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STATISTICAL ANALYSIS PLAN

Open Label Interventional Multicenter Phase 3b Study to Evaluate the Skeletal Response to Eliglustat in Adult Patients Who Successfully Completed the Phase 2 or Phase 3 Studies (EXOSKEL)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ATC:	anatomic category
BMD:	bone mineral density
BMI:	body mass index
BQL:	below quantification level
CRF:	case report form
CTx:	C-telopeptide-bone resorption
CYP2D6:	Cytochrome P450 2D6
DXA:	dual-energy X-ray absorptiometry
ECG:	electrocardiogram
ERT:	enzyme replacement treatment
FAS:	full analysis set
GD1:	Gaucher disease type 1
GL-1:	Glucosylceramide
HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high-level term
LLOQ:	lower limit of quantification
LLT:	lower-level term
lyso-GL-1:	lyso glucosylceramide
MCS:	mental component scale
MedDRA:	Medical Dictionary for Regulatory Activities
MIP 1 β:	Macrophage inflammatory protein-1 beta
MN:	multiples of normal
MRI:	Megnetic Resonance Imaging
P1NP:	Procollagen type I N-terminal propeptide
PCS:	physical component scale
PK:	pharmacokinetic
PT:	preferred term
QOL:	quality of life
SAE:	serious adverse event
SD:	standard deviation
SOC:	system organ class
TEAE:	treatment emergent adverse event
URM:	ultra-rapid metabolizer
WHO-DD:	World Health Organization-Drug dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is an open label, interventional, non-comparative, multicenter, multinational Phase 3b study to evaluate long term skeletal response to eliglustat and eliglustat safety and effect on quality of life in adult patients who successfully completed one of the Phase 2 (GZGD00304) or Phase 3 studies (GZGD02507, GZGD02607, GZGD03109) in the eliglustat program. This study is considered an extension of these previous studies and will continue to evaluate the safety of eliglustat and patients' quality of life (SF-36).

Participating investigators will enroll patients who successfully completed one of the Phase 2 or Phase 3 studies. Patients will be treated for a minimum of 2 years and up to 4 years, or until eliglustat is approved and available to patients through reimbursement. If after 4 years since the beginning of the study eliglustat is not approved and available to patients in participating country, patients in this country may continue to receive study treatment until eliglustat is available to patients through the compassionate use (expanded access) program or is approved and available through reimbursement, whichever comes first.

Note: Eliglustat (United States Adopted Name [USAN]: eliglustat tartrate, previously Genz-112638) is an L-tartaric acid salt, and exists in plasma as a free base, Genz-99067, which is the active moiety. Throughout this SAP, Genz-99067 is used when referring to drug exposure (eg, plasma concentrations), and eliglustat is used in all other instances.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate long term skeletal response to eliglustat in adult patients who successfully completed one of the Phase 2 or Phase 3 studies.

1.2.2 Secondary objectives

The secondary objectives are to evaluate:

- The safety of eliglustat by (S)AE continuous monitoring,
- The quality of life by Short Form-36 Health Survey and
- Biomarkers of GD1 (chitotriosidase, plasma GL-1 and lyso-GL-1).

1.3 DETERMINATION OF SAMPLE SIZE

This study will enroll all eligible patients having completed one of the Phase 2 or Phase 3 trials (approximately 32 patients).

This is a long term extension study. No sample size calculation has been performed. The patients who will be enrolled have already been receiving the IMP for approximately 4 to 8 years prior to the start of the study. The aim of the study is to continue collecting long term data on the efficacy and safety of the IMP.

1.4 STUDY PLAN

This is an open label, interventional, non-comparative, multicenter, multinational Phase 3b study to evaluate long term skeletal responses to eliglustat, eliglustat safety and effect on quality of life in adult patients who successfully completed one of the Phase 2 or Phase 3 studies in the eliglustat program.

The study includes a screening period from Day -45 to Day -1 and a long-term treatment period from Day 1 to the end of study. The duration of study participation for individual patients will be at least 2 years (unless early discontinuation occurs) and up to 4 years, or until commercial eliglustat is available to patients through reimbursement.

Analysis will be performed on safety and efficacy endpoints at 2 points in this study:

- After the last patient enrolled has completed 2 years of treatment (two-year analysis period)
- At the study completion

Table 1 - Study schedule

Variable	Visit schedule
Gaucher disease clinical assessment (mobility, bone crisis and bone pain)	Screening, every 52 weeks (yearly) until end of study visit
X-ray femurs and lumbar spine	Screening, every 104 weeks (every 2 years) until end of study visit
DXA (hip and lumbar spine)	Screening, every 52 weeks (yearly) until end of study visit
MRI (entire bilateral femur and lumbar spine, Spleen and liver volume)	Screening, every 52 weeks (yearly) until end of study visit
QOL questionnaire (SF36)	Screening, every 26 weeks (every half year) until end of study visit
Hematology (including HGB and PLAT)	Screening, every 26 weeks (every half year) until end of study visit
Serum chemistry (AST, ALT, AP, Total bilirubin, albumin, GGT)	Screening

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The definition for treatment-emergent period was added for clarification, specifying the on-treatment period and residual treatment periods, respectively in Section 2.1.4.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline is referred to study baseline, which is defined as available assessment result or status before the first dose of eliglustat in this study.

All baseline safety and efficacy parameters are presented along with the on-treatment summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are gender (Male, Female), race (Caucasian/white, Black, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other), Jewish Descent (Jewish Ashkenazi, Jewish Sephardic, Non-Jewish), age at study entry in years (quantitative), ethnicity (Hispanic/Latino, non-Hispanic/Latino).

Medical or surgical history

Medical (or surgical) history will be completed according to the protocol.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database.

Medical (or surgical) history recorded in the previous study will not be re-entered as medical (or surgical) history in this study, but will be used in the analysis of this study.

Disease characteristics at baseline

Specific disease history includes the following:

- Time since initial Gaucher diagnosis relative to enrollment (in years)
- Time since first symptoms of Gaucher relative to enrollment (in years)
- CYP2D6 metabolizer status (poor, intermediate, extensive, ultra-rapid)

Vital signs

Vital signs at baseline are height at study entry (quantitative), weight at study entry (quantitative) and BMI at study entry (quantitative).

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken within 30 days prior to patient providing written, informed consent to the study until the end of the study, including eliglustat if the last dose of eliglustat in the previous study happened in this period of time, are to be reported in the case report form pages. Enzyme replacement treatment (ERT) should also be included if the patient was on ERT during the period between the end of the previous study and the screening visit.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are all ongoing medications at the time of screening, and medications received during the 30 day period prior to screening even if no longer taken at the time of screening, including eliglustat and enzyme replacement therapy (ERT). Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly with eliglustat, during the on-treatment period. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started after the on-treatment period (as defined in the observation period in Section 2.1.4).

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

The detailed assessment schedule refers to Table 1 in Section 1.4. No imputation will be conduct for all the endpoints.

2.1.3.1 Primary efficacy endpoint(s)

Five common skeletal manifestations of Gaucher disease will be assessed:

- Mobility, bone pain and bone crisis, as assessed by the Gaucher Disease clinical assessments;
- Bone marrow infiltration;
- BMD;
- Lytic lesions, osteonecrosis, fractures and infarcts;
- Bone biomarkers.

2.1.3.1.1 Gaucher disease clinical assessments (mobility, bone pain, bone crisis)

Patients will be asked to rate mobility and bone pain as below:

- Current mobility
  - Unrestricted mobility
  - Walks with difficulty
  - Walks with orthopedic aid
  - Requires wheelchair
  - Bedridden
- Level of bone pain during the last 4 weeks as
  - None
  - Very mild
  - Mild
  - Moderate
  - Severe
  - Extreme

In addition, investigators will report the number of bone crisis since the previous assessment. Bone crisis is defined as pain with acute onset, which requires immobilization of the affected area, narcotics for relief of pain, and may be accompanied by one or more of the following: periosteal elevation, elevated white blood cell count, fever, or debilitation of >3 days. Category of number of bone crisis defined as:

- No bone crisis
- 1 – 2 bone crisis
- >2 bone crisis

Gaucher disease clinical assessments will be performed at screening and then yearly.

2.1.3.1.2 Bone marrow infiltration

The assessment of bone marrow infiltration is based on the sum of seven bone marrow burden scores for spine (T1-weighted, T2-weighted, infiltration pattern and fat in basivertebral region) and femur (T1-weighted, T2-weighted, and sites of involvement) assessed by MRI views. BMB scores range from 0 to 16 and will only be calculated for patients who have non-missing values for all seven scores.

The BMB score for this study will be assessed by two readers. The primary readers will read in pairs, blinded to patient, treatment, and time point. If readers differ by a score of one or more, for each of the questions, for the femur subtotal, for the spine subtotal and for the overall score, a third reader will serve as the adjudicator and will provide a third read. The average of the three reader results will be used in the analysis. Bone marrow infiltration will be measured at screening and then yearly.

Bone MRI will be read locally and centrally. The central reads will be used for analysis.

Lumbar Spine:

T1-weighted:
0 = Slightly hyperintense
1 = Isointense
2 = Slightly hypointense
3 = Hypointense
NA = Not assessable

T2-weighted:
0 = Isointense
1 = Slightly hypointense
1 = Slightly hyperintense
2 = Hypointense
2 = Hyperintense
NA = Not assessable

Infiltration Pattern:
0 = None
1 = Patchy
2 = Diffuse

Fat in basivertebral vein region
0 = Preservation of fat
1 = Absence of fat
NA = Not assessable

Femur:

T1-weighted:
0 = Slightly hyperintense or isointense
1 = Slightly hypointense
2= Hypointense
NA = Not assessable

T2-weighted:
0 = Isointense
1= Slightly hypointense
1= Slightly hyperintense
2= Hypointense
2= Hyperintense
3= Mixed type
NA = Not assessable

Sites of Involvement:
0 = No site involvement
1 = Diaphysis
2 = Proximal epiphysis / apophysis
3 = Distal epiphysis
NA = Not assessable

2.1.3.1.3 Bone mineral density (BMD)

BMD will be measured by DXA of both hips and the lumbar spine. T and Z scores, and bone mineral densities will be provided by the DXA report.

Centrally reviewed DXA data will be used to determine each patient's bone density category:

T-score Bone Density Categories:

- Normal: T-score > -1
- Osteopenia: -2.5 < T-score ≤ -1
- Osteoporosis: T-score ≤2.5

Z-score Bone Density Categories:

- Normal: Z-score > -2
- Below Normal: Z-score ≤ -2

Bone mineral density will be measured at screening and then yearly.

2.1.3.1.4 Lytic lesions, osteonecrosis, fractures and infarcts

Lytic lesions, osteonecrosis, infarcts and fractures will be assessed on bone MRI and bone X-Ray. Bone MRI will be assessed at screening and then yearly. Bone X-Ray will be collected at screening and every 2 years.

Spine:
Infarction:
0 = Not Present
1 = Present
2 = Present, Unchanged
3 = Present, Larger
4 = Present, Smaller
NA = Not Available
NV = Not Viewable

Avascular Necrosis:
0 = Not Present
1 = Present
2 = Present, Unchanged
3 = Present, Larger
4 = Present, Smaller
NA = Not Available
NV = Not Viewable

Lytic lesion:
0 = Not Present
1 = Present
2 = Present, Unchanged
3 = Present, Larger
4 = Present, Smaller
NA = Not Available
NV = Not Viewable

Fracture:
0 = Not Present
1 = Present
2 = Present, Unchanged
3 = Present, Larger
NA = Not Available
NV = Not Viewable

Femur:
Infarction:
0 = Not Present
1 = Present
2 = Present, Unchanged
3 = Present, Larger
4 = Present, Smaller
NA = Not Available
NV = Not Viewable

Avascular Necrosis (represents infarction in the subchondral bone of the epiphysis):
0 = Not Present
1 = Present
2 = Present, Unchanged
3 = Present, Larger
4 = Present, Smaller
NA = Not Available
NV = Not Viewable

Dark Marrow (Bone Infiltration)
0 = Not Present
1 = Present
2 = Present, Unchanged
3 = Present, Larger
4 = Present, Smaller
NA = Not Available
NV = Not Viewable

Fracture
0 = Not Present
1 = Present
NA = Not Available
NV = Not Viewable

2.1.3.1.5 Bone biomarkers

Bone biomarkers include:

- Total procollagen type 1 N-terminal propeptide (P1NP), a marker of bone formation.
- C-terminal telopeptide of type 1 collagen (CTx), a marker of bone resorption.
- MIP 1 β

These biomarkers will be measured at baseline and then every 6 months.

These markers will be measured by a central laboratory.

Results of centrally read assessments will be available to Investigators during or after the study depending on the assessment.

2.1.3.2 Secondary efficacy endpoint(s)

Blood levels of biomarkers of GD1 (chitotriosidase, plasma GL-1 and lyso-GL-1) will be evaluated at baseline and twice yearly. These markers will be measured in a central laboratory.

Measured values as well as absolute and percent changes from study baseline and eliglustat baseline will be summarized.

2.1.3.2.1 Chitotriosidase Values

Prior to being used in analyses, chitotriosidase values will be normalized using chitotriosidase genotyping information.

Chitotriosidase Genotype	Chitotriosidase value used in analyses
Normal	Value reported from the lab
Heterozygous	Value reported from the lab, multiplied by 2 Homozygous
Mutation	BQL, set to missing (see Section 2.5.1)

2.1.3.3 Additional efficacy endpoint(s)

Spleen volume and liver volume for non-URM patients will be evaluated at screening and every year by MRI. Hemoglobin and platelet results of non-URM patients will be assessed at screening and every half-year along with hematology laboratory test.

For URM patients, the frequency of spleen and liver volume MRI scan can be increased to every 3 months till Week 52. And the frequency of hematology and platelet test can be performed every 6 months till Week 52.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data. The safety endpoints to be analyzed include:

Observation period

The observation period will be divided into 4 periods:

- The **pre-treatment period** is defined as the time from the signed informed consent to first dose of IMP administration in this study.
- The **treatment-emergent period** is defined as the time from the first administration of the IMP to the last administration of the IMP + 5 days. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment** period is defined as the period from the first IMP administration to the last administration of the IMP + 1 day.
  - The **residual treatment** period is defined as the time from the last administration of IMP to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of treatment-emergent period.

The treatment-emergent adverse event (TEAE) observation period includes both on-treatment and residual treatment periods.

The on-study observation period is defined as the time from screening until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events [SAEs] and adverse events of special interest [AESIs]).

2.1.4.1 Adverse events variables

Adverse event observation period

- Pre-treatment adverse events are adverse events that developed or worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs) are adverse events that developed or worsened or became serious during the treatment-emergent period (treatment-emergent adverse event observation period).
- Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period.

Continuous monitoring will be performed for (S)AEs and concomitant medications. Results of pregnancy testing for female patients of childbearing potential will be collected. Patients with an SAE or AESI should be followed until event resolution or when follow-up is no longer considered medically necessary, or the patient is lost to follow-up.

All adverse events (including SAEs and AESIs) will be will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Adverse events (including serious adverse events and adverse event of special interest) will be recorded from the time of signed informed consent until the end of the study.

Any SAE (including death) brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to Global Pharmacovigilance department and will not be recorded in the clinical database.

Serious adverse events and adverse events of special interest (AESI) are defined in the protocol (refer to protocol Section 10.5.1.2 and 10.5.1.3). AESI will be identified and summarized based on CRF information, not standardized or customized MedDRA queries.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at visits described in the protocol or early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation:** Red Blood Cells (RBC), Hemoglobin, Hematocrit, Platelet Count
  - **White blood cells:** White Blood Cells (WBC), Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes
- Clinical chemistry
  - **Markers of liver synthetic function:** Albumin, Total Bilirubin
  - **Markers of hepatocellular damage and cholestasis**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase
  - **Pregnancy test**: Serum β-human chorionic gonadotropin for all female patients of childbearing potential

- **HIV and Hepatitis screen**: Human immunodeficiency virus (HIV) , hepatitis B surface antigen, anti-hepatitis-C antibody

- Urine samples will be collected as follows:
  - **Urinalysis:** Urine pregnancy test.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

No vital sign variables are collected in this study.

2.1.4.5 Electrocardiogram variables

No electrocardiogram and Holter assessment variables are collected in this study.

2.1.4.6 Other safety endpoints

Complete physical exam and complete neurological exam with ocular motility test will be performed. Height and weight will be monitored as well.

2.1.5 Pharmacokinetic variables

Although PK samples are not scheduled, unscheduled PK samples may be collected in individual. There is no planned analysis for these PK samples.

2.1.6 Quality-of-life endpoints

Patients' quality of life (Short Form-36 Health survey) will be evaluated at baseline and twice yearly. Total 8 scales including physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health will be assessed based on SF-36. The two overall summary measures, physical component scale (PCS) and mental component scale (MCS), will be summarized from the 8 scales for quality of life assessment as well. SF-36 health survey is presented in Appendix A.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patient who met the study criteria and signed the informed consent.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Treated patients
- Patients who completed the 2-year study period
- Patients who did not complete the 2-year study treatment period as per protocol
- Patients who completed the whole study period as per protocol
- Patients who did not complete study treatment period as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation

For all categories of patients, percentages will be calculated using the number of screened patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages overall. Listing of permanent and temporary treatment discontinuation reasons by site and by patient will be provided respectively.

A patient is considered lost to follow-up at the end of the study if he/she is not assessed at the last protocol planned visit and failed to response to 3 attempts of contact via phone or registered letter.

All critical or major deviations potentially impacting efficacy analyses, inclusion, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages overall and by site.

Additionally, the analysis populations for safety and efficacy will be summarized in a table by number of patients included in the study.

- Efficacy population
- Safety population
- Pharmacokinetics population

2.2.1 Randomization and drug dispensing irregularities

Since the study is an open-label follow-up study and IVRS was not implemented, the randomization and drug dispending irregularities is not applicable.

2.3 ANALYSIS POPULATIONS

2.3.1 Efficacy populations

Primary and secondary efficacy will be evaluated in the Full Analysis Set population (FAS) defined as all patients enrolled who receive at least 1 dose of eliglustat treatment in this study.

2.3.2 Safety population

Safety analyses will be performed on the Safety Set, which is equivalent to the FAS for this study.

2.3.3 Pharmacokinetic population

Pharmacokinetic (PK) population: a subset of safety population containing patients who have at least one PK sample taken. Patients will be analyzed in the treatment group corresponding to those defined in the safety population.

2.4 STATISTICAL METHODS

Analysis will be performed on safety and efficacy endpoints at 2 points in this study:

- After the last patient enrolled has completed 2 years of treatment (two-year analysis period)
- At the study completion

Both efficacy and safety results will be calculated both in reference to study entry (study period) and to first eliglustat treatment (eliglustat treatment period). Because patients will enter this study having been treated with eliglustat for various durations, two baselines will be used:

- Study baseline, defined as status at study entry, which is the last non-missing value before the first dose of eliglustat of this study; and
- Eliglustat baseline, defined as status at first dose of eliglustat in the previous Phase 2 or Phase 3 studies. The definition of eliglustat baseline should be the last non-missing value prior to first dose of eliglustat in prior studies.

The eliglustat baseline can only be obtained if the assessments in EFC13781 study and the previous studies are comparable. Assessment method, location, parameters, result evaluation, etc should be considered for comparability check if applicable. In addition, eliglustat baseline definition of hemoglobin and platelet for Phase 2 and ENCORE study were defined separately in Section 2.5.2.

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum in overall group. Categorical and ordinal data will be summarized using the number and percentage of patients in overall group.

Parameters will be summarized on the full analysis population analyzed in the overall group to which they were enrolled.

Parameters described in Section 2.1.1 will be summarized in overall treatment groups using descriptive statistics.

Medical and surgical history

Medical and surgical history will be summarized by primary SOC and PT in overall group. The table will be sorted by SOC internationally agreed order and decreasing frequency of PT based on the overall incidence in the overall treatment group. No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

No specific description of the efficacy parameters will be provided at baseline. If relevant, the baseline values will be described along with each efficacy analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the full analysis population.

Medications will be summarized in overall group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of eliglustat exposure and compliance will be assessed and summarized for the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of eliglustat exposure will be assessed by the duration of eliglustat exposure over the course of the study.

Duration of eliglustat exposure is defined as last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of eliglustat exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the

following categories and cumulatively according to these categories: ≤1 year, 1 to ≤2 years, 2 to ≤3 years, 3 to ≤4 years, 4 to ≤5 years, and >5 years.

Additionally, the cumulative duration of eliglustat treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years. A listing of exposure will be produced.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol over the course of the study period. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of capsules taken from Day 1 to end of treatment divided by the total number of capsules that the patient should have taken from Day 1 to end of treatment as per the protocol (BID = 2 capsules per day, QD = 1 capsule per day).

Above-planned dosing percentage for a patient is defined as the number of administrations that the patient took more than 105% of planned dose during the on-treatment period.

Under-planned dosing percentage for a patient is defined as the number of administrations that the patient took less than 90% of planned dose during the on-treatment period. Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum).

The overall compliance will be summarized in categories (<80%, 80% - 90%, 90% - 105%, >105%). In addition, numbers and percentages of patients with at least 1 above-planned dose administration will also be provided, as well as numbers and percentages of patients with 0, (0, 20%], and >20% under-planned dose administrations.

Cases of overdose (defined as actual IMP dose administration is greater than planned dose administration per day) will constitute by protocol as an adverse event of special interest and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

In reference to the study period, efficacy result will be evaluated for all patients at the 2 year point by measured values (eg, category of bone pain, or bone density value in g/cm^2) and changes from baseline (eg, shift in category of bone pain or absolute and percent change from baseline in BMD g/cm^2 or incidence over 2 years, as appropriate).

In reference to the period of eliglustat treatment, efficacy result will be evaluated 2 years after study entry, but results will be grouped by duration of eliglustat treatment at the time of analysis. The actual groupings will depend on the distribution of treatment duration at the time of analysis (eg, ≤5 years verses >5 years).

When the study has completed, summaries will be performed comparing to the 2 baselines as described above if applicable.

All efficacy endpoints will be summarized descriptively; no hypothesis testing will be performed. In general, descriptive statistics (number, mean, standard deviation, minimum and maximum) of the absolute value, change from baseline and/or percentage change from baseline for continuous endpoints will be analyzed. Summary statistics (count, percentage) will be summarized for the categorical endpoints. Cumulative incidence (n, percentage), incidence rate (n/year), or other descriptive statistics will also be displayed as appropriate. Calculations and summaries will include all non-missing data at a given time point, imputation will not be performed.

By-patient data listings containing efficacy endpoints will be produced if necessary.

All the below mentioned other efficacy endpoint analyses will be produced for the full analysis population. Refer to Section 2.5.3 for details on handling dropouts, missing data, and patients who have more than one value assessed within the same time frame.

2.4.4.1 Analysis of primary efficacy endpoint(s)

The main efficacy endpoints of interest are five common manifestations of Gaucher's disease summarized separately which includes:

- Mobility, bone pain and bone crisis, as assessed by the Gaucher Disease clinical assessments;
- Bone marrow infiltration;
- BMD;
- Lytic lesions, osteonecrosis, fractures and infarcts;
- Bone biomarkers.

2.4.4.1.1 Mobility, bone pain and bone crisis

Category of mobility status and bone pain, as well as number of new bone crises, will be summarized by visit. Absolute value, change from baseline and percent change from baseline of bone crisis over time will be summarized using descriptive statistics by visit using two baselines (study baseline and eliglustat baseline). Additionally, shifts in category of mobility and pain from study and eliglustat baseline by each post-baseline visit will be presented.

2.4.4.1.2 Bone marrow infiltration

Bone marrow infiltration score by location and total bone marrow infiltration score will be summarized both continuously and categorically. Absolute values, change and percent change from baseline (study baseline and eliglustat baseline) will be summarized by visit. Category of total infiltration score (Mild: 0 to 4; Moderate: 5 to 8; Severe: 9-16) will be constructed and summarized by visit. Shifts in category of infiltration from study and eliglustat baseline will be summarized by each post-baseline visit.

2.4.4.1.3 BMD

Absolute value, change and percent change from baseline (study baseline and eliglustat baseline) for bone mineral density in (g/cm^2), T and Z scores by location will be summarized by visit. Shift in bone density categories of T and Z scores will be summarized by visit. In addition, mean plots of absolute values and percent change from baseline for total BMD, T-scores, and Z-scores for all patients with standard deviation will be provided.

2.4.4.1.4 Lytic lesions, osteonecrosis, fractures and infarcts

Total incidence of new or worsening lytic lesions, new or worsening AVN, new or worsening infarctions and new fractures among all locations will be summarized since study entry until all the patients completed their 2-year follow-up period and at end of study. Summary statistics (N, mean, standard deviation, median, minimum and maximum) will be displayed by visit. Annual incidence rates and will also be calculated as total number of incidence divided by the total number of person-years. MRI and X-ray assessment result will be summarized separately.

2.4.4.1.5 Bone biomarkers

Absolute values, change and percent change from baseline (study baseline and eliglustat baseline) for levels of P1NP, CTx and MIP 1 β will be summarized by visit.

2.4.4.2 Analyses of secondary efficacy endpoints

For secondary analysis blood levels of biomarkers of GD1 (chitotriosidase, GL-1 and lyso-Gl-1), for all patients and separately for CYP2D6 URMs patients will be evaluated at baseline (study baseline and eliglustat baseline) by visits. Measured values as well as absolute and percent changes from study baseline and eliglustat baseline will be summarized. Analysis similar to those described in Section 2.4.4.1 will be conducted and reproduced.

For lyso-GL-1, analyses will include all available data.

Refer to Section 2.1.3.2.1 for details on how chitotriosidase values will be normalized prior to being used in analyses and for definitions of bone density categories.

2.4.4.3 Multiplicity issues

Not applicable.

2.4.4.4 Additional efficacy analysis(es)

Summary statistics (including number, mean, median, standard deviation, minimum and maximum) of the absolute value, change and percentage change from baseline (study baseline and eliglustat baseline) for spleen volume, liver volume, hemoglobin and platelet results will be presented by visit. Descriptive statistics for CYP2D6 URMs patients will be analyzed separately.

2.4.5 Analyses of safety data

The summary of safety results will be presented for data from the 2-year eliglustat treatment period as well as at study completion by overall. Descriptive summaries will be produced as described below.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not included) will be listed separately.
- The study baseline value is defined as the last available value before the first dose of eliglustat of this study. The eliglustat baseline value is defined as the last available value before the first dose of eliglustat of corresponding initial study.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and overall group.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events (TEAEs). Pre-treatment adverse events and post-treatment adverse events will be described separately, if applicable.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, the undetermined adverse event should be treated as treatment-emergent adverse event. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for overall group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment and treatment-emergent). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the overall group.

Analysis of all pre-treatment adverse events

- Overview of pre-treatment adverse events, summarizing number (%) of patients with any
  - Adverse event
  - Serious adverse event
  - Adverse event with special interest (AESI)
  - Adverse event leading to death
  - Severe adverse event

By-patient listing of all pre-treatment adverse event

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Treatment-emergent serious adverse event
  - Treatment-emergent adverse event of special interest (AESI)
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
  - Treatment- related treatment-emergent adverse event
  - Severe treatment-emergent adverse event
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified
- All treatment-emergent adverse events regardless of relationship and related by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above

- By-patient listing of all treatment-emergent adverse events
- By-patient listing of all severe treatment-emergent adverse event

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order.
- By-patient listing of all serious treatment-emergent adverse events

Analysis of all treatment-emergent adverse event(s) leading to permanent treatment discontinuation

- All treatment-emergent adverse events leading to permanent treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- By-patient listing of all treatment-emergent adverse events leading to permanent treatment discontinuation

Analysis of treatment-emergent adverse events of special interest

- All pre-specified treatment-emergent adverse events of special interest, by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- By-patient listing of all treatment-emergent adverse events of special interest

Analysis of all post-treatment adverse events

- Overview of post-treatment adverse events, summarizing number (%) of patients with any
  - Adverse event
  - Serious adverse event
  - Adverse event of special interest (AESI)
  - Adverse event leading to death
  - Severe adverse event
- By-patient listing of all post-treatment adverse events

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- All adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC and PT showing the number (%) of patients sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC and PT showing the number (%) of patients sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- Number (%) of patients who died by study period (on-study, on-treatment)
- By-patient listing of all AE leading to death

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (central and local laboratory values and changes from baseline, percentage change from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point) in overall group. Both study baseline and eliglustat baseline will be applied to the summary statistics.

By-patient listings for those patients with abnormal laboratory values will be provided by category of laboratory tests. Hemoglobin and platelet test result will be analyzed as above separately. A by-patient data listing of all pregnancy testing for female patients will be produced.

2.4.5.4 Analyses of vital sign variables

No vital sign variables are collected in this study.

2.4.5.5 Analyses of electrocardiogram variables

No electrocardiogram variables are collected in this study.

2.4.5.6 Analyses of other safety endpoints

2.4.5.6.1 Physical examinations

A summary statistics of physical exam findings interpretations will be presented by visit for each body system.

2.4.5.6.2 Weight, height and BMI

A summary statistics of absolute value, changes from baseline and percentage change from baseline (study baseline as well as Eliglustat baseline) in height, weight and BMI will be analyzed by visit.

2.4.5.6.3 Complete neurological examination

A summary statistics of quantitative neurological examinations findings will be presented by visit.

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

No scheduled PK data are collected in this study. But unscheduled PK samples may be collected in individual cases after discussion between the investigator and Genzyme. By-patient listing may be provided if necessary.

2.4.7 Analyses of quality of life/health economics variables

The score for each scale will be estimated from the Short Form-36 Health survey [SF-36]. The overall physical component scale (PCS) and mental component scale (MCS) will be computed. Summary statistics as well as change and percentage change from baseline (study and eliglustat) by visit by all SF-36 QOL variables will be presented.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

For all safety and efficacy parameters, values that are reported as BQL (below quantification level) or LLOQ (lower limit of quantification) will have numeric values set equal to the BQL or LLOQ lower limit (eg, if BQL < 2, then value will be set equal to 2). However, the original value will be displayed in by-patient data listings.

The only exception is for chitotriosidase values. Patients who have a chitotriosidase genotyping category of “Homozygous Mutation” have no expected chitotriosidase activity. Therefore, patients who have a value of BQL reported will have numeric values set equal to missing.

Demographic formulas

Age will be presented as the number of years between date of birth and the reference date. The following ages (in years) may be computed using the formula [(Study (EXOSKEL) reference date – date of birth) + 1 day]/365.25, with reference dates indicated as follows:

Age	Reference Date
Age at study informed consent	Date of study informed consent
Age at Day 1 study dose	Date of first Eliglustat dose of the study
Age at Gaucher disease diagnosis	Date of Gaucher Disease Diagnosis
Age at first Gaucher disease symptom onset	Date of First Gaucher Disease Symptom Onset

If the date of diagnosis is not complete or date of symptom onset is not complete then age at diagnosis or symptom onset will be determined by the month and/or year of date of birth and diagnosis or symptom onset.

Certain assessments may be summarized by age categories which will be determined prior to database lock based on the frequency of ages reported (eg, ≤ median age for all patients, > median age for all patients).

Vital signs formulas

Weight in pounds will be multiplied by 0.4536 to be converted to kilograms (kg); and height in inches will be multiplied by 2.54 to be converted to centimeters (cm).

BMI (kg/ m^2) will be calculated using the following formula:

$$\text{BMI} = \frac{Weight\ (kg)}{Height\ (m^2)}, where\ height\,(m^2) = (height\ (cm) \times 0.01)^2$$

2.5.2 Data handling conventions for secondary efficacy variables

Eliglustat baseline for hemoglobin and platelet count for patients originated from Phase 2 and Encore study

To obtain a single Study Baseline value for Hemoglobin and Platelet Count, the average of the last two measurements prior to receiving Day 1 dose of Eliglustat in the study will be calculated. This average value will be referred to as the Baseline value. If either of the 2 measurements is missing, the Study Baseline value will refer to the non-missing value.

To obtain a single Eliglustat Baseline value for Hemoglobin and Platelet Count, the average of the last two measurements prior to receiving Day 1 dose of Eliglustat in the previous Phase 2 or Phase 3 trials will be calculated. This average value will be referred to as the Eliglustat Baseline value. If either of the 2 measurements is missing, the Eliglustat Baseline value will refer to the non-missing value.

Formulas for calculation of organ Multiples of Normal (MN)

The following equations will be used to calculate multiples of normal (MN) values for spleen and liver volume. If a patient does not have weight assessed on the same date as the spleen/liver volume assessment, the weight having the closest date to the spleen/liver assessment will be used.

$$\text{Spleen Multiple of normal} = \frac{Volume\ [cc]}{2\ \times\ weight\ [kg]}$$

$$\text{Liver Multiple of normal} = \frac{Volume\ [cc]}{25\ \times\ weight\ [kg]}$$

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and posttreatment medication.

Handling of adverse events with missing or partial date/time of onset

In case of missing or inconsistent information, an adverse event (AE) will be counted as a treatment-emergent adverse event (TEAE), unless it can clearly be ruled out that it is not a TEAE (eg, by partial dates or other information).

If the start date of an AE is incomplete or missing, it will be counted as TEAE except if an incomplete date indicates that the AE started prior to treatment.

No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of enrollment should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

No imputation of the severity of AEs will be performed.

2.5.4 Windows for time points

The time window is defined as below to create analysis visit. The relative day below is referred to the first dose intake in the EFC13781 study. The end of study is defined as patient completed at least 2 years of follow-up (unless early discontinuation) up to 4 years or early discontinued from the study or until commercial eliglustat is available to the patients. Thus, the analysis visit list may be longer than the list below. The same algorithm will be applied to the trailing visits after the Week 416 if applicable.

Table 2 - Analysis visit schedule

Analysis visit	Target day	Schedule A	Schedule B	Schedule C	Schedule D
Baseline	1	[-45, 1]	[-45, 1]	[-45, 1]	[-45, 1]
Week 26	182	[2, 272]		[2, 272]	
Week 52	364	[273, 454]	[2, 545]	[273, 454]	
Week 78	546	[455, 636]		[455, 636]	
Week 104	728	[637, 818]	[546, 909]	[637, 818]	[2, 1091]
Week 130	910	[819, 1000]		[819, 1000]	
Week 156	1092	[1001, 1182]	[910, 1273]	[1001, 1182]	
Week 182	1274	[1183, 1364]		[1183, 1364]	
Week 208	1456	[1365, 1546]	[1274, 1637]	[1365, 1546]	[1092, 1819]
Week 234	1638	[1547, 1728]		[1547, 1728]	
Week 260	1820	[1729, 1910]	[1638, 2001]	[1729, 1910]	
Week 286	2002	[1911, 2092]		[1911, 2092]	
Week 312	2184	[2093, 2274]	[2002, 2365]	[2093, 2274]	[1820, 2547]
Week 338	2366	[2275, 2456]		[2275, 2456]	
Week 364	2548	[2457, 2638]	[2366, 2729]	[2457, 2638]	
Week 390	2730	[2639, 2820]		[2639, 2820]	
Week 416	2912	[2821, 3002]	[2730, 3093]	[2821, 3002]	[2548, 3275]

Note: Target day is calculated as number of week times 7 days.
The relative day is calculated as date of assessment - first eliglustat administration date in EFC13781 + 1.
Schedule A should be applied to complete physical examination and blood pregnancy test.
Schedule B should be applied to Gaucher disease clinical assessment, DXA, MRI (femur, lumbar, spleen, liver) assessment.
Scheduled C should be applied to QOL (SF36), Biomarkers and Hematology assessment.
Scheduled D should be applied to X-ray (femurs, lumbar spine) assessment.

Analysis flag will be generated to ensure only one assessment per parameter per analysis visit time window can be included in the analysis. The assessment closest to the targeted visit date will be used in the presence of multiple measurements within the same time window. When there are multiple measurements have the same distance compare to the target day, then scheduled visit should be selected first, than unscheduled visit can be considered. If there is still “tie” situation, we will choose the later one.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries (unless it is for repeat liver or spleen volume assessment), but will be used for computation of baseline and/or worst values.

2.5.6 Pooling of centers for statistical analyses

None planned.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

There is no interim analysis planned. However, early analysis, including major efficacy and safety endpoints, will be performed after the last patient enrolled and completed 2 years of treatment (two-year analysis period).

Only data collected up to the date of all patients completed 2-year analysis period will be used for this early analysis.

Summary of patient disposition, demographics and key baseline characteristics, prior and concomitant medications, extent of IMP exposure and compliance will be provided, as described in Section 2.2, Section 2.4.1, Section 2.4.2, and Section 2.4.3, respectively, in the analysis report.

For efficacy endpoints, the 2-year analysis will be performed for the following efficacy endpoints in which details are provided in Section 2.4.4.

- Mobility, bone pain and bone crisis, as assessed by the Gaucher Disease clinical assessments
- Bone marrow infiltration
- BMD
- Lytic lesions, osteonecrosis, fractures and infarcts
- Bone biomarkers
- Blood levels of biomarkers of GD1 (chitotriosidase, plasma GL-1 and lyso-GL-1)
- Gaucher disease related hematology assessment (hemoglobin, platelet)
- Spleen volume and liver volume

For safety endpoints, key safety results including TEAE, SAE, AESI, death, AEs leading to treatment discontinuation along with related laboratory values, in which details are provided in Section 2.4.5 will be provided in the 2-year analysis report.

4 DATABASE LOCK

The 2-year analysis is planned to be locked approximately 28 days after last patient completed 2-year follow-up. The final database is planned to be locked at approximately 28 days after last patient last visit.

5 SOFTWARE DOCUMENTATION

All tables, listings, and figures will be generated in a validated environment using SAS® version 9 or higher.

6 REFERENCES

1. Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish MW. User's Manual for the SF-36v2 Health Survey, 2nd ed. QualityMetric Incorporated, Lincoln, RI; 2007.

7 LIST OF APPENDICES

Appendix A SF-36 health survey

A number of computations must be carried out to go from SF-36 questionnaire responses to summary scores. These computations are described in this section.

Each questionnaire item has a final item value, which will be used in the computation of the raw score for each of the eight scales. Many questionnaire items have a final item value that is equivalent to its pre-coded item value. Prior to any summary scores being calculated, ten items in the questionnaire will be re-coded according to the developer's instructions as follows:

Item 7

Response Choices	Pre-coded Item Value	Final Item Value
None	1	6.0
Very Mild	2	5.4
Mild	3	4.2
Moderate	4	3.1
Severe	5	2.2
Very Severe	6	1.0

Item 8 – if both Items 7 and 8 are answered.

Response Choices	Item 8 Pre-coded Item Value	Item 7 Pre-coded Item Value	Final Item Value
Not At All	1	1	6
Not At All	1	2 through 6	5
A Little Bit	2	1 through 6	4
Moderately	3	1 through 6	3
Quite A Bit	4	1 through 6	2
Extremely	5	1 through 6	1

Item 8 – if Item 7 is not answered.

Response Choices	Pre-coded Item Value	Final Item Value
Not At All	1	6.0
A Little Bit	2	4.75
Moderately	3	3.5
Quite A Bit	4	2.25
Extremely	5	1.0

Item 1

Response Choices	Pre-coded Item Value	Final Item Value
Excellent	1	5.0
Very Good	2	4.4
Good	3	3.4
Fair	4	2.0
Poor	5	1.0

Items 11b and 11d

Response Choices	Pre-coded Item Value	Final Item Value
Definitely True	1	5
Mostly True	2	4
Don't Know	3	3
Mostly False	4	2
Definitely False	5	1

Items 9a, 9d, 9e and 9h

Response Choices	Pre-coded Item Value	Final Item Value
All of the Time	1	5
Most of the Time	2	4
Some of the Time	3	3
A Little of the Time	4	2
None of the Time	5	1

Item 6

Response Choices	Pre-coded Item Value	Final Item Value
Not At All	1	5
Slightly	2	4
Moderately	3	3
Quite A Bit	4	2
Extremely	5	1

Item 2

Response Choices	Pre-coded Item Value	Final Item Value
Much Better	1	5
Somewhat Better	2	4
About the Same	3	3
Somewhat worse	4	2
Much worse	5	1

Raw scale scores are calculated using final item values. The raw scale scores will be computed by taking the sum of the items for that particular scale (see Table below). A respondent has to have answered at least 50% of the items contributing to a particular scale for a raw scale score to be computed. If the respondent did not answer at least 50% of the items contributing to a particular scale at a particular time point, the raw scale score will be set to missing for that scale for that respondent for that particular time point. If a respondent has answered at least 50% of the items contributing to a particular scale but some of the items were not answered, the missing items will be estimated by the average score across the items that were answered.

Each raw scale score will then be transformed to a 0 to 100 scale using the following formula:

$$\text{Transformed Scale} = \frac{[\text{Actual raw score} - \text{Lowest possible raw score}]}{\text{Possible raw score range}} \times 100$$

Lowest possible raw score and possible raw score range values are:

SF-36 Raw and Transformed Scale Score Specifications

Scale	Sum of Final Item Values for Raw Scale Score	Lowest And Highest Possible Raw Scores	Possible Raw Score Range
Physical Functioning (PF)	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j	10, 30	20
Role-Physical (RP)	4a + 4b + 4c + 4d	4, 20	16
Bodily Pain (BP)	7 + 8	2, 12	10
General Health (GH)	1 + 11a + 11b + 11c + 11d	5, 25	20
Vitality (VT)	9a + 9e + 9g + 9i	4, 20	16
Social Functioning (SF)	6 + 10	2, 10	8
Role-Emotional (RE)	5a + 5b + 5c	3, 15	12
Mental Health (MH)	9b + 9c + 9d + 9f + 9h	5, 25	20

The two overall summary scores will be calculated by first determining the Z-scores for the eight scales as follows:

$$\text{Z} - \text{score} = \frac{(\text{raw scale score} - \text{mean})}{SD}$$

where mean and SD are the appropriate mean and standard deviation of the 1998 general U.S. population (1). Z-scores are in standard deviation units.

The raw PCS and MCS summary scores will be computed by multiplying the z scores for the raw component scores (PCS: PF, RP, BP, GH, VT, SF, RE, MH; MCS: PF, RP, BP, GH, VT, SF, RE, MH) by the corresponding scoring coefficients (from the general U.S. population [1]) and taking the sum of those values. Finally, the PCS and MCS will be standardized as follows:

$$\text{PCS} = (\text{raw PCS x } 10) + 50$$

$$\text{MCS} = (\text{raw MCS x } 10) + 50$$

Appendix B Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	***Analysis population***	***Primary analysis***	***Supportive analysis***	***Subgroup analysis***	***Other analyses***
Primary endpoints					
Gaucher Disease clinical assessments: Mobility, bone pain, bone crisis	*FAS*	*Descriptive statistics*	*No*	*No*	*No*
Bone marrow infiltration	*FAS*	*Descriptive statistics*	*No*	*No*	*No*
Bone mineral density (BMD)	*FAS*	*Descriptive statistics*	*No*	*No*	*No*
Lytic lesions, osteonecrosis, fractures and infarcts	*FAS*	*Descriptive statistics*	*Annual incidence rate*	*No*	*No*
Bone biomarker	*FAS*	*Descriptive statistics*	*No*	*No*	*No*
Secondary endpoints					
GD-1 biomarker	*FAS*	*Descriptive statistics*	*No*	*No*	*No*

SAFETY ANALYSES

Endpoint	***Analysis population***	***Primary analysis***	***Supportive analysis***	***Subgroup analysis***	***Other analyses***
Adverse events	*Safety*	*Descriptive statistics*	*No*	*No*	*No*
Laboratory, other safety	*Safety*	*Descriptive statistics*	*No*	*No*	*No*

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