<tr>
<td>Urine or Serum Pregnancy Test</td>
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<td></td>
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</tr>
<tr>
<td>Urimalysis</td>
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<tr>
<td>Genz-112638 Administration</td>
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<td></td>
<td>DAILY BID DOsing</td>
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<tr>
<td>Hematology (including hemoglobin level and platelet count)</td>
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<td>Serum Chemistry</td>
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<tr>
<td>Hemoglobin Level and Platelet Count</td>
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<tr>
<td>Iron, RBC, Folate, and Vitamin B-12</td>
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<td></td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Biomarkers (CCL18 and Chitotriosidase)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exploratory Biomarkers: GL-1 (Plasma and DBS on filter paper)</td>
<td></td>
<td></td>
<td>X</td>
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<td>Exploratory Biomarkers: Ceramide, Sphingomyelin, GM3, MPI1-β-Plasma (Plasma)</td>
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<td>Liver Volume (by MRI)</td>
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<td>Chest X-ray (posterior-anterior and lateral views)</td>
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**Amendment 7 Final: 05 February 2013**
A follow-up phone call will be performed 30 to 37 days after the patient’s last dose of treatment as part of safety follow-up procedures.

B A complete physical examination (including the measurement of weight) will be performed, including but not limited to examination of the skin; head, eyes, ears, nose, and throat (HEENT); lymph nodes; heart, lungs, and abdomen; extremities and joints; and neurological and mental status. Whenever possible, the same physician will perform the examination at each designated study visit.

C Vital signs will be measured pre-dose (at 0 hours) and as needed.

D Pregnancy testing is for women of childbearing potential only, and urine or serum pregnancy tests will be performed. At each study visit, the investigator or designee must review the pregnancy test results. Also at each visit, prior to performing any radiologic study assessment, the radiologist/technician must review the patient’s pregnancy test results and document that the pregnancy test result is negative. When going to the radiology laboratory for a radiological assessment, the patient must bring her pregnancy test results with her, or results must be immediately delivered from the clinic directly to the radiologist/technician for review prior to any study assessments being performed. The radiologist/technician is required to sign, date, and note the time of their review on the pregnancy result report. For those study sites that cannot obtain serum pregnancy test results immediately, a urine pregnancy test will be performed prior to any scheduled study assessments. After Week 4, women of childbearing potential must also perform a pregnancy test every 4 weeks (monthly) between their study site visits and as part of the safety follow-up procedures (30 to 37 days after the patient’s last dose of treatment).

The pregnancy test may be performed at home.

E Patients should fast approximately 8 hours prior to the blood sample collection for serum chemistry. Note: The blood samples for serum chemistry will be assessed at the central laboratory; the blood samples for hematology will be assessed at the local laboratory (platelet count will be assessed using automated counts).

F The blood sample collected for the second hemoglobin level and platelet count will be collected at least 24 hours after the first sample. The blood samples for hemoglobin level and platelet count will be assessed at the local laboratory (platelet count will be assessed using automated counts).

G Vitamin B-12, RBC folate, and iron levels will be measured only upon patient discontinuation/withdrawal.

H Collect blood sample for PK analyses pre-dose (a.m. at 0 hours) and at 2 hours post-dose. Pharmacokinetic samples may be collected for patients receiving concomitant medications (see Section 9.5 for further details).

I One 12-Lead ECG will be performed at 1, 2, 3, and 4 hours post-dose. If ECGs and blood samples are scheduled at the same time, ECGs will be performed first.

J Holter monitoring will be performed only if a patient discontinues/withdraws from the study prior to Week 52.

K If the patient’s spleen or liver volume increases > 30%, in MN relative to the patient’s Baseline value, a measurement (by MRI) must be repeated in approximately 4 weeks. Additionally, patients are required to fast at least 6 hours prior to the MRI being performed to reduce the meal effect; however water and juice (excluding grapefruit juice) are allowed.

L If possible, spleen and liver volumes to be assessed prior to withdrawal if patient withdraws prior to Week 26.

M QOL questionnaires must be administered before any blood is collected from the patient.

N To be collected for patients who discontinue due to an adverse event.
O Additional 24-hour Holter monitoring and ECGs are required if the patient has a Genz-99067 peak plasma concentration ≥150 ng/mL that is accompanied by a related AE, a cardiac concern, or an MEOI, or is >250 ng/mL.

P Excess stored serum samples from the analysis of chitotriosidase will be used for bone biomarker analysis; a separate sample will NOT be collected. See Section 9.3.9.3 for further details.

R Patients will be contacted approximately every 2 weeks for safety monitoring and will be asked if they have had any significant experiences or begun taking any new medications.

† To be performed if it has been more than 6 months since the prior assessment.
9.2 Study Assessments

9.2.1 Screening Assessments

Screening assessments are described in Section 9.2.1.1 to Section 9.2.1.9.

For patients who are re-screened, these guidelines should be followed for assessments:

- If the re-screening is within 3 months after the original screening:
  - The following must be repeated:
    - Local laboratories: hematology (including hemoglobin and platelet count), pregnancy test (if applicable).
    - Central laboratory: electrolytes, ALT, AST, gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin (total, direct, and indirect), blood urea nitrogen (BUN), creatinine, and biomarkers (CCL18 and chitotriosidase).
    - Clinical: physical exam, weight, vital signs.
  - Additional tests may be requested on a case-by-case basis, depending on the original reason for screen failure.
  - The following need not be repeated: echocardiogram, ECG, Holter, HIV testing, hepatitis B and C testing, MMSE, QOL questionnaires, neurological exam, genotyping (Gaucher disease mutation, chitotriosidase, and CYP2D6 mutation), Gaucher disease enzyme assay, and hemoglobinopathies.

- If the re-screening is longer than 3 months after the original screening, all tests must be repeated except the following: MRIs for spleen/liver volume, chest X-ray, and bone disease assessments (if done within 15 weeks before randomization), genotyping, Gaucher disease enzyme assay and hemoglobinopathies.

9.2.1.1 Demographic Information and Medical History

At Screening, demographic information including gender, date of birth, and ethnicity will be collected from each patient. Additionally, patients will provide a complete medical history. Specific information relating to any relevant prior or existing medical conditions/surgical procedures and history of smoking usage will be recorded on the patient’s eCRF. The patient’s diagnosis of Gaucher disease and first symptom date will also be collected and recorded.
For patients who have received Cerezyme/Ceredase treatment prior to randomization, information may be obtained regarding SAEs related to Cerezyme/Ceredase treatment. The SAEs obtained should be recorded as medical history and will be reported directly to Genzyme Global Pharmacovigilance and Epidemiology (refer to Section 9.4.11.3 for further details).

### 9.2.1.2 Genotyping of Gaucher Disease Mutation

At Screening, genotyping of Gaucher disease mutation will be performed, unless the patient’s Gaucher genotype is already available. The coding regions and flanking sequences of the acid β-glucosidase gene will be sequenced.

### 9.2.1.3 Genotyping of Cytochrome P450 2D6 (CYP2D6)

At Screening, molecular analysis of the CYP2D6 genes will be performed, unless the patient’s CYP2D6 genotype is already available, and patients will be categorized as poor to ultra-rapid metabolizers.

### 9.2.1.4 Genotyping of Chitotriosidase

At Screening, genotyping of chitotriosidase will be performed, unless the patient’s chitotriosidase genotype is already available. The chitotriosidase gene will be analyzed for the presence or absence of the 24-base pair duplication mutation by polymerase chain reaction (PCR). Patients will be described as homozygous normal, homozygous abnormal, or heterozygous.

### 9.2.1.5 Gaucher Disease Enzyme Assay

At Screening, the Gaucher Disease Enzyme Assay will be performed on leukocytes collected from patients. The results from the assay must be available prior to patient randomization in the study to document a deficiency in acid β-glucosidase activity.

### 9.2.1.6 Hemoglobinopathies

At Screening, testing for hemoglobinopathies using high-performance liquid chromatography (HPLC) will be performed to rule out thalassemia or sickle cell anemia. Patients with thalassemia minor or sickle cell trait may be eligible for randomization. A central laboratory will conduct analysis of all samples and will provide reports.
9.2.1.7 HIV, Hepatitis B and C

At Screening, patients will be tested for the presence of HIV antibody, Hepatitis C antibody, and Hepatitis B surface antigen, as one of the exclusion criteria. Blood samples will be processed by the local laboratory facility and laboratory reports will be made available to the Investigator to assure appropriate patient inclusion.

9.2.1.8 Total Iron Binding Capacity, Ferritin, Homocysteine, and MMA

At Screening (and at Week 39), total iron binding capacity, ferritin, homocysteine, and methylmalonic acid (MMA) will be assessed in addition to iron, red blood cell (RBC) folate and vitamin B-12 levels, to evaluate deficiency of iron, folate, and vitamin B-12. A central laboratory will conduct analysis of all samples and will provide reports of all laboratory parameters.

After Screening, any patient who does not meet the entrance criteria because of a deficiency in folate, iron, or vitamin B-12 may be allowed to enroll after the deficiency has been treated for at least 3 months; re-screening may be done during the third month of treatment. The Investigator must discuss the patient’s appropriateness for re-screening with the Genzyme Medical Monitor and document that the patient’s hemoglobin levels have stabilized on at least 2 measurements.

At the Investigator’s discretion, patients who enter the study after re-screening may continue treatment with folate, iron, or vitamin B-12 while dosed. Patients with another etiology for anemia (e.g., a bleeding ulcer) will not be eligible for re-screening.

9.2.1.9 Coagulation Study (PT, PTT, and INR)

Coagulation studies (prothrombin time [PT], partial thromboplastin time [PTT], and international normalized ratio [INR]) will be performed at Screening to evaluate bleeding tendency. A local laboratory will conduct analyses and will provide reports.

9.3 Efficacy Assessments

A list of the primary and secondary efficacy endpoints is presented in Section 6.1.

9.3.1 Spleen Volume

Spleen volume will be assessed by MRI at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. If possible, spleen volume will be assessed prior to withdrawal if the patient withdraws prior to Week 26.
The MRI of the spleen will be performed 2 times at Week 26 for a subset of patients (up to 20 patients) who complete 6 months of treatment (Week 26) to test/re-test variability of volumetric MRIs. The Week 26 MRI can be performed on the same day, after a short break, without food or drink (water is allowed) between the test/re-test MRIs or up to 3 days after the 26 week timepoint MRI. The MRI should be performed at the same time of day. Patients are required to fast at least 6 hours prior to the MRI being performed to reduce the meal effect; however water and juice (excluding grapefruit juice) are allowed. For patients who have 2 values assessed at 6 months, the average of these 2 values will be displayed in the analyses.

Note: At study visits during the treatment period, if the patient’s spleen volume, in MN, increases > 30% above the patient’s Baseline value, a spleen volume measurement must be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses. All images of the spleen will be sent to a central blinded reviewer for analysis of spleen volume. Refer to the imaging core lab manual and the SOM for further details.

9.3.2 Platelet Count

Platelet count will be assessed using automated counts at Screening, Weeks 4 and 13, every 3 months thereafter, and at study completion. Two blood samples will be collected at least 24 hours apart only at Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion. The average of the 2 platelet count values for each of these visits will be used in the efficacy analyses. In the event that a patient is missing 1 of the 2 assessments at a particular timepoint, then the single assessment will be used in the analyses. A local laboratory will conduct these analyses and will provide reports.

9.3.3 Hemoglobin Level

Hemoglobin level will be assessed at Screening, Weeks 4 and 13, every 3 months thereafter, and at study completion. Two blood samples will be collected at least 24 hours apart only at Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion. The average of the 2 hemoglobin values for each of these visits will be used in the efficacy analyses. In the event that a patient is missing 1 of the 2 assessments at a particular timepoint, then the single assessment will be used in the analyses. A local laboratory will conduct these analyses and will provide reports.
9.3.4 Liver Volume

Liver volume will be assessed by MRI at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. If possible, liver volume will be assessed prior to withdrawal if the patient withdraws prior to Week 26. The MRI of the liver will be performed 2 times at Week 26 for a subset of patients (up to 20 patients) who complete 6 months of treatment (Week 26) to test/re-test variability of volumetric MRIs. The Week 26 MRI can be performed on the same day, after a short break, without food or drink (water is allowed) between the test/re-test MRIs or up to 3 days after the 26 week timepoint MRI. The MRI should be performed at the same time of day. Patients are required to fast at least 6 hours prior to the MRI being performed to reduce the meal effect; however water and juice (excluding grapefruit juice) are allowed. For patients who have 2 values assessed at 6 months, the average of these 2 values will be displayed in the analyses.

Note: Additionally, at study visits during the treatment period, if the patient’s liver volume, in MN, increases > 30% above the patient’s Baseline value, a liver volume measurement must be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses. All images of the liver will be sent to a central blinded reviewer for analysis of liver volume. Refer to the imaging core laboratory manual and the SOM for further details.

9.3.5 Biomarkers (CCL18 and Chitotriosidase)

Biomarkers (CCL18 and chitotriosidase) will be assessed at Screening, Weeks 4, 13, 26, 39, 45, 52, 65, 78, 91, 104, 117, and 130, every 3 months thereafter, and at study completion. Refer to the SOM for guidelines on the collection, processing, and shipping procedures of samples for the assessment of CCL18 and chitotriosidase levels.
9.3.6 **Bone Disease Assessments (X-ray, DXA, MRI, and Bone Marrow Burden Score)**

Bone disease assessments (DXA, MRI, and Bone Marrow Burden Score) will be performed at Screening (these may be performed on the same day as the spleen and liver volume MRIs), Weeks 39, 78, and 130, every 12 months thereafter, and at study completion unless the assessment was performed within the previous 6 months. Bone X-rays will be performed at Screening, Weeks 39, 78, every 24 months thereafter, and at study completion unless the assessment was performed within the previous 6 months. Bone X-rays will include a lateral view of the spine and DXA will assess spine and bilateral femur providing total density measurements as well as T- and Z- scores. MRI will include a view of the entire bilateral femur and lumbar spine. Bone Marrow Burden Score will be calculated using MRI (Maas, 2008, *Skeletal Radiol.*). All bone images will be sent to a central reviewer for blinded analysis of potential bone disease. Refer to the SOM for further details.

Patients who do not meet the entrance criteria due to symptomatic bone disease at Screening will be allowed to be re-screened after 6 months.

9.3.7 **Gaucher Disease Assessments (Mobility, Bone Crisis, and Bone Pain)**

Gaucher disease assessments (mobility, bone crisis, and bone pain) will be assessed at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. Refer to the SOM for further details.

9.3.8 **Quality of Life (Health and Fatigue)**

9.3.8.1 **Brief Pain Inventory**

The BPI is a self-reported questionnaire used to measure a patient’s perceived level of pain. The BPI measures the patient’s intensity of pain (sensory dimension), the interference of pain in the patient’s life (reactive dimension), and questions the patient about pain relief, pain quality, and the patient’s perception of the cause of pain (Cleeland, 1989, *Advances in Pain Research and Therapy, Volume 12: Issues in Pain Measurement* and Cleeland, 1994, *Ann Acad Med. Singapore*). The BPI will be completed by patients (if necessary aided by their parent/legal guardian) at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. *Note:* At specific study visits, all QOL questionnaires must be administered before any blood is collected from the patient at the particular visit. If any response on the BPI is a clinically significant change from Screening, the AE must be documented on the AE page of the patient’s eCRF.
9.3.8.2 Fatigue Severity Scale

The FSS is a self-reported questionnaire used to measure a patient’s perceived level of fatigue (Krupp, 1989, Arch Neurol.). The questionnaire includes 9 statements that attempt to explore a patient’s severity of fatigue symptoms as they relate to daily activities such as physical functioning, exercise and work, family, or social life. The FSS will be completed by patients (if necessary aided by their parent/legal guardian) at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. Note: At specific study visits, all QOL questionnaires must be administered before any blood is collected from the patient at the particular visit. If any response on the FSS is a clinically significant change from Screening, the AE must be documented on the AE page of the patient’s eCRF.

9.3.8.3 SF-36 Health Survey

The SF-36 Health Survey is a self-reported questionnaire used to measure a patient’s profile of functional health and well-being as well as psychometrically-based physical and mental health summary measures. The SF-36 Health Survey is a multi-purpose, short-form health survey with 36 questions. Accordingly, the SF-36 Health Survey has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments (Rogers, 2000, Pain Med.). The SF-36 Health Survey will be completed by patients (if necessary aided by their parent/legal guardian) at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. Note: At specific study visits, all QOL questionnaires must be administered before any blood is collected from the patient at the particular visit. If any response on the SF-36 Health Survey is a clinically significant change from Screening, the AE must be documented on the AE page of the patient’s eCRF.

9.3.9 Exploratory Assessments

9.3.9.1 Gaucher Disease Severity Score

The Gaucher disease severity score system (DS3) will be completed at Screening, Weeks 39, 78, 130, every 12 months thereafter, and at study completion.
9.3.9.2 Exploratory Biomarkers (GL-1, GM3, Ceramide, Sphingomyelin, MIP1-β, and Lyso-GL-1)

GL-1 assayed from DBS on filter paper and from plasma and MIP1-β assayed from plasma will be assessed at Screening, Weeks 4, 13, 26, 39, 45, 52, 65, 78, 91, 104, 117, and 130, every 3 months thereafter (GL-1) or every 6 months thereafter (MIP1-β), and at study completion. GM3, ceramide, and sphingomyelin will be assessed at Screening, Weeks 26, 39, 65, 78, 104, and 130, every 6 months thereafter, and at study completion. Plasma lyso-GL-1, an analyte that is elevated in GD1 patients and hypothesized to interfere with osteoblastic bone formation, will be assessed at Screening, Weeks 4, 13, 26, 39, 45, 52, 65, 78, 104, 130, every 6 months thereafter, and at study completion (Dekker, 2011, Blood; Mistry, 2010, PNAS). Refer to the SOM for guidelines on collection, processing, and shipping procedures of samples for assessment of GL-1, GM3, ceramide, sphingomyelin, and MIP1-β.

9.3.9.3 Exploratory Biomarkers of Bone Formation and Bone Resorption

In a Phase 2 study, clinically meaningful and statistically significant changes in lumbar spine bone mineral density (BMD) T-scores and Z-scores were observed in GD1 patients after one year of treatment with Genz-112638 (GZGD00304 CSR[clinical study report]). These results are consistent with observed improvements in bone mass in GD1 patients receiving treatment with miglustat (Zavesca®) (Pastores, 2007, Clin Therap.) and Cerezyme (Sims, 2008, Clin Genet; Wentrup, 2007, J Bone Miner Res.). Although the pathophysiology of Gaucher-related osteopenia is not clearly understood, it is thought that impaired bone formation and/or accelerated bone resorption may be contributing factors (Mistry, 2010, PNAS; van Dussen, 2011, J Clin Endocrinol Metab; van Breemen, 2007, Biochimica et Biophysica Acta).

In this study, biomarkers of bone formation and resorption will be assessed at screening and Weeks 26, 39, 65, 78, 104, 130, every 6 months thereafter, and at study completion. Samples will not be collected specifically for bone biomarker analysis. Instead, excess stored serum samples from the analysis of serum chitotriosidase (see Section 9.3.5) will be used for analysis of bone biomarkers. The exploratory analysis of bone biomarkers will be performed ONLY for those patients who have available serum samples at screening and a minimum of one on-treatment time point (see above) that are of sufficient volume to assay for at least one bone biomarker.

Bone-specific alkaline phosphatase will be analyzed as a biomarker of bone formation, and CTx-I will be analyzed as a biomarker of bone resorption. Additional biomarkers predictive of bone formation or bone resorption may be analyzed, if sample volume permits.
9.3.10 Iron, RBC Folate, and Vitamin B-12

Iron, RBC folate, and vitamin B-12 levels will be assessed at Screening, Week 39, and at study completion.

At any time during the Open-Label Period, if an Investigator suspects that a patient has a deficiency in their iron, folate, and/or vitamin B-12 levels, the Genzyme Medical Monitor will be contacted and the patient will have those levels assessed. Total iron binding capacity, ferritin, homocysteine, and MMA will be also be assessed at Week 39 in addition to iron, RBC folate and vitamin B-12 levels to evaluate deficiency of iron, folate, and vitamin B-12.

When the test results are available, the Investigator will contact the Genzyme Medical Monitor for a consultation to discuss the test results, the hematological status of the patient, and potential change or initiation of any additional treatment or dietary supplements to correct the iron, folate, and/or vitamin B-12 deficiency. In the event that the Investigator and Genzyme Medical Monitor agree that the patient will receive treatment to correct one or more deficiencies, the patient will continue to receive their usual Genz-112638 treatment regimen. Note: No new vitamin supplementation is allowed during the Double-Blind Primary Analysis Period.

Patients receiving treatment for an iron, folate, and/or vitamin B-12 deficiency will have their hematology panel monitored (including mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], and mean corpuscular hemoglobin concentration [MCHC]) for at least 3 months until stable (stability will be assessed by the Investigator based on at least 2 sequential values). Re-screening may be done during the third month of treatment. Refer to the SOM for further details.
9.4 Safety Assessments

The safety of Genz-112638 during the Double-Blind Primary Analysis Period and the Open-Label Period will be assessed by evaluation of standard clinical parameters listed in Section 6.1, described in detail below, and at the timepoints outlined in Table 9-1 and Table 9-2.

The Investigator will determine if any findings from the safety assessments are clinically significant. Clinical significance is defined as any variation in assessment results that has medical relevance and may result in an alteration in medical care. Any clinically significant changes from Screening will be documented on the AE page of the patient’s eCRF and reported to Genzyme Global Pharmacovigilance and Epidemiology within 24 hours for SAEs and Medical Event of Interest (MEOI), as appropriate.

The Investigator will continue to monitor any clinically significant AEs until either (1) assessments have returned to normal and/or are consistent with those observed at Screening, or (2) the Investigator determines that follow up is no longer medically necessary, or (3) the patient is lost to follow-up. AEs will be captured from the time the patient (and/or their parent/legal guardian) provides signed informed consent through the safety follow-up period (30 to 37 days after the patient’s last dose of treatment). Refer to the SOM for further details.

An independent DMC will oversee safety monitoring in the study.

9.4.1 Data Monitoring Committee

An independent DMC will operate according to the DMC Charter and provide an ongoing, expert, independent review of safety data to provide risk management during the conduct of the study. This committee will be comprised of experts in relevant biomedical fields who have no direct relationship with the study. The DMC will receive aggregate listings of patient safety data approximately every 6 months. All SAEs considered unexpected per the IB and potentially related (i.e. possible, probable, definite) to Genz-112638 will be provided to the DMC for full review on an expedited basis. All other SAEs and patient discontinuations/withdrawals will be reviewed on at least a periodic basis (refer to Section 7.3). Following each DMC review, the DMC recommendations may be provided to Institutional Review Board/Independent Ethics Committee (IRBs/IECs), regulatory, and competent authorities if required. The DMC may recommend suspension of randomization in the study to evaluate a safety issue that arises during the conduct of the study. Genzyme will be responsible for determining if any changes to the study conduct are required based on DMC recommendations.
9.4.2 Physical Examinations

A complete physical examination will be performed for all patients at each study visit and at study completion including, but not limited to, examination of the skin; head, eyes, ears, nose, and throat (HEENT); lymph nodes; heart, lungs, and abdomen; extremities and joints; and neurological and mental status. Whenever possible, the same physician will perform the physical examination at each designated study visit. The patient’s weight will be measured without shoes and wearing the lightest possible clothing. At visits where height is measured (Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion), the patient will be measured without shoes. Results will be recorded on the patient’s eCRF.

9.4.3 Vital Signs

Vital signs including systolic and diastolic blood pressures (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C or °F) will be measured after the patient has been in a supine position for approximately 5 to 10 minutes at each study visit (or patient discontinuation/withdrawal); vital signs will be measured pre-dose (at 0 hours) and as needed. At study visits where blood samples will be collected, vital signs will be measured just prior to the blood sample collection. Results will be recorded on the patient’s eCRF.

The Investigator will determine if any of the abnormal vital signs are clinically significant or not clinically significant. Any clinically significant changes observed from Screening through study completion will be documented on the AE page of the patient’s eCRF and reported to Genzyme Global Pharmacovigilance and Epidemiology within 24 hours if SAEs. The Investigator will continue to monitor any clinically significant finding until it returns to the Baseline condition or, in the judgment of the Investigator, no further medical follow-up is required. Refer to the SOM for further details.

9.4.4 Neurological Examination

A complete neurological examination will be performed by a neurologist at Screening, Week 39, Week 78, Week 104, every 12 months after Week 104, and at study completion. Neurological examinations will be performed at Screening to exclude patients who have neurologic involvement (e.g., peripheral neuropathy, tremor, seizures, Parkinsonism, or cognitive impairment). Results of all examinations will be recorded on the patient’s eCRF. Refer to the SOM for further details.
9.4.5 Neuropsychological Testing

Neuropsychological testing will be performed at Screening, Week 39 and at study completion. The MMSE will be used to assess the patient’s cognitive mental status (Grigoletto, 1999, *Neurology*; Tinklenberg, 1990, *Int Psychogeriatr*). Results will be recorded on the patient’s eCRF. Refer to the SOM for further details.

9.4.6 Chest X-ray

A chest X-ray (posterior-anterior and lateral views) will be performed at Screening and at study completion. The Screening chest X-ray will be reviewed prior to randomization to determine if the patient has any detectable abnormalities which may prevent participation. Results will be recorded on the patient’s eCRF. Refer to the SOM for further details.

9.4.7 Echocardiograms

A standard 2-dimensional ECHO with Doppler will be obtained at Screening, Week 39, and at study completion. Examination will include but is not limited to valve characterization, ejection fraction, ventricular wall thickness, and regional wall motion. The review of these assessments will be performed locally by a certified cardiologist. Whenever possible, the same cardiologist will perform all evaluations per patient. Results will be recorded on the patient’s eCRF. Refer to the SOM for further details.

9.4.8 Clinical Laboratory Tests

Routine clinical laboratory tests include serum chemistry, hematology, and urine and will be performed at Screening, Weeks 4, 13, 26, 39, 45, 52, 65, 78, 91, 104, 117, and 130, every 3 months thereafter, and at study completion. *Note:* Patients should fast approximately 8 hours prior to the blood sample collection for serum chemistry. The blood samples for serum chemistry will be assessed at the central laboratory; the blood samples for hematology will be assessed at the local laboratory. Results will be recorded on the patient’s eCRF. Refer to the SOM for further details.
The following serum chemistry, hematology, and urine tests will be performed:

1. Blood chemistries, liver function, renal function, proteins, and lipids, performed by central laboratory.
   a) RBC folate, vitamin B-12, and iron (only tested at Screening, Week 39, and at study completion). Refer to Section 9.3.10 for further details regarding patients who have a deficiency in iron, folate, and/or vitamin B-12.
   b) Total iron binding capacity, ferritin, MMA, and homocysteine (only tested at Screening and Week 39). Refer to Sections 9.2.1.8 and 9.3.10 for further details regarding patients who have a deficiency in iron, folate and/or vitamin B-12.
   c) Sodium, potassium, calcium, chloride, bicarbonate, magnesium, and phosphate.
   d) Blood urea nitrogen (BUN), creatinine, uric acid, ALT, AST, bilirubin (total, direct and indirect), and GGT.
   e) Lactate dehydrogenase (LDH), ALP, and creatine kinase (CK).
   f) Total protein, albumin, glucose, total cholesterol (high-density lipoprotein [HDL] and low-density lipoprotein [LDL]), and triglycerides.

2. Hematology panel, performed by local laboratory.
   a) Hematocrit, hemoglobin, MCV, MCH, MCHC, and reticulocyte count.
   b) RBC, white blood cells (WBC), and platelet counts.
   c) WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

3. Urinalysis, performed by central laboratory: Dipstick for pH, ketones, glucose, bilirubin, protein, and blood.

4. Serum β human chorionic gonadotropin (HCG) or urine pregnancy tests for females of childbearing potential, performed by local laboratory. Refer to Section 9.4.11.5 for further details regarding pregnancy reporting procedures.

All blood and urine samples will be assessed by a central clinical laboratory, with the exception of HIV, Hepatitis B and C, hematology laboratory tests, and pregnancy testing which will be assessed by a local laboratory or at home, in the case of urine pregnancy safety follow up procedures. Safety and laboratory reports will be made available to the Investigator in a timely manner to assure appropriate clinical review. Procedures for sample handling and shipment to the central laboratory will be included in the laboratory manual provided by the central clinical laboratories.
Clinical laboratory values will be flagged as either high (H), normal (N), or low (L) based on the normal ranges for each laboratory parameter. The Investigator will determine if any of the abnormally high or low results are clinically significant or not clinically significant. The diagnosis for any clinically significant worsening from Screening in any clinical laboratory assessments will be documented on the AE page of the patient’s eCRF. If the diagnosis is unknown, abnormal clinical laboratory results will be recorded on the patient’s eCRF. The Investigator will continue to monitor the patient with additional assessments until either (1) assessments have returned to normal and/or are consistent with those observed at Screening, or (2) the Investigator determines that follow-up is no longer medically necessary, or (3) the patient is lost to follow up.

9.4.9 12-Lead ECGs

A standard 12-Lead ECG will be performed on each patient based on the schedule in Table 9-3.

During the Double-Blind Primary Analysis Period and the Open-Label Period, three 12-Lead ECGs will be performed prior to the morning pre-dose on Day 1 (a.m. at 0 hours) for each patient. These ECGs should be started no more than 15 minutes before, and completed approximately 5 minutes before the corresponding PK sample. Single ECGs will be obtained at all other timepoints. Single ECGs should be obtained no more than 15 minutes before and no less than 5 minutes before any corresponding PK timepoints. ECGs will be performed while the patient remains in a supine position for approximately 5 to 10 minutes prior to conducting the ECG. Vital signs and PK blood samples will not be collected until approximately 5 minutes after the ECG timepoint. If ECGs and blood samples are scheduled at the same time, ECGs will be performed first.

Additional ECGs are required in the case of a Genz-99067 peak plasma concentration ≥150 ng/mL, when the peak is accompanied by a related AE, a cardiac concern, or an MEOI, or is >250 ng/mL. A single reading will be obtained when the patient returns to the site, and then at 0, 1, 2, 3, and 4 hours post-dose.

All study ECGs will be read by the Investigator at the time they are performed to determine if there are any safety concerns. The 3 pre-dose ECGs on Day 1 will be evaluated at the study site by the Investigator to determine whether dosing of the patient will occur. Any clinically significant changes from Screening will be documented on the AE page of the patient’s eCRF. Any clinically significant cardiac arrhythmia will be considered an MEOI and will be collected by Genzyme Global Pharmacovigilance and Epidemiology, whether serious or non-serious events. Refer to the SOM and Section 9.4.11.4 for further details.
ECGs will be collected in a digital format to allow accurate assessments of any potential cardiac effects. All ECGs will be collected and read centrally by a third party independent reviewer. The ECG assessment will include standard comments on Normal/Abnormal, Rhythm, Arrhythmia, Conduction, Morphology, MI, ST Segment, T Wave, and U Wave observations. Interval measurements for the RR, PR, QRS, and QT for each of the 3 pre-dose ECGs will be determined by the independent reviewer who will use a set of graphic tools to perform manual measurements of the RR, PR, QRS, and QT interval. The mean of the 3 readings for each interval will be considered the “Baseline” value for the patient, to which post-dose readings will be compared. The absolute measurement of the QT interval will be determined, as well as QTc using the following formulae: Bazett and Fridericia correction. While QTc will be calculated and reported using both formulas, decisions regarding safety will be based on Fridericia correction.
### Table 9-3 Schedule of 12-Lead ECG Assessments: Screening through Study Completion (Including Assessments Repeated after Week 130)

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Screening Period Day -45 to Day -1</th>
<th>Open-Label Period (Post-Week 39 [Day 1 of the Open-Label Period] to Study Completion)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Wk 13 Wk 26 Wk 39 Wk 39 +1 Day Wk 41, 43, 45, 47 Wks 52 65 78 91 104 117 130 Every 6 Months</td>
</tr>
<tr>
<td>a.m.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pre-dose (a.m. at 0 hours)</td>
<td>X&lt;sup&gt;C&lt;/sup&gt;</td>
<td>X&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| 1 hour    | X                                | X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X X .

A single, 12-Lead ECG will be performed at study completion.

B Week 39 +1 Day refers to the first dosing day in the Open-Label Period after all Week 39 study assessments have been completed. This is the day that determines the timing of subsequent visits.

C Three 12-Lead ECGs will be performed prior to the morning pre-dose on Day 1 (a.m. at 0 hours). If ECGs and blood samples are scheduled at the same time, ECGs will be performed first. These ECGs should be started no more than 15 minutes before, and completed approximately 5 minutes before the corresponding PK sample.

D Performed at Week 47 only.

E If ECGs, vital signs, and blood samples are scheduled at the same time, ECGs will be performed first. Single ECGs should be obtained no more than 15 minutes before and no less than 5 minutes before any corresponding PK timepoints.

F If the patient has a Genz-99067 peak plasma concentration $\geq 150$ ng/mL that is accompanied by a related AE, a cardiac concern, or an MEOI, or is $> 250$ ng/mL, a single ECG is required upon the patient’s return to the site, and then at 0, 1, 2, 3, and 4 hours post-dose.
9.4.10 Holter Monitoring

24-hour Holter monitoring will be performed at Screening (prior to Day -7) and at Weeks 13 and 52 (at Week 13, patients who initially received Genz-112638 will be at steady state; at Week 52, patients who initially received placebo then transitioned to Genz-112638 at Week 39 will be at steady state). Note: If a patient discontinues/withdraws from the study prior to Week 52, Holter monitoring will be performed at discontinuation/withdrawal. Holter monitoring data will be reviewed by the ECG core laboratory, and the results will be reported to the Investigator and Sponsor.

Additional 24-hour Holter monitoring is required in the case of a Genz-99067 peak plasma concentration ≥150 ng/mL, when the peak is accompanied by a related AE, a cardiac concern, or an MEOI, or is >250 ng/mL.

Results will be recorded on the patient’s eCRF. Any clinically significant cardiac arrhythmias are considered MEOIs and will be reported to the Genzyme Global Pharmacovigilance and Epidemiology Department, whether serious or non-serious events according to the SAE reporting timelines; refer to Section 9.4.11.4 for further details. Refer to the ECG core laboratory manual for further details.

9.4.11 Adverse Events

AEs will be captured from the time the patient (and/or their parent/legal guardian) provides signed informed consent through the safety follow-up period (30 to 37 days after the patient’s last dose of treatment). An independent DMC will oversee safety monitoring in the study (refer to Section 9.4.1).

At each study visit, the Investigator will evaluate and ask open-ended questions of the patients to determine the occurrence of any AEs. Patients will be contacted approximately every 2 weeks for safety monitoring, and will be asked if they have had any significant experiences or begun taking any new medications. Details of any new AEs will be recorded on the patient’s eCRF. The occurrence of any AEs will also be assessed as part of the post-treatment follow-up phone call performed 30 to 37 days after the patient’s last dose of treatment. All AEs will be recorded on the patient’s eCRF.

9.4.11.1 Adverse Event Definition

An AE is defined as any undesirable physical, psychological, or behavioral effect experienced by a patient during their participation in an investigational study, in association with the use of the
drug or biologic, whether or not product-related. This includes any clinically significant untoward signs or symptoms experienced by the patient and clinically significant changes from Screening in laboratory parameters or other study findings.

The Investigator will assess the relationship of all AEs as definitely, probably, possibly, unlikely related or not related to the study drug. In the event of an unrelated AE, the Investigator will also determine if the AE is due to underlying disease. The Investigator will continue to monitor the event until follow-up is no longer medically necessary or the patient is lost to follow-up.

Disease signs, symptoms, and/or laboratory abnormalities, which existed prior to the study, are not considered AEs unless they have changed in nature, or worsened in intensity or frequency after patient dosing.

### 9.4.11.1 Severity Scoring

The severity of all AEs will be graded as mild, moderate, or severe. The AE severity assessment is subjective and the Investigator should use medical judgment to compare the reported AE to similar type experiences observed in clinical practice. Severity categories are defined as follows:

- **Mild**: Symptom(s) barely noticeable to the subject/patient or does not make the subject/patient uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

- **Moderate**: Symptom(s) of a sufficient severity to make the subject/patient uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) may be needed.

- **Severe**: Symptom(s) of a sufficient severity to cause the subject/patient severe discomfort. Severity may cause cessation of treatment with the study drug. Treatment for symptom(s) may be given.

**NOTE**: Severity is not equivalent to seriousness. Severity describes the intensity of a specific event. Seriousness is based on the patient/event outcome (refer to Section 9.4.11.2 for SAE definition of serious outcomes).
9.4.11.2 Serious Adverse Events

An SAE is defined as having at least 1 of the following outcomes or characteristics:

- Death.
- Life-threatening (any AE that places the patient, in the view of the Investigator, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that had it occurred in a more severe form, might have caused death).
- Required or prolonged in-patient hospitalization.
- Persistent or significant disability/incapacity (a substantial disruption of a person’s ability to conduct normal life functions).
- Congenital anomaly/birth defect.
- Important medical events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

9.4.11.3 Serious Adverse Event Reporting

The necessity and time requirements for reporting SAEs to Genzyme are as follows:

- Initial notification of all SAEs must be provided within 24 hours of the Investigator’s first knowledge of the event by telephone/fax, even if the event does not appear to be related to Genz-112638. Such communications are to be directed to Genzyme Global Pharmacovigilance and Epidemiology.

- A written SAE report must be provided to Genzyme Global Pharmacovigilance and Epidemiology within 48 hours of telephone/fax notification. All SAE reports will include a detailed description of the event(s). The Investigator will provide any follow-up information regarding the SAE(s) as soon as it is available. Copies of relevant patient records, autopsy reports, and other documents may be requested by and will be sent to Genzyme Global Pharmacovigilance and Epidemiology. Telephone contact information is provided in the SOM.
Each study site’s IRB/IEC (or in accordance with local requirements) must be notified in writing of any SAEs occurring at that study site. It is the responsibility of the Investigator or Genzyme, depending on local regulations, to notify the IRB/IEC. All investigators will be notified when serious unexpected related adverse events (i.e., Suspected Unexpected Serious Adverse Reaction [SUSAR]) occur. Genzyme will be responsible for the notification of any SUSAR to all Competent Authorities according to local regulatory requirements.

All AEs and SAEs will be noted in the eCRF, with a full description including the nature, date, and time of onset and resolution, determination of seriousness, severity, action(s) taken, outcome, and relationship to Genz-112638 and to underlying disease.

For patients who have received Cerezyme/Ceredase treatment prior to randomization, information may be obtained regarding SAEs related to Cerezyme/Ceredase treatment that occurred during a previous clinical study and/or commercial Cerezyme/Ceredase treatment. These SAEs should be recorded as medical history and will be reported directly to Genzyme Global Pharmacovigilance and Epidemiology in accordance with SAE reporting processes described above (within 24 hours). Global Pharmacovigilance and Epidemiology will assess these solicited SAEs for possible submission to regulatory authorities.

9.4.11.4 Medical Events of Interest: Cardiac Arrhythmias and/or Syncope from Any Cause

Clinically significant cardiac arrhythmias detected by electrophysiological monitoring such as ECG or Holter monitoring that do not meet criteria for an SAE, as well as syncope from any cause, will be reported to Genzyme Global Pharmacovigilance and Epidemiology as MEOIs. (Note: events occurring prior to initiation of study treatment are not required to be reported as MEOIs). The timeframe and process for reporting of cardiac arrhythmia and/or syncopal events
is the same as SAEs defined in Section 9.4.11.3.

9.4.11.5 Pregnancy Reporting

Genz-112638 is not expected to cross the placenta. Teratology studies and pre- and post-natal development studies were negative for reproductive toxicity in non-human species. The effects of Genz-112638 during pregnancy are unknown. For this reason, female patients who are pregnant or lactating will be excluded from the study. Female patients of childbearing potential must use a medically acceptable form of contraception throughout the study (either a barrier method or hormonal contraceptive with ethinyl estradiol and norethindrone or similar active components).

For all female patients of childbearing potential, a urine or serum pregnancy test is required at Screening and all study visits, except during the dose adjustment period. During the dose adjustment period, visits for patients taking Genz-112638 are biweekly; pregnancy testing is required monthly and therefore done either at home or at a study visit.

Beyond the dose adjustment period, women of childbearing potential receiving Genz-112638 must also perform a pregnancy test monthly between their site visits and as part of the safety follow-up procedures (30 to 37 days after the patient’s last dose of treatment). The pregnancy test may be performed at home in which case the patient will record the date and time of pregnancy testing and the result.

The investigator or designee is responsible for reviewing all pregnancy test results. The site’s clinical staff will contact the patient to confirm the negative pregnancy test results during their biweekly assessment of the patient. If the pregnancy test is positive, the patient will be instructed not to wait for the phone call but to call the study site immediately and must not receive additional study drug treatment (Genz-112638). If a pregnancy is medically confirmed, the patient will be discontinued from the study.

Prior to performing any radiologic study assessment, the radiologist/technician must review the patient’s pregnancy test results and document that the pregnancy test result is negative. When going to the radiology laboratory for a radiological assessment, the patient must bring her pregnancy test results with her, or results must be immediately delivered from the clinic directly to the radiologist/technician for review prior to any study assessments being performed. The radiologist/technician is required to sign, date, and note the time of their review on the pregnancy result report. For those sites that cannot obtain serum pregnancy test results immediately, a urine pregnancy test will be performed prior to any scheduled study assessments.
The Genzyme Global Pharmacovigilance and Epidemiology Department must be notified within 24 hours if a patient or female partner of a male patient becomes pregnant at any point during this study. Male patients with pregnant partners may continue in the study.

The Genzyme Global Pharmacovigilance and Epidemiology Department must also be notified within 24 hours of the Investigator’s first knowledge if a patient becomes pregnant within 40 days after discontinuing treatment with Genz-112638, or if a female partner of a male patient in the study becomes pregnant within the 37-day safety follow-up period for the male partner.

The progress of pregnancies, in either female patients or female partners of male patients, must be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). The Investigator must also complete all appropriate pregnancy forms, which are supplied in the SOM and fax them to the Genzyme Global Pharmacovigilance and Epidemiology Department according to the procedures outlined in the SOM.

If an adverse pregnancy outcome occurs in any exposed pregnancy, the Genzyme Global Pharmacovigilance and Epidemiology Department must be notified within 24 hours of the Investigator’s first knowledge of the event by telephone/fax, even if the event does not appear to be related to the study drug. A written SAE report must be provided to the Genzyme Global Pharmacovigilance and Epidemiology Department within 48 hours of telephone/fax notification (refer to Section 9.4.11.3 for further details regarding reporting SAEs). If the pregnancy results in the birth of a child, additional follow-up information will be requested by Genzyme Global Pharmacovigilance and Epidemiology.

9.5 Pharmacokinetic Assessments

Blood samples for PK analyses will be collected for all patients according to the timepoints in Table 9-4.

Additional samples outside these schedules may be requested and are discussed in this section.

During the Double-Blind Primary Analysis Period, blood samples for PK analyses will be collected at the following timepoints:

- Day 1: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, and 4 hours post-dose.
- Week 2: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 4: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose.
- Week 13: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
- Week 26: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.
• Week 39: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose

During the dose-adjustment period in the Open-Label Period, blood samples for PK analyses will be collected at the following timepoints:

• Post-Week 39 (Day 1 of the Open-Label Period, blinded): Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, and 4 hours post-dose.

• Week 41: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.

• Week 43: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose.

• Week 45: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.

• Week 47: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose for all patients, and also at 0.5, 6, 12, 16, 22, and 24 hours post-dose for patients who qualify for a dose increase to 150 mg BID.

During the treatment period in the Open-Label Period, blood samples for PK analyses will be collected at the following timepoints:

• Weeks 52, 65, 91, 104, 117, 130 and every 3 months thereafter until study completion: Pre-dose (a.m. at 0 hours) and at 2 hours post-dose.

• Week 78: Pre-dose (a.m. at 0 hours) and at 1, 1.5, 2, 3, 4, and 8 hours post-dose.

Blood samples for PK analyses will be collected from peripheral venous sites.

Patients receiving a 50-mg QD dose will have a PK profile at least 2 weeks after the start of this dose at the following timepoints: Pre-dose (a.m. at 0 hours) and at 1, 2, 3, 4, 6, 8, and 24 hours post-dose.

If a patient initiates chronic treatment with a strong or moderate inhibitor of CYP2D6 or CYP3A4 or chronic treatment with an inducer of CYP3A4, or changes current chronic treatment of these medications (including discontinuation of such medication), during the Open-Label Period (when permitted by protocol; refer to Section 8.3.2.2), a pre-dose and 1, 2, 3, 4, and 8 hours post-dose PK blood samples will be collected at approximately 2 weeks after the start of or change in concomitant treatment.

After Day 1 of the double-blind primary analysis period, dose and time of administration of Genz-112638 will be collected for the 2 days prior to each PK sampling day. With the exception of the pre-dose timepoint, all blood samples will be collected within a ± 10 minute window. With the exception of the Day 1 pre-dose timepoint, all pre-dose timepoints should be 12 hours,
±1 hour, from the previous study medication dose, or 24 hours ±1 hour, in the case of 50 mg QD doses.

If a patient experiences a peak Genz-99067 plasma concentration ≥150 ng/mL, PK samples will be collected as follows:

- If the peak is accompanied by a related AE, a cardiac concern, or an MEOI, or is >250 ng/mL, samples will be taken at pre-dose and 2 hours post-dose upon reintroduction of Genz-112638 and at pre-dose and 2 hours post-dose 2 weeks later.

- Otherwise, PK samples will be taken at pre-dose and 2 hours post-dose 2 weeks after reintroduction of Genz-112638.

In addition to analyzing the blood samples for Genz-99067, select samples from the serial sampling scheme at each dose level, along with a few trough samples, may be analyzed for metabolites of Genz-99067. This analysis is considered exploratory.

To maintain the integrity of the study blind, PK samples will be collected from all patients during the Double-Blind Primary Analysis Period. However, Genz-99067 and metabolites will be analyzed only for patients randomized to Genz-112638. The bioanalytical lab will receive a copy of the randomization code from Genzyme Clinical Pharmacy Research Services for this purpose.

Specific details for sample collection, labeling and shipping will be provided in the SOM.
### Table 9-4 Schedule of Pharmacokinetic Assessments: Screening through Study Completion (Including Assessments Repeated after Week 130)

<table>
<thead>
<tr>
<th>Timepoint&lt;sup&gt;F, G, H, I&lt;/sup&gt;</th>
<th>Double-Blind Primary Analysis Period (Day 1 to Week 39)</th>
<th>Open-Label Period (Post-Week 39 [Day 1 of the Open-Label Period] to Study Completion)</th>
<th>Treatment Period</th>
<th>Assessments Repeated (± 14 days)</th>
<th>Study Completion or Patient Discontinuation / Withdrawal&lt;sup&gt;J&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-dose</strong></td>
<td><strong>Day 1</strong></td>
<td><strong>Wk 4</strong></td>
<td><strong>Wk 13</strong></td>
<td><strong>Wk 26</strong></td>
<td><strong>Wk 39</strong></td>
</tr>
<tr>
<td>(a.m. at 0 hours)</td>
<td>X</td>
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<td><strong>Total Timepoints</strong></td>
<td>6</td>
<td>2</td>
<td>7</td>
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<sup>A</sup> The PK assessments on Day 1 of the Open-Label Period will be blinded. Week 39 +1 Day refers to the first dosing day in the Open-Label Period after all Week 39 assessments have been completed. This is the day that determines the timing of subsequent visits.
B. On Weeks 41 and 45, only a pre-dose (a.m. at 0 hours) and 2-hour post-dose sample will be collected.

C. Collected at Weeks 43 and 47.

D. Collected at Week 47 for patients who qualify for a dose increase to 150 mg BID.

E. In the event that a site does not have the capability of collecting a sample at 16 hr and/or 22 hr post-dose, these samples may be omitted with prior approval from Genzyme.

F. With the exception of the pre-dose timepoint, all blood samples will be collected within a ±10 minute window. With the exception of the Day 1 pre-dose timepoint, all pre-dose timepoints should be 12 hours, ±1 hour, from the previous study medication dose, or 24 hours ±1 hour, in the case of 50 mg QD doses.

G. If a patient experiences a peak Genz-99067 plasma concentration ≥150 ng/mL, PK samples will be collected as follows: If the peak is accompanied by a related AE, a cardiac concern, or an MEOI, or is >250 ng/mL, samples will be taken at pre-dose and 2 hours post-dose upon reintroduction of Genz-112638 and at pre-dose and 2 hours post-dose 2 weeks later. Otherwise, PK samples will be taken at pre-dose and 2 hours post-dose 2 weeks after reintroduction of Genz-112638.

H. Patients receiving a 50-mg QD dose will have a PK profile at least 2 weeks after the start of this dose at the following timepoints: Pre-dose (a.m. at 0 hours) and at 1, 2, 3, 4, 6, 8, and 24 hours post-dose (see Section 9.5).

I. If a patient initiates chronic treatment with a strong or moderate inhibitor CYP2D6 or CYP3A4 or chronic treatment with an inducer of CYP3A4, or changes current chronic treatment of these medications (including discontinuation of such medications), a pre-dose and 1, 2, 3, 4, and 8 hours post-dose PK blood samples will be collected at approximately 2 weeks after the start of or change in concomitant treatment.

J. In case of early termination; if no dose is administered during the visit, a single sample will be collected anytime during the visit.
9.6 Pharmacogenetic Assessments

If permitted according to local regulations, blood will be collected for DNA analysis from patients who consent to this optional component of the clinical study. Refusal to participate in the pharmacogenetic component of this study will not result in ineligibility for participation in the main part of the clinical study.

There are two parts to the pharmacogenetic component of this study, as described in Section 9.6.2 and Section 9.6.3. Patients will be given the option to participate in Part 1, Part 2, both parts, or neither part of the pharmacogenetic component of this study.

A patient may withdraw consent for pharmacogenetic testing at any time. If a patient withdraws consent for pharmacogenetic testing, any DNA extracted from the patient’s blood will be destroyed provided that the sample has not yet undergone conversion to the non-identifiable format. If the sample has already undergone conversion to the non-identifiable format, Genzyme will notify the investigator in writing.

Refer to the SOM for details regarding the processing, labeling, and shipment of pharmacogenetic samples. Blood samples should be shipped at ambient temperature (not frozen) to the central laboratory.

9.6.1 Rationale for Pharmacogenetic Analysis

Genetic variation within the population may be an important contributing factor in inter-individual differences in drug safety, efficacy, and response, and may also serve as a marker for disease susceptibility and prognosis. A genetic association between polymorphisms in candidate genes and clinical outcomes may help to identify a population subgroup that is likely to better respond to or better tolerate the drug. Therefore, it is valuable to collect DNA samples in this clinical study to help address emerging clinical issues and to develop a safe, more effective drug.

Genetic variation in drug metabolizing enzymes has been extensively studied and has been shown to be of clinical significance for a number of drugs. For several of these enzymes, particularly the Cytochrome P450 isozymes, the genetic basis for variable activity, are already well understood. The clinical significance of a genetic polymorphism will depend on a number of factors, including whether the isozyme is part of a major metabolic pathway for the drug and whether the drug is administered as an active moiety or as a pro-drug. Genotyping may help determine the influence of a given polymorphism on the pharmacokinetic profile of the drug that may ultimately translate into variable response.
Genes encoding the drug target (e.g., glucosylceramide synthase) and corresponding signaling pathways (e.g., chitotriosidase), off-targets (e.g., sodium, potassium, and calcium ion channels), and genes involved in disease etiology (e.g., (acid β-glucosidase) are also candidates for determining differences in drug response. In contrast to drug metabolizing enzymes, these genes and their variations are generally less thoroughly characterized and understood. However, it is expected that with scientific developments, more information will become available regarding genetic variations in these genes that are important determinants of disease susceptibility, prognosis, and therapeutic efficacy.

9.6.2 Analysis of Candidate Genes (Part 1)

Part 1 of the pharmacogenetic assessment allows for the analysis of genes that may influence the pharmacokinetics of, or response related to safety and/or efficacy, of Genz-112638 for the treatment of Gaucher’s disease. Genotyping of these candidate genes will only be performed if it is believed or hypothesized by Genzyme that such genetic analysis might help clarify issues with the clinical data (e.g., variable PK, AEs in a subgroup of patients, or efficacy in a subgroup). Categories of candidate genes are listed below, and specific examples of candidate genes are provided in Appendix 14.1.

1. Genes involved in absorption, distribution, metabolism, excretion (ADME), and transport;
2. Genes potentially involved in cardiac arrhythmias including QT-associated genes;
3. Genes related to the drug target and corresponding signaling pathways;
4. Genes related to Gaucher’s disease;
5. Genes encoding off-target proteins.

9.6.3 DNA Storage (Part 2)

Part 2 of the pharmacogenetic assessment allows for the storage of DNA samples for future testing of additional genes that are discovered at a later date or are found to have an association with the pharmacokinetics and pharmacodynamics (PD) of Genz-112638 or Gaucher’s disease. Samples may also be used to help identify new genes that are related to Genz-112638 or Gaucher’s disease. Stored DNA samples and relevant clinical data will be held in a non-identifiable format, such that no link will be made between the genetic information and an individual patient.
10. DATA COLLECTION, QUALITY ASSURANCE, AND MANAGEMENT

10.1 Recording of Data

Clinical data will be captured using electronic data capture (EDC) technology unless otherwise specified in this document. Required data for this study are to be recorded in the patient’s medical notes/source documents first and then entered into the eCRF by authorized study site personnel. Any changes made to the data after initial entry into the eCRF will be captured via an electronic audit trail. Clinical data that are not recorded on the eCRF, which includes central laboratory data, will be captured and transferred to Genzyme or its designee. The Investigator must provide direct access to the source documents to Genzyme or its designee.

10.2 Data Quality Assurance

Data entered on the patient’s eCRF will be verified against source documents at the study site. A clinical monitor from Genzyme or a representative of Genzyme will manually review the eCRFs against the source documents at the study site for validity and completeness. Upon completion of data collection, the database will receive a quality assurance check to ensure acceptable accuracy and completeness.

10.3 Data Management

The format and content of the eCRF will be approved by Genzyme or its designee prior to the start of the trial. Genzyme or its designee will be responsible for EDC database creation and management of data from sources other than the EDC database (e.g., non-safety specialty lab data).

All decisions concerning the data for each patient will be determined prior to finalizing and locking the database by appropriate data management, clinical and statistical personnel. Any exclusions will be documented.

Protocol deviations will be tracked by Genzyme Corporation or its designee.
11. STATISTICAL METHODS AND PLANNED ANALYSES

11.1 General Considerations

All data collected during the study will be presented in summary tables, figures, or by-patient data listings. Continuous variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency distributions.

A clinical study report (CSR) will be produced at the end of the Double-Blind Primary Analysis Period, which will include efficacy, safety, and PK analyses. A final CSR to summarize long-term efficacy, safety, and PK parameters will be produced at study completion, which will include data on all patients in the study for at least 130 weeks.

11.2 Determination of Sample Size and Power

Allowing for a drop-out rate of 20%, approximately 36 male and female patients will be randomized in this study in a 1:1 ratio to receive Genz-112638 or placebo in order to yield at least 28 evaluable patients at the end of the Double-Blind Primary Analysis Period (39 weeks). This sample size assumes a 25% decrease in spleen volume in MN for Genz-112638 and a 5% decrease in spleen volume in MN for placebo at 39 weeks. This sample size also assumes a standard deviation of 15%, a two-sided, two-sample t-test test with a 5% level of significance and power of 92%. Patients who discontinue/withdraw from participation in the study will not be replaced.

The analyses of the secondary efficacy endpoints of hemoglobin levels, liver volumes (MN), and platelet counts are powered at 91%, 89%, and 56.5%, respectively, based on the above sample size calculation for the primary efficacy endpoint (spleen volume). These power estimates assume a two-sided, two-sample t-test test with a 5% level of significance for each efficacy endpoint and a 20% drop-out rate. Furthermore, these power estimates also assume increases from Baseline of 1.3 vs. 0 in hemoglobin levels (in g/dL) for Genz-112638 vs. placebo at 39 weeks, decreases from Baseline of 12.5% vs. 0% in liver volumes (in MN) for Genz-112638 vs. placebo at 39 weeks, and increases from Baseline of 25% vs. 0% in platelet counts for Genz-112638 vs. placebo at 39 weeks. Standard deviations of 1 g/dL, 10%, and 30% are also assumed for hemoglobin levels, liver volumes, and platelet counts, respectively.
11.3 **Analysis Population**

Efficacy analyses will be performed on the Intent-to-Treat [ITT] population as well as on a Per Protocol (PP) population. The ITT population will include all patients who receive at least 1 dose of Genz-112638 or placebo. Any patient missing 20% or more of the doses during the Double-Blind Primary Analysis Period will not be included in the PP population. Likewise, ITT patients with major protocol deviations that would be expected to interfere with the assessment of efficacy will not be included in the PP population. In addition, the PP population will exclude patients with hematological decline as a result of medically determined etiologies other than Gaucher disease. Major protocol deviations will be prospectively defined in the Statistical Analysis Plan (SAP). The PP population will be determined prior to database lock and unblinding of the study.

Safety analyses will be performed on the safety population defined as all patients who receive at least 1 dose of Genz-112638 or placebo.

PK analyses will be performed on all patients who receive at least 1 dose of Genz-112638 and who have evaluable PK data.

11.4 **Demographics and Baseline Characteristics**

Demographic and Baseline characteristic variables will be summarized overall for all patients. For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (mean, median, SD, and minimum and maximum).

11.5 **Patient Accountability**

All patients randomized in the study will be included in the summary of patient disposition and accountability, which will summarize the number of patients randomized in the study, frequency and percentage of patients who completed or discontinued/withdrew from the study, along with reason for discontinuation/withdrawal.

11.6 **Study Drug Usage and Compliance**

A summary of Genz-112638 and placebo administration and compliance will be presented for all patients.
11.7 **Efficacy Analyses**

Efficacy analyses will be performed on the ITT population as well as the PP population.

11.7.1 **Primary Efficacy Analyses**

The primary efficacy endpoint is the percentage change in spleen volume in MN from Baseline to 39 weeks of treatment with Genz-112638 as compared to placebo. Analysis of Covariance (ANCOVA) will be used to analyze the ITT population. If the percentage change in spleen volume data from Baseline to Week 39 is normally distributed, based on the Shapiro-Wilk test using a 5% level of significance, ANCOVA will be used to analyze the primary efficacy endpoint. If the percentage change in spleen volume data from Baseline to Week 39 is not normally distributed then the change in spleen volume data will be ranked and the ANCOVA will be performed on the ranked data. In either case, the ANCOVA will include treatment (Genz-112638 vs. placebo) and Baseline spleen severity (the randomization stratification variable).

The statistical tests will be conducted at the 5% level of significance. The assessment of spleen volume prior to randomization will be used as the Baseline assessment. The spleen volume assessment obtained at Week 39 or the last available spleen volume assessment in the case of early withdrawal will be used as the Week 39 assessment.

*Note:* If an increase of > 30% in spleen volume is observed, the parameter will be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses. If a patient withdraws after Week 26 and prior to Week 39, and this patient is included in the MRI Test-Re-Test Analysis, then the average of these 2 values will be used in the primary analysis as the last available spleen assessment. The PP population analyses of the primary efficacy endpoint will also be conducted in a similar manner. Likewise, as a sensitivity analysis, the subset of the ITT population who complete 39 weeks of treatment and have the Baseline and Week 39 assessment for spleen volume will also be analyzed in a similar manner for the primary efficacy endpoint.

11.7.2 **Secondary Efficacy Analyses**

For the Double-Blind Primary Analysis Period, there will be 3 secondary efficacy endpoints in the study: (1) the absolute change in hemoglobin levels (in g/dL) from Baseline to Week 39, (2) the percentage change in liver volumes (in MN) from Baseline to Week 39, and (3) the percentage change in platelet counts from Baseline to Week 39. These secondary efficacy endpoints will be analyzed, using ANCOVA in the same manner as described for the primary
efficacy endpoint, for the ITT population. *Note:* If an increase of > 30% in liver volume is observed, the parameter will be repeated in approximately 4 weeks. The value from the repeated measurement will be used in the study analyses. When performing the analyses for these 3 secondary efficacy endpoints, a closed-testing procedure will be used. First, the absolute change in hemoglobin levels (in g/dL) from Baseline to Week 39 will be analyzed at the 5% level of significance. If there is a statistically significant Genz-112638 treatment effect for the change in hemoglobin levels, then the percentage change in liver volumes (in MN) from Baseline to Week 39 will be analyzed at the 5% level of significance. If there is a statistically significant Genz-112638 treatment effect for the percentage change in liver volumes (in MN), then the percentage change in platelet counts from Baseline to Week 39 will be analyzed at the 5% level of significance. The PP and ITT completer populations will also be analyzed in a similar manner for the secondary efficacy endpoints.

An additional secondary analysis for patients treated with Genz-112638 will look at the within-patient change from Baseline to Week 39 for these 4 endpoints: percentage change in spleen volume (MN); absolute change in hemoglobin level (in g/dL), percentage change in liver volume (in MN), and percentage change in platelet count. For this analysis, Baseline for the original placebo patients will be the start of the Open Label Period (Day 1 of the Open Label Period) and Baseline for the original Genz 112638 patients will be the start of the Double Blind Primary Analysis Period (Day 1). This will provide a Baseline prior to the start of Genz 112638 treatment. The data from both treatment groups will be aligned based on time on Genz 112638 treatment and changes from Baseline will be summarized. If the with-in patient changes on the mentioned endpoints are normally distributed then paired T-test procedure will be used to analyze the ITT population. If the with-in patient changes are not normally distributed then Wilcoxon signed-ranks test will be used to analyze the ITT population. The PP population analysis will also be conducted in similar manner. The spleen volume assessment obtained at Week 39 or the last available spleen volume assessment in the case of early withdrawal will be used as the Week 39 assessment. Likewise, the subset of the ITT population who complete 39 weeks of treatment and have the Baseline and Week 39 assessment for spleen volume will also be analyzed in a similar manner. Note: For the original placebo patients, appropriate aligned week assessment will be used for analysis.

11.7.3 Tertiary Efficacy Analyses

Tertiary efficacy endpoints include the following: Biomarkers (CCL18 and chitotriosidase); bone disease assessments (X-ray, DXA, MRI, and bone marrow burden score); Gaucher assessments (mobility, bone crisis, and bone pain); and QOL questionnaires (BPI, FSS, and SF-36) For the Double-Blind Primary Analysis Period, the continuous tertiary efficacy endpoint
parameters and changes (absolute or percentage) in these endpoints will be summarized and analyzed by treatment group as detailed in the SAP. Likewise, any categorical tertiary endpoint parameters will be summarized and analyzed by treatment groups as detailed in the SAP. The biomarkers will be analyzed using ANCOVA in the same manner as described for the primary efficacy endpoint.

11.7.4 Exploratory Efficacy Analyses

Exploratory efficacy endpoints include Gaucher disease severity score system (DS3) and investigational biomarkers including GL-1 assayed from DBS on filter paper and from plasma, as well as GM3, ceramide, sphingomyelin, MIP1-β, and lyso-GL-1 (assayed from plasma) and serum biomarkers of bone formation (e.g., BAP) and bone resorption (e.g., CTx-I). For the Double-Blind Primary Analysis Period, the continuous exploratory efficacy endpoint parameters and changes (absolute or percentage) in these endpoints will be summarized and analyzed by treatment group as detailed in the SAP. Likewise, any categorical exploratory endpoint parameters will be summarized and analyzed by treatment groups as detailed in the SAP. GL-1 will be analyzed using ANCOVA in the same manner as described for the primary efficacy endpoint.

11.7.5 Open-Label Period Efficacy Analyses

Long-term efficacy will be summarized for the various parameters based on patients who remain in the study during the Open-Label Period and who have data at the particular timepoints. Long-term efficacy analysis in the primary, secondary, tertiary, and exploratory continuous parameters will be based upon absolute or percent changes from Baseline (as outlined in the SAP). In the Open-Label Period, Baseline for the original placebo patients will be the start of the Open-Label Period (Day 1 of the Open-Label Period) and Baseline for the original Genz-112638 patients will be the start of the Double-Blind Primary Analysis Period (Day 1). This will provide a Baseline prior to the start of Genz-112638 treatment. The data from both treatment groups will be aligned based on time on Genz-112638 treatment and changes from Baseline will be summarized. Any categorical endpoints will be summarized according to appropriately timepoints.

11.8 Safety Analyses

Safety analyses will be performed on the safety population defined as all patients who receive at least 1 dose of Genz-112638 or placebo.

For the Double-Blind Primary Analysis Period, safety results will be reported by treatment...
group. For the Open-Label Period, safety results will also be reported by treatment group as changes from Baseline to study completion, where Baseline refers to start of Genz-112638 treatment.

For the Double-Blind Primary Analysis Period, AEs will be summarized by incidence, preferred term, system organ class (SOC), seriousness, severity and relationship to treatment overall and by treatment group. Concomitant medications will also be summarized by incidence/frequency overall and by treatment group. Both pre-treatment and treatment-emergent AEs will be summarized. Changes from Baseline (start of placebo or Genz-112638 treatment) in vital signs, laboratory assessments (chemistry, hematology, and urinalysis), ECG assessments and ECHOs with Doppler will be summarized by treatment group. The changes from Baseline in ECG parameters such as RR, PR, QRS, QTc, QTcB, and QTcF intervals will be summarized by gender and treatment group. Electrophysiological assessments will be summarized by treatment group. Neurologic examinations, chest X-rays, bone disease assessments, physical examinations, Holter monitoring, and MMSE will also be summarized by treatment group for the different timepoints. Likewise, analysis of clinical laboratory tests will be based upon changes from Baseline (mean, median, SD, and range) and shift tables (L, normal [N], H) will be summarized by treatment group.

For the Open-Label Period, data from both treatment groups will be aligned based on time on Genz-112638 treatment for all safety parameters. AEs will be summarized by incidence, preferred term, SOC, seriousness, severity, and relationship to Genz-112638 and to underlying disease. Concomitant medications will also be summarized by incidence/frequency. Changes from Baseline (start of Genz-112638 treatment) in vital signs, laboratory assessments (chemistry, hematology, and urinalysis), ECG assessments, and ECHOs with Doppler will be summarized. The changes from Baseline in ECG parameters such as RR, PR, QRS, QTc, QTcB, and QTcF intervals will be summarized by gender. Electrophysiological assessments will be summarized. Neurologic examinations, chest X-rays, bone disease assessments, physical examinations, Holter monitoring, and MMSE will also be summarized for the different timepoints. Likewise, analysis of clinical laboratory tests will be based upon changes from Baseline (mean, median, SD, and range) and shift tables (L, N, H) for all treated patients will be produced.

11.8.1 Adverse Event Coding and Categorization

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 10 or higher. The incidence of overall AEs will be summarized by preferred term, SOC,
seriousness, severity, and relationship to treatment as well as by treatment group at onset of the AE. AEs will be considered drug-related if classified by the Investigator as definitely, probably, or possibly related to study drug and not related if classified by the Investigator as unlikely/remote or unrelated to study drug, or related to underlying disease.

All AEs will be summarized by both event counts and patient counts and stratified by treatment group. For patient counts, if a patient has more than one occurrence of an AE for a specific preferred term or SOC, the patient will be counted only once for that preferred term or SOC. The most severe occurrence of an AE, as well as the most extreme relationship of the AE will be indicated in cases of multiple occurrences of the same AE at onset of the AE.

11.8.2 Laboratory Parameters

Abnormal clinical laboratory values will be flagged as either L or H based on the normal ranges for each laboratory parameter. Analysis of clinical laboratory tests will be based upon changes from Baseline (mean, median, SD, and range) and shift tables (L, N, H) will be presented. All laboratory parameters will also be provided in by-patient listings. Graphical displays will be presented as appropriate.

11.9 Pharmacokinetic Analysis

Serial plasma concentration time data collected for Genz-99067 will be analyzed using non-compartmental methods for all patients with evaluable data. Actual sample and dosing times will be used for pharmacokinetic analyses. Pharmacokinetic parameters, as data permit, will be reported for individual patients and summarized using descriptive statistics by dose and visit. Trough concentrations will be summarized separately, along with other single time-point plasma concentration data by dose and visit. Exploratory PK-PD analyses may be performed as deemed necessary.

Exploratory metabolite analysis will be performed on select plasma samples. If data permit, pharmacokinetic parameters will be estimated for metabolites using non-compartmental methods. These will be reported for individual subjects and summarized using descriptive statistics.

In addition to non-compartmental analyses or when the data do not lend to a non-compartmental approach, pharmacokinetic data will be analyzed using non-linear mixed-effects modeling approach for population pharmacokinetic analyses. For population PK analyses, data from this clinical study will be pooled with data from other clinical studies with extensive and/or sparse sampling. The population PK analyses will characterize the inter- and intra-subject variability in
pharmacokinetic parameters and evaluate the effect of covariates such as, but not limited to, demographics (e.g. age, gender, body weight, race), disease status and CYP2D6 status on oral clearance and volume. Exploratory population PK-PD analyses may also be performed to evaluate and characterize exposure-response relationships.

Raw and derived data will be summarized using descriptive statistics and presented graphically, as appropriate.

All PK-PD analyses, with the exception of pooled population PK and population PK-PD analyses, will be summarized in the clinical study report. The pooled population PK and population PK-PD analysis will be summarized in a standalone report.

11.10 Pharmacogenetic Analyses

The pharmacogenomics analysis is considered exploratory. The relationship of pharmacogenetic variability of known ADME and transporter, efficacy and/or safety genes will be examined graphically with respect to pharmacokinetics and pharmacodynamics, respectively. If any relationships are apparent, these will be described in the final clinical study report.

11.11 MRI Test-Retest Analysis

For the subset of patients (up to 20 patients) who complete 6 months of treatment (Week 26) and who have an MRI of the spleen/liver performed 2 times at Week 26, all images of the spleen/liver will be sent to a central imaging vendor for blinded analysis.

11.12 Other Statistical Issues

11.12.1 Significance Levels

Efficacy analyses will be conducted at the 5% level of significance.

11.12.2 Missing or Invalid Data

Note: At Screening, Weeks 39, 78, and 130, every 12 months thereafter, and at study completion, 2 assessments of hemoglobin level and platelet count will be obtained and the average will be used in analyses involving the primary and secondary efficacy endpoints. In the event that a patient is missing 1 of the 2 assessments at a particular timepoint, then the single assessment will be used in the analyses.
For analyses of the Primary Analysis Period, last observation carried forward (LOCF) will be used for patients who withdraw prior to Week 39 in that the last available value in the case of early withdrawal will be used as the Week 39 assessment. For patients who withdraw after Week 26 but prior to Week 39 who have 2 sets of spleen and liver assessments performed (Test-Re-test analysis), the average of these 2 values will be used as the Week 39 assessment.

11.12.3 Computing Environment

Efficacy and safety analyses will be performed using SAS for Windows, Version 9.0 or higher (SAS Institute Inc., Cary, NC).

PK analyses will be performed using WinNonlin Professional, Version 5.0 or higher (Pharsight Corp., Mountain View, CA) or SAS for Windows, Version 9.0 or higher (SAS Institute Inc., Cary, NC).
12. SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) regulations. These requirements are stated in “Guidance for Good Clinical Practice,” ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use.

12.1 Institutional and Ethical Review

This protocol and informed consent form must be reviewed and approved by an IRB/IEC complying with the requirements of the ICH guidelines before randomization of patients. Genzyme must receive the letter or certificate of approval from the IRB/IEC prior to delivery of clinical supplies.

This protocol is designed and will be conducted, recorded, and reported in compliance with the principles of GCP regulations established by the basic principles defined in the ICH Guideline for Industry E6 Good Clinical Practice: Consolidated Guidance.

12.2 Changes to the Conduct of the Study or Protocol

No change in the study procedures shall be effected without the mutual agreement of the Investigator and Genzyme. All significant changes to this protocol must be documented by signed protocol amendments. If changes to the design of the study are made, the amendment must be submitted to and approved by the IRB/IEC, or any other appropriate regulatory authority.
12.3 Investigator's Responsibilities

12.3.1 Patient Informed Consent

Written, informed consent for the study is required from each patient (and/or their parent/legal guardian) prior to Screening and performance of any study-related procedures. Written, informed consent for the optional pharmacogenetic component of the study is required from each patient (and/or their parent/legal guardian) prior to collection of the optional pharmacogenetic sample. It is the responsibility of the Investigator to obtain such consent. Investigators will be expected to remain informed of and to ensure that the informed consent form is compliant with all applicable international and national authority regulations for clinical trial conduct.

Genzyme and the Investigator will develop the informed consent forms for submission to the IRB/IEC. Upon approval by the IRB/IEC, the Investigator must furnish: (1) a photocopy of the approved informed consent forms, and (2) the letter stating formal approval for the study has been granted by the IRB/IEC prior to release of clinical supplies.

Patient confidentiality will be maintained to the extent permitted by applicable laws and regulations. It is the responsibility of the Investigator to report results of evaluations to the patient.

12.3.2 Electronic Case Report Forms

Data will be entered by the study site into the eCRFs. Copies of pertinent records in connection with the study, including patient charts, laboratory data, etc. will be made available to Genzyme or designee on request in a timely manner throughout the course of the study, with due precaution towards protecting the privacy of the patient.

12.3.3 Record Retention

Essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Genzyme. It is the responsibility of Genzyme to inform the investigator/institution as to when these documents no longer need to be retained.
Essential documents are those documents, which individually and collectively, permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Genzyme, and monitor with the standards of GCP and with all applicable regulatory requirements.

Any or all of the documents will be available for audit by Genzyme or designee and inspection by the regulatory authority.

12.3.4 Monitoring

A representative of Genzyme or its designee will visit the Investigator(s) periodically for the purpose of monitoring the progress of this study in accordance with GCP regulations. It is the responsibility of the Investigator(s) to be present or available for consultation during such scheduled monitoring visits. During these routine visits, all data pertaining to a patient’s participation in this clinical investigation must be made available to the monitor.

12.3.5 Study or Site Termination

If the Sponsor, Investigator, DMC, or Regulatory Authorities discover conditions during the study that indicate that the study or study site should be terminated, this action may be taken after appropriate consultation between the Investigator and Genzyme’s Medical Monitor. Conditions that may warrant termination of the study include, but are not limited to the following:

- The discovery of an unexpected, serious, or unacceptable risk to patients randomized in the study.
- The decision on the part of Genzyme to suspend or discontinue testing, evaluation, or development of Genz-112638.
- Failure of the Investigator to comply with pertinent national regulations.
- Submission of knowingly false information from the research facility to Genzyme, IRB/IEC or any national regulatory officials.
- Nonadherence to protocol requirements.

Study termination and follow-up will be performed in compliance with the conditions set forth in applicable local regulations and Sponsor Standard Operating Procedures.
12.3.6  **Investigational Product Control**

12.3.6.1  **Receipt of Clinical Supplies**

A Proof of Receipt (POR), which details the quantity and description of the investigational product, will accompany each shipment of the investigational product from Genzyme to the pharmacist or pharmacy designee. This receipt must be signed, dated, and returned to Genzyme or Genzyme representative by fax transmission. A copy of the signed and dated POR will be retained in the study site pharmacy files. The pharmacist or pharmacy designee must ensure that the investigational product, while in their possession, is maintained in accordance with Sections 8.2.2.1 and 8.2.2.2 of this protocol. Further instructions can be found in the Investigational Product Handling Manual.

12.3.6.2  **Disposition of Unused Clinical Supplies**

All unused blister packs and bottles of investigational product at the study site must be maintained under adequate storage conditions in a limited access area. If any unused investigational product remains on site at study completion, the study site will be instructed to destroy or return the investigational products to Genzyme only after accountability has been performed by a Genzyme Clinical Research representative and upon completion of the required destruction/return forms as supplied by Genzyme or designee. No investigational product will be destroyed or returned unless authorized by a Genzyme Clinical Pharmacy Research Services representative or designee. Further instructions on the disposition of unused investigational product can be found in the Investigational Product Handling Manual.

12.3.7  **Warnings, Precautions, Contraindications**

For specific information concerning warnings, precautions, and contraindications, the Investigator is asked to refer to Section 6 of the Genz-112638 IB.

12.3.8  **Disclosure of Data**

All information obtained during the conduct of this study will be regarded as confidential, and written permission from Genzyme is required prior to disclosing any information relative to this study. Submission to Genzyme for review and comment prior to submission to the publisher will be required at least 30 days prior to submission. This requirement should not be construed as a means of restricting publication, but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware.
12.3.9 Clinical Study Report

A CSR will be produced at the end of the Double-Blind Primary Analysis Period, which will include efficacy, safety, and PK analyses. A final CSR to summarize long-term efficacy, safety, and PK parameters will be produced at study completion, which will include data on all patients in the study for at least 130 weeks.

In accordance with European regulatory requirements, a Coordinating Investigator will be designated by the Sponsor to review and sign the completed CSR. The Coordinating Investigator shall be identified by the Sponsor upon the completion of the study, based on factors including, but not limited to, prior clinical research experience and publications, research advisory capacity, patient randomization and level of involvement in the study.
13. REFERENCES


ELELYSO (taliglucerase alfa) [package insert]. New York, NY; Pfizer Labs; 2012.


14. APPENDICES

14.1 Pharmacogenetic Analysis of Candidate Genes

Genotyping of the candidate genes will be performed if it is believed or hypothesized by Genzyme that such genetic analysis might help clarify issues with the clinical data. Potential candidate genes within each category of interest are listed below.

1. **Genes involved in absorption, distribution, metabolism, excretion, and transport**, e.g., ABCB1 (MDR1), ABCB4 (MDR3), ABCC1 (MRP1), ABCC2 (MRP2), ADH, AHR, ALDH, ARNT, CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4, CYP3A5, CYP4B1, EPHX1, EPHX2, FMO1-4, GSTM1, GSTP2, GSTT1, MEH, MPO, NAT1, NAT2, NFE2L2, NR1I2 (PXR), SULT1A1, SULT1A2, SULT2A1, TPMT, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT2B15, UGT2B4, UGT2B7, SLC22A6-8, and 11 (OAT gene family), SLC21A3, SLC21A9, SLC21A11 and SLC21A12 (OATP gene family).

2. **Genes potentially involved in cardiac arrhythmias including QT-associated genes**, e.g., GJA1, GJA5, LMNA, NKX2.5, KCNE1, KCNE2, KCNQ2 (HERG), KCNQ1, and SCN5A.

3. **Genes related to the drug target and corresponding signaling pathways**, e.g., UGCG (Ichikawa, 1997, *Cytogenet Cell Genet.*), CHIT1

4. **Genes related to Gaucher’s disease**, e.g., GBA

5. **Genes encoding off-target proteins**, e.g., RYR2, CLCN3, CACNA1C/CACNB2/CACNA2D1, CACNA1H, HCN2, HCN4, KCNJ2, KCNJ3/KCNJ5, KCNJ11/ABCC9, KCNA5, KCNH2, KCND2, KCND3/KCNIP2, KCNQ1/KCNQ1, KCNQ1/KCNQ2, SCN5A, TRPC1, TRPC3, TRPC5, TRPM4

**References**