NCT02536755

AMENDED CLINICAL TRIAL PROTOCOL 02

COMPOUND: Eliglustat (GZ385660)

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

STUDY NUMBER: EFC13781

STUDY NAME: EXOSKEL

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NAMES AND ADDRESSES OF

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OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: GZ385660	**STUDY No: EFC13781** **STUDY NAME: EXOSKEL**
TITLE	Open Label Interventional Multicenter Phase 3b Study to Evaluate Skeletal Response to Eliglustat in Adult Patients Who Successfully Completed the Phase 2 or Phase 3 Studies
INVESTIGATOR/TRIAL LOCATION	The study centers that participated in the eliglustat Phase 2 or Phase 3 studies are eligible to participate in this study.
PHASE OF DEVELOPMENT	Phase 3b
STUDY OBJECTIVE(S)	**Primary objective** Evaluate long term skeletal response to eliglustat in adult patients who successfully completed one of the Phase 2 or Phase 3 eliglustat studies. **Secondary objective(s)** Evaluate the safety of eliglustat (by (serious) adverse event (AE) continuous monitoring), the quality of life (Short Form-36 Health Survey (SF-36)) and biomarkers of Gaucher disease type 1 (GD1) (chitotriosidase, plasma glucosylceramide (GL-1) and lyso glucosylceramide (lyso-GL-1)) in adult patients who successfully completed one of the Phase 2 or Phase 3 studies.
STUDY DESIGN	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 or Phase 3 studies 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.
STUDY POPULATION **Main selection criteria**	Adult patients who completed successfully the Phase 2 (GZGD00304) or a Phase 3 study (GZGD02507, GZGD02607 or GZGD03109). **Inclusion criteria** I 01. The patient must have successfully* completed the Phase 2 (GZGD00304) or a Phase 3 study (GZGD02507, GZGD02607 or GZGD03109). * Successful completion is defined as patients enrolled in one of the above mentioned studies who received eliglustat through the end of the study and completed the end of study visit without having

	discontinued or been withdrawn prematurely.
	I 02. The patient is willing and able to provide signed informed consent prior to any protocol required procedures being performed.
	I 03. Female patients of childbearing potential must have a documented negative pregnancy test prior to enrollment and while they are receiving eliglustat treatment.
	I 04. Female patients of childbearing potential must be willing to practice true abstinence in line with their preferred and usual lifestyle, or use a medically accepted form of contraception (either a barrier method, such as condom or diaphragm + spermicide, or a non-barrier method such as oral, injected, or implanted hormonal methods, or an intra-uterine device or system) while receiving eliglustat.
	Exclusion criteria
	E 01. The patient is unwilling to comply with the requirements of the protocol.
	E 02. The patient has received an investigational product (other than eliglustat) within 30 days prior to enrollment.
	E 03. The patient has received miglustat within the 6 months prior to enrollment.
	E 04. The patient has documented prior esophageal varices or liver infarction or current liver enzymes (alanine transaminase [ALT]/aspartate aminotransferase [AST]) or Total Bilirubin >2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.
	E 05. The patient has any clinically significant disease, other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic (eg, hypokalemia, hypomagnesemia), psychiatric disease, other medical conditions, or serious intercurrent illnesses that may preclude participation in the study.
	E 06. The patient is known to have any of the following: cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, or current treatment with Class IA or Class III antiarrhythmic medicinal products.
	E 07. The patient has tested positive for the human immunodeficiency virus (HIV) antibody, hepatitis C antibody, or hepatitis B surface antigen.
	E 08. The patient has a history of cancer within 6 months of enrolment, with the exception of basal cell carcinoma.
	E 09. The patient is cytochrome P450 (CYP) 2D6 intermediate (IMs), extensive (EMs) or ultra-rapid (URM) metabolizer and taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
	E 10. The patient is CYP2D6 poor metabolizer (PMs) having taken a strong CYP3A inhibitor within 2 weeks prior to enrolment.
	E 11. If a female patient of childbearing potential has a positive pregnancy test blood β-Human Chorionic Gonadotropin (β-HCG) or is breastfeeding prior to first dosing of eliglustat in this study, the patient cannot enroll in the study at this time, but may be rescreened

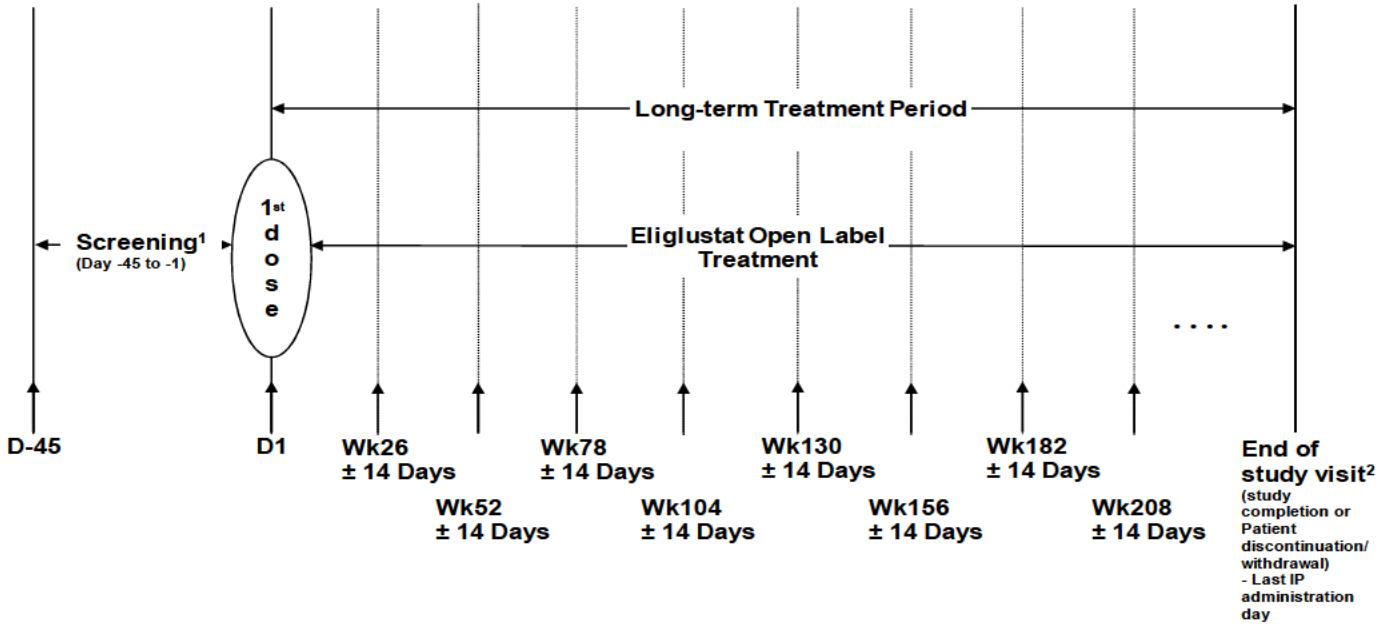
	after the end of the pregnancy, and/or when she is no longer breast feeding, provided rescreening takes place before the end of the enrollment period. E 12. Women of childbearing potential who are unwilling or unable to be tested for pregnancy.
Total expected number of patients	Approximately 32 patients
Expected number of sites:	Approximately 4 sites
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	Eliglustat Eliglustat is supplied as 84 mg hard gelatin capsules. Each 84 mg capsule contains 100 mg eliglustat tartrate, which is equivalent to 84 mg eliglustat free base
Route(s) of administration	Oral
Dose regimen	Cytochrome P450 2D6 (CYP2D6) IMs, EMs and URMs will be treated with 84 mg twice daily (BID). CYP2D6 PMs will be treated with 84 mg once daily (QD).
Noninvestigational medicinal product(s) (if applicable) **Formulation**	N/A
Route(s) of administration	N/A
Dose regimen	N/A
ENDPOINT(S)	**Primary endpoint** The main purpose in this extension study is to evaluate long term skeletal response to eliglustat, i.e., change in bone disease after 2 years of additional treatment with eliglustat. The elements of bone disease to be evaluated include bone pain, bone crisis, mobility, bone marrow infiltration, bone mineral density (BMD), lytic lesions, infarcts, fractures, osteonecrosis, and bone biomarkers (Procollagen type I N-terminal propeptide (P1NP; bone formation) and C- terminal telopeptide (CTX; bone resorption), and macrophage inflammatory protein-1 beta (MIP-1 β). These efficacy assessments will be collected at baseline and thereafter at twice-yearly (bone biomarkers) or yearly (pain, crisis, mobility, bone marrow infiltration, bone mineral density, lytic lesions, infarcts, fractures) intervals. **Secondary endpoint(s)** Evaluation of patients' quality of life (Short Form-36 Health Survey) and biomarkers of GD1 (chitotriosidase, plasma GL-1 and lyso-GL-1). Quality of Life (QOL) and biomarkers of GD1 will be performed at baseline and twice yearly. The safety of eliglustat (i.e., incidence of (S)AEs, concomitant medications, changes from study baseline in physical examinations, routine laboratory assessments (hematology) and pregnancy testing for female patients of childbearing potential). Safety assessments will be performed at baseline and twice yearly. Continuous monitoring will be performed for (S)AEs and

	concomitant medications.
ASSESSMENT SCHEDULE	V1-2 (Day -45 to -1): screening V3 (D1): baseline, 1st eliglustat administration in this study From V3 onwards, at 6 month intervals up to 4 years or until eliglustat is approved and available to patients through reimbursement or through the compassionate use (expanded access) program: efficacy, safety and general patient condition assessment parameters Last visit: last dose of IMP; efficacy, safety and general patient condition assessment parameters. For all visits, a time frame of ± 14 days is acceptable, using Day 1 as reference (If one visit date is changed, the next visit should take place according to the original schedule). Note: patients who prematurely discontinue treatment have to perform the discontinuation visit.
STATISTICAL CONSIDERATIONS	**Sample size determination:** This study will enroll all eligible patients having successfully completed one of the Phase 2 or Phase 3 trials (approximately 32 patients). **Analysis population:** Efficacy analyses will be performed on the Full Analysis Set (FAS) population, defined as all patients who enroll in this study and who received at least 1 dose of eliglustat treatment in this study. Safety analyses will be performed on the Safety Set, which is equivalent to the FAS for this study. **Primary analysis:** Analysis will be performed at two time points in this study. The main analysis will be performed after all patients have completed the 2 year assessments (two-year analysis period). An additional analysis will be performed upon study completion. For both efficacy and safety outcomes summary statistics will be calculated and presented. Hypothesis testing will not be performed. For bone disease outcomes, summary statistics as well as cumulative incidence and incidence rates will be calculated, as appropriate. For continuous variables, change from study baseline as well as change from eliglustat baseline, defined as the change from first dose of eliglustat in the Phase 2 or 3 study, will be presented. Incidence and incidence rates will also be calculated separately, from study baseline and eliglustat baseline. **Analysis of secondary endpoints:** Quality of Life assessments, physical examinations, hematology, biomarkers and pregnancy testing for female patients of childbearing potential will be summarized at each time point. Additionally, the change from study baseline and eliglustat baseline (1st dose received in the previous study) will be summarized, as appropriate. Adverse experience will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or higher. All adverse experiences will be summarized by body system and MedDRA preferred term (PT) overall, by relationship and severity and seriousness. All deaths will be summarized. Concomitant medications will be reported.

DURATION OF STUDY PERIOD (per patient)	The study will include a screening period (Day -45 to -1) and a long-term treatment period up to 4 years, or until eliglustat is approved and available to patients through reimbursement with minimum duration of treatment of 2 years. 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. Enrollment: up to 20 months. After study completion, patients will be encouraged to enroll in the International Collaborative Gaucher Group (ICGG) Gaucher Registry.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



[1] - Final GZGD00304, GZGD02507, GZGD02607, and GZGD03109 study assessments may serve as entry evaluation fort the study if performed less than 3 months for laboratory testing, 1 year for bone imaging, and 6 months for other assessments.
-However, Safety (S)AE, Concomitant Medication and prior Medication History, Physical examinations, Human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen, Urine pregnancy test, Height, Medical/Surgical History and Patient Demography will have to be performed in all cases.
[2] Study duration will be up to 4 years or until eliglustat is approved and available to patients through reimbursement with minimum duration of 2 years. 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.

1.2 STUDY FLOW CHART

	Screening (Day -45 to -1)[a]		Treatment Observations												
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Assessments after Week 208**			**Study completion or Patient Discontinuation/Withdrawal** [b]
WEEKS			**Day 1**	**Wk 26** (±14 days	**Wk 52** (±14 days)	**Wk 78** (±14 days)	**Wk 104** (±14 days)	**Wk 130** (±14 days)	**Wk 156** (±14 days)	**Wk 182** (±14 days)	**Wk 208** (±14 days)	**Every 6 months** (±14 days)	**Every 12 Months** (±14 days	**Every 24 months** (±14 days)	
Assign identification number[c]	X														
Inclusion criteria	X														
Exclusion criteria		X													
Patient demography	X														
Medical/surgical history[d]	X														
Prior medication History[e]	X														
Complete physical examination (including weight)	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Gaucher disease clinical assessments (mobility, bone crisis and bone pain)		X			X		X		X		X		X	X	X
QOL Questionnaire (SF-36 survey)		X		X	X	X	X	X	X	X	X	X	X	X	X
Treatment															
Eliglustat Administration			X	Daily dosing											X[f]

	Screening (Day -45 to -1)[a]		Treatment Observations												
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Assessments after Week 208**			**Study completion or Patient Discontinuation/Withdrawal** [b]
WEEKS			**Day 1**	**Wk 26** (±14 days	**Wk 52** (±14 days)	**Wk 78** (±14 days)	**Wk 104** (±14 days)	**Wk 130** (±14 days)	**Wk 156** (±14 days)	**Wk 182** (±14 days)	**Wk 208** (±14 days)	**Every 6 months** (±14 days)	**Every 12 Months** (±14 days	**Every 24 months** (±14 days)	
Concomitant Medications (including grapefruit)	**CONTINUOUS MONITORING**[g]														
IP compliance				X	X	X	X	X	X	X	X	X	X	X	X
Efficacy[a]															
X-ray: femurs and lumbar spine		X					X				X			X	X
DXA (hips and lumbar spine)		X			X		X		X		X		X	X	X
Magnetic Resonance Imaging (MRI; entire bilateral femur and lumbar spine)		X			X		X		X		X		X	X	X
General patient condition															
Spleen and liver Volume (MRI)		X			X		X		X		X		X		X
Safety															
AE /SAE recording (if any), concomitant medications, urine pregnancy test performed at home every 4 weeks	**CONTINUOUS MONITORING**[g]														
Laboratory testing[a]															

	Screening (Day -45 to -1)[a]		Treatment Observations												
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Assessments after Week 208**			**Study completion or Patient Discontinuation/Withdrawal** [b]
WEEKS			**Day 1**	**Wk 26** (±14 days	**Wk 52** (±14 days)	**Wk 78** (±14 days)	**Wk 104** (±14 days)	**Wk 130** (±14 days)	**Wk 156** (±14 days)	**Wk 182** (±14 days)	**Wk 208** (±14 days)	**Every 6 months** (±14 days)	**Every 12 Months** (±14 days	**Every 24 months** (±14 days)	
Human immunodeficiency virus (HIV) antibody, Hepatitis C antibody, or Hepatitis B surface antigen.	X														
Hematology (including hemoglobin, platelet)	X			X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry (AST, ALT, AP, Total bilirubin, albumin, GGT)	X														
Biomarkers: serum chitotriosidase, plasma MIP- 1 β, serum P1NP, serum CTX [h], plasma GL-1 and lyso-GL-1	X			X	X	X	X	X	X	X	X	X	X	X	X
Blood pregnancy test (for women of childbearing potential) [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening (Day -45 to -1)[a]		Treatment Observations												
VISIT	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Assessments after Week 208**			**Study completion or Patient Discontinuation/Withdrawal** [b]
WEEKS			**Day 1**	**Wk 26** (±14 days	**Wk 52** (±14 days)	**Wk 78** (±14 days)	**Wk 104** (±14 days)	**Wk 130** (±14 days)	**Wk 156** (±14 days)	**Wk 182** (±14 days)	**Wk 208** (±14 days)	**Every 6 months** (±14 days)	**Every 12 Months** (±14 days	**Every 24 months** (±14 days)	

a Final GZGD00304, GZGD02507, GZGD02607 and GZGD03109 study assessments may serve as entry evaluation for this study if performed less than 3 month for laboratory testing, 1 year for bone imaging (X-ray femur and lumbar spine, dual-energy X-ray absorptiometry (DXA) hips and lumbar spine, Magnetic Resonance Imaging (MRI) femur and lumbar spine) and 6 months for other assessments.
However, safety (S)AE, concomitant medication and prior medication history, physical examinations, human immunodeficiency virus (HIV) antibody, hepatitis C antibody, or hepatitis B surface antigen, blood pregnancy test for female of childbearing potential, height, will have to be performed in all cases.
The screening procedures do not have to be performed over 2 visits. Scheduling will be based on investigator, patient and resources availability. Screening can be performed at the same time as the end-of-study visit of the previous study the patient was enrolled in.

b Study duration will be up to 4 years, or until eliglustat is approved and available to patients through reimbursement with minimum duration of 2 years. 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. At study completion or patient discontinuation/withdrawal certain radiological assessments will not be repeated (bone X-Ray if performed less than 2 years prior; DXA, bone MRI and liver and spleen MRI if performed less than 1 year prior).

c A unique patient ID number will be assigned. The ID of the previous study the patient was enrolled in and the patient's ID in that study will be collected in the new clinical database.

d Medico-surgical history already collected in the previous study database should not be re-entered. Should be entered in the Medical/surgical history CRF 1/ adverse events (AEs) started during the previous study, which are closed at the time of the screening visit and are still considered clinically significant by the investigator at the time of the screening visit; 2/ medical/surgical events started after the follow-up phone call of the previous study and before the ICF signing in the current study, whether ongoing or closed, if they are considered clinically significant by the investigator.

e 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).

f Only at Study completion visit and not at Patient discontinuation/withdrawal visit.

g Patients will be contacted approximately every 4 weeks for safety monitoring and will be asked if they have had any significant experiences, begun taking any new medications, changed the dose of any medications they are taking. In addition patients of child bearing potential will be asked about the result of the urine pregnancy test performed every 4 weeks at home.

h Serum samples for CTX should be collected after overnight fasting.

i Urine pregnancy test must be performed before radiological assessments and the result provided to the personnel performing the assessment so that he/she can verify the result is negative and sign off on it before performing the exam. All positive urine pregnancy tests will be verified with a blood pregnancy test.

Note:

Central reading will be set up for liver and spleen MRI and bone imaging. All laboratory tests will be done at the local laboratories at the exception of the biomarkers, which will be done in central laboratories.

Cytochrome P450 2D6 URM patients will have liver and spleen MRI and hematology performed every 6 month till week 52. However, the frequency of liver and spleen MRI and hematology can be increased to every 3 month till week 52 at the discretion of the Investigator. After week 52 CYP2D6 URM patients will follow the standard schedule.

Although pharmacokinetic (PK) samples are not scheduled, unscheduled PK samples may be collected after discussion between PI and Genzyme.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE:	adverse event
ALT:	alanine transaminase
AP:	alkaline phosphatase
AST:	aspartate aminotransferase
AUC:	area under the concentration-time curve
AUC_{last}:	area under the concentration-time curve from time zero to the last measurable concentration
BID:	twice daily
BMD:	bone mineral density
CFDA:	China Food and drug administration
CRF.:	Case Report Form
CTX:	C-terminal telopeptide
CV:	curriculum vitae
CYP2D6:	cytochrome P450 2D6, cytochrome P450 2D6
CYP3A:	cytochrome P450 3A
CYP3A4:	cytochrome P450 3A4
DRF:	discrepancy resolution form
DXA:	dual-energy X-ray absorptiometry
EM:	extensive metaboliser
EOS:	end of study
ERT:	enzyme replacement therapy
FAS:	Full Analysis Set
FDA:	US Food and Drug Administration
GCP:	good clinical practice
GD1:	Gaucher disease type 1
GL-1:	glucosylceramide
HIV:	human immunodeficiency virus
ICGG:	International Collaborative Gaucher Group
IM:	intermediate metaboliser
IRB/IEC:	Institutional Review Board/Independent Ethics Committee
LC/MS/MS:	liquid chromatography coupled to tandem mass spectrometry
LS:	least squares
lyso-Gl-1:	lyso glucosylceramide
MCS:	mental component summary
MedDRA:	Medical Dictionary for Regulatory Activities
MIP1-β:	macrophage inflammatory protein-1 beta
MRI:	Magnetic Resonance Imaging
P1NP:	Procollagen type I N-terminal propeptide
PAP:	primary analsyis period
PCS:	physical component summary
PK:	Pharmacokinetic

PM:	poor metaboliser
PMDA:	Pharmaceuticals Medical Devices Agency
PT:	preferred term
QD:	once daily
QOL:	Quality of Life
SAE:	serious adverse event
SD:	standard deviation
SF-36:	Short Form-36 Health Survey
SOC:	system organ class
TGA:	Therapeutic Goods Administration
ULN:	upper limit of normal
URM:	ultra-rapid metabolizer
β-hCG:	β-Human Chorionic Gonadotrophin

4 INTRODUCTION AND RATIONALE

Sanofi Genzyme has developed Cerdelga® (International Nonproprietary Name: eliglustat) as an oral therapy for Gaucher disease type 1. Eliglustat is a member of a class of glucosylceramide (GL-1) synthase inhibitors that resemble 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 (1)(2)(3)(4)(5).

The hallmark of Gaucher disease is the presence of lipid-engorged cells derived from the monocyte/macrophage lineage (Gaucher cell), which show a characteristic histological appearance and are distributed in tissues where macrophages reside (eg, liver, spleen, lung, and bone marrow). It is believed that the storage material within these Gaucher cells originates from phagocytosis of blood cells, while in neurons, the storage material is believed to originate from endogenous synthesis (5).

Gaucher disease type 1 is rare, with an estimated frequency of 1 in 60,000 births in the general population (6). Although it is pan-ethnic, 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 (5).

Gaucher disease type 1 has a broad spectrum of severity (5). Thrombocytopenia is the most common hematological abnormality. Anemia is frequently mild, but occasionally quite severe. Some patients with severe enlargement of the spleen and liver have minimal skeletal involvement, while others 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 severity of the other manifestations of the disease.

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) (7)(8)(9)(10)(11)(12). Elelyso (Pfizer, New York) was approved in the United States on 01 May 2012 as an ERT for the treatment of GD1. An alternative approach is the use of substrate reduction therapy using eliglustat, which acts by partially inhibiting the enzyme GL-1 synthase. The goal of this approach is to reduce the synthesis of GL-1 to a level where the residual enzymatic activity of the mutant acid β-glucosidase, the enzyme deficient in Gaucher disease, can degrade GL-1, thus preventing its accumulation.

Certain disease affected tissues such as bone marrow and cortical bone are not optimally targeted with existing treatments (13). Because the biodistribution of a small molecule drug is likely to be more extensive than that of an enzyme, the substrate reduction therapy (SRT) approach is expected to provide benefit in tissues that are less accessible to ERT (14) and in cells that lack mannose receptors (15). In fact, preclinical studies with eliglustat demonstrated a wide distribution to tissues, including bone marrow.

Bone involvement is a nearly universal and clinically relevant aspect of Gaucher disease, which affects both the osseous tissue and the bone marrow. As skeletal involvement can be severe and lead to significant morbidity, improvement in bone disease is important to patients as well as expert physicians (16) as evidenced by its inclusion as a key therapeutic goal for ERT (9) and in the schedule of recommended assessments in the ICGG Registry irrespective of treatment status. Some experts consider skeletal disease to be the most challenging aspect of the disease to treat. For example, Deegan et al. argue, having studied 100 patients with GD1 from 3 major referral centers in the United Kingdom, who had been treated with ERT, that Gaucher disease should no longer be viewed as a disorder with cytopenia causing bleeding, anemia and susceptibility to infection due to bone marrow infiltration and splenomegaly, but rather as a principally skeletal disorder with disabling effects on bone structure and metabolism, which once established are refractory to therapy (17).

Eliglustat was approved by the US Food and Drug Administration (FDA) on 19 August 2014, the European Commission on 19 January 2015, the Health Canada on 21 April 2017, and the Australian Therapeutic Goods Administration (TGA) on 10 February 2015. Eliglustat marketing authorization applications are being assessed by other health authorities.

The efficacy of eliglustat in the treatment of adult patients with GD1 and posology in intermediate metabolizers (IMs) and extensive metabolizers (EMs) with a dose of 100 mg BID and poor metabolizers (PMs) with a dose of 100 mg QD is based on an extensive clinical development program and robust clinical results from 2 adequate, well controlled Phase 3 studies (ENGAGE and ENCORE), with supportive long term data from the Phase 2 study and ENGAGE and ENCORE extension periods (comprising data from 225 treated adult patients with GD1), and from extensive population based pharmacokinetic (PBPK) simulations.

The benefits of eliglustat treatment include clinically meaningful reductions in organ volumes in treatment naïve patients and maintenance of organ volume stability in patients switching from ERT; increases in hematological values in treatment naïve patients and maintenance of hematological stability in patients switching from ERT (hemoglobin level and platelet count; improvement of bone disease in treatment naïve patients and maintenance of bone disease stability in patients switching from ERT (bone marrow infiltration and bone mineral density (BMD); a well defined mechanism of action and clinical pharmacology profile, and limited safety risk. These benefits have been demonstrated across a wide range of GD1 severity.

The efficacy of eliglustat compares favorably to those of other marketed products for GD1. Eliglustat's safety profile is distinct from ERTs, with different common TEAEs, and is unlike miglustat, wherein high incidences of diarrhea, weight loss, and tremor result in a therapy with limited tolerability and acceptance by treating physicians and patients with GD patients. In addition to comparable efficacy to other approved ERTs and a favorable safety profile, eliglustat

has certain advantages over ERTs. Enzyme replacement therapy requires regular intravenous (IV) infusions (generally every 2 weeks) for the duration of a patient's lifetime, and some patients are unable or unwilling to receive ERT.

Overall, eliglustat shows a favorable safety profile. Based on review of all available safety data, the adverse drug reaction profile of eliglustat is characterized by diarrhea, headache, arthralgia, flatulence, abdominal pain, fatigue, and nausea, each occurring in <6% of the treated population. Most reported adverse events (AEs) were mild in severity, and few patients discontinued due to AEs. The risks of greatest concern with eliglustat treatment have not been observed in clinical trials, but modeling suggests the possibility for clinically significant electrocardiogram (ECG) interval increases, which are mild in scope, in the setting of high eliglustat exposure. Also, since eliglustat is extensively metabolized by CYP2D6 and to a lesser extent by CYP3A4, the potential for drug-drug interactions that could lead to increases in eliglustat exposure exists.CYP2D6 phenotype based dosing regimen allows managing potential for drug-drug interactions by restricting the patient population to PM, IM, and EM patients only, to ensure that patient exposure to eliglustat will remain within the therapeutic range.

As seen in the Phase 2 study, ENGAGE, and ENCORE, and commensurate with the general population, more than 90% of GD1 patients are CYP2D6 PMs, IMs, or EMs, can be safely and effectively dosed at 100 mg daily (QD) (PMs) or 100 mg BID (IMs and EMs). The sufficiency of the IM and EM proposed dose is supported in particular by the Phase 2 study and ENGAGE, where most treatment naïve patients with IM and EM phenotypes were successfully treated at the 100 mg BID dose.

While patients of all phenotypes were successfully treated in clinical trials using dose titration, Sanofi Genzyme recommends an eliglustat dosing regimen comprised of 100 mg BID for IM and EM patients and 100 mg QD for PM patients in the post approval setting.

During the clinical development program, a limited number of GD1 patients who were ultra rapid metabolizers (URMs) (1 in ENGAGE and 4 in ENCORE) were treated with eliglustat. The single URM patient in ENGAGE who received 100 mg BID was a nonresponder, suggesting that the 100 mg dose may result in a maximum concentration (C_{max}) too low to be effective for URMs. For indeterminate metabolizers, a phenotype cannot be predicted based on genotype, and therefore a dose cannot be recommended. Other treatment options are available for this minority of patients who would be ineligible for treatment with eliglustat.

In vitro, eliglustat is a substrate of the efflux transporter P glycoprotein (P-gp). In addition, CYP2D6 and to a lesser degree cytochrome P450 3A4 (CYP3A4) are involved in eliglustat metabolism in vitro. Consequently, moderate and strong inhibitors of CYP2D6 and CYP3A increase its exposure, and potent cytochrome P450 3A (CYP3A) inducers decrease it. In addition, mild QTc interval prolongation is predicted to occur in a dose proportional fashion at eliglustat plasma concentrations beyond the therapeutic range. For these reasons, the restrictions on concomitant medications shown in Table 1 (Concomitant Medications Recommendations for Use with Eliglustat) have been proposed in product labeling for eliglustat. These restrictions will help ensure that exposure to eliglustat will remain within the range shown to be safe and effective in the clinical studies.

Previous clinical studies of eliglustat have provided evidence of its efficacy on bone manifestations. In Study GZGD00304, a Phase 2 open label study, 56% (n = 10) of the patients had reduced bone marrow infiltration of the femur as assessed by MRI after 4 years of treatment with eliglustat, and the mean lumbar spine BMD (g/cm2) increased by 9.9% (n = 15, p = 0.0176). The mean standard deviation (SD) lumbar spine BMD T-score was in the osteopenic range at baseline, -1.63 (1.07), and reached the normal range, -0.88 (1.26), after 4 years of treatment (p = 0.0139). The mean (SD) lumbar spine BMD Z-score was -1.17 (0.92) at baseline and increased to -0.48 (1.07) after 4 years of treatment (p = 0.0044) (GZGD00304: 48-month period clinical study report).

In the Pivotal Phase 3 Study GZGD02507 where patients were randomized to eliglustat or placebo, the total bone marrow infiltration score, as assessed by MRI in lumbar spine and femur, decreased by a mean of 1.1 point after 9 months (n = 20) and 2.15 points after 18 months (n = 18) in the eliglustat group. The percentage of eliglustat treated patients with a clinically significant reduction of at least 2 points in the total bone marrow infiltration score increased from 26% (n = 5) after 9 months to 44% (n = 8) after 18 months. After 18 months of eliglustat treatment the mean (SD) lumbar spine BMD T score increased from -1.06 (0.82) (n = 17), within the osteopenic range, to -0.91 (0.88) (n = 15), within the normal range. Statistically significant reductions in plasma MIP-1 β, which is considered to be a biomarker of active bone disease, were observed with eliglustat compared with placebo (least squares [LS] mean treatment difference = -43.5%, p<0.0001). After 18 months and 30 months of treatment, BMB score had decreased by a mean of 2.2 points (n=18) and 2.7 (n=15) points, respectively, for the patients originally randomized to eliglustat, compared to a mean decrease of 1 point (n=20) and 0.8 (n=16) in those originally randomized to placebo, and the percentage of eliglustat-treated patients with a significant reduction of at least 2 points in the total BMB score increased to 44% (n=8). After 18 and 30 months of treatment with eliglustat in an open-label extension phase, the mean lumbar spine Z-score in all patients increased from -1.208 (1.0546) at Baseline (n=38) to -0.949 (1.1447) (n=31). After 30 months and 4.5 years, the Z score further increased to -0.761 (1.0760) (n=31) and -0.478 (0.7870) (n=9), respectively (GZGD02507: 39-week [primary analysis period] and 78-week clinical study reports).

In the Pivotal Phase 3 Study GZGD02607 where patients who had reached the Gaucher disease therapeutic goals (9) on ERT were randomized to eliglustat or ERT, lumbar spine BMD and total bone marrow infiltration score remained stable after 12 months, with similar mean changes in both treatment arms. Bone parameters remained stable after 24 months of eliglustat treatment. After completion of the primary analysis period (PAP), all patients who transitioned to the long-term treatment period were treated with eliglustat. Individual disease parameters of spleen volume, liver volume, hemoglobin levels and platelet count remained stable through 4 years. With regard to BMD, lumbar spine and femur BMD T- and Z-scores were maintained within the normal range in patients treated with eliglustat for up to 4 years (GZGD02607: 52-week [primary analysis period] and 104-week clinical study reports).

In the 3rd Phase 3 study, EDGE GZGD03109, which evaluated the efficacy, safety, and pharmacokinetics (PK) of QD versus BID eliglustat in patients with GD1 who have demonstrated clinical stability on BID dosing of eliglustat, the majority of patients (83%) reached or maintained all 5 therapeutic goals (bone crises, hemoglobin, platelet count, spleen, and liver volume). Marked reductions in MIP1 β concentrations assessed as investigational biomarker of active bone disease

were observed after eliglustat treatment between 6 and 18 months (GZGD03109: 78-week clinical study report).

More detailed efficacy and safety information is provided in the Investigator Brochure.

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

The main purpose of this extended treatment study is to evaluate long term skeletal response to eliglustat, i.e., change in bone disease after 2 additional years of treatment with eliglustat. The elements of bone disease to be evaluated include bone marrow infiltration, BMD, lytic lesions, incidence of fractures and infarcts, bone biomarker levels (P1NP [bone formation], CTX and MIP1-β) and Gaucher disease assessments (mobility, bone crisis, and bone pain). These efficacy assessments will be collected at baseline and thereafter at twice-yearly (bone biomarkers, Gaucher disease assessments) and yearly (bone marrow infiltration, bone mineral density, lytic lesions, infarcts, osteonecrosis, fractures) intervals.

As secondary endpoints the study will continue to evaluate patients' quality of life (SF-36) and biomarkers of GD1 (chitotriosidase, plasma GL-1 and lyso-GL-1). Quality of life questionnaires will be administered and biomarkers of GD1 will be measured at baseline and twice-yearly thereafter. The safety of eliglustat (ie, incidence of [S]AEs), concomitant medications, changes from baseline in physical examinations, hematology will be monitored. Results of pregnancy testing for female patients of childbearing potential will be collected. Safety assessments will be performed at baseline and twice yearly. Continuous monitoring will be performed for (S)AEs and concomitant medications.

Approximately four of the study centers that participated in the eliglustat Phase 2 or Phase 3 studies will participate in this study. Participating physicians will enroll patients who successfully completed the Phase 2 or Phase 3 studies. The study will run for a minimum of 2 years and up to 4 years, or until eliglustat is approved and available to patients through reimbursement or through the compassionate use (expanded access) program, whichever comes first.

The study will enroll approximately 32 patients who will be treated with eliglustat and who have provided a signed informed consent.

The study will include a screening period (Day -45 to -1) and a long-term treatment period up to 4 years or until eliglustat is available to patients through reimbursement or through the compassionate use (expanded access) program, whichever comes first. After study completion patients will be encouraged to enroll in the ICGG Gaucher Registry.

Cytochrome P450 (CYP) 2D6 IM, EM and URM patients will be treated with eliglustat 84 mg twice daily (BID). Cytochrome P450 (CYP) 2D6 PM patients will be treated with eliglustat 84 mg once daily (QD). Doses may have to be decreased when certain concomitant medications are administered (see Section 8.5.1.2).

Eliglustat tartrate (the drug substance) is an L tartaric acid salt, and exists in plasma as a free base, Genz-99067, which is the active moiety. Throughout this document, Genz-99067 is used when referring to drug exposure (eg, plasma concentrations), and eliglustat is used in all other instances with doses reflecting the tartrate form.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the long term skeletal response to eliglustat in adult patients who successfully completed one of the Phase 2 or Phase 3 studies of eliglustat.

5.2 SECONDARY

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).

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

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. This study is considered an extension of these previous studies with the goal of obtaining longer term data.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

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. 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.

The study will include

- A screening period that can extend from Day -45 to Day-1,
- A long-term treatment period up to 4 years or until eliglustat is available to patients through reimbursement or through the compassionate use (expanded access) program, starting on Day 1

After study completion, patients will be encouraged to enroll in the ICGG Gaucher Registry.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as the last visit for the last patient.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEES

The study data will not be reviewed by a Data Monitoring Committee. The IMP is approved for the treatment of Gaucher disease type 1 patients, the study population, by the FDA, EMA and

TGA. This is an extension study for patients who have been receiving the IMP for 4-8 years prior to enrollment in the study.

7 SELECTION OF PATIENTS

The patients who have completed successfully the Phase 2 study (GZGD00304) or one of the Phase 3 studies (GZGD02507, GZGD02607 or GZGD03109) in the eliglustat program will be invited to participate in this study.

7.1 INCLUSION CRITERIA

I 01. The patient must have successfully* completed the Phase 2 (GZGD00304) or a Phase 3 study (GZGD02507, GZGD02607 or GZGD03109).

* Successful completion is defined as patients enrolled in one of the above mentioned studies who received eliglustat through the end of the study and completed the end of study (EOS) visit without having discontinued or being withdrawn prematurely.

I 02. The patient is willing and able to provide signed informed consent prior to any protocol required procedures being performed.

I 03. Female patients of childbearing potential must have a documented negative pregnancy test prior to enrollment and while they are receiving eliglustat treatment

I 04. Female patients of childbearing potential must be willing to practice true abstinence in line with their preferred and usual lifestyle, or use a medically accepted form of contraception (either a barrier method, such as condom or diaphragm + spermicide, or a non-barrier method such as oral, injected, or implanted hormonal methods, or an intra-uterine device or system) while receiving eliglustat.

7.2 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria that are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. The patient is unwilling to comply with the requirements of the protocol.

E 02. The patient has received an investigational product (other than eliglustat) within 30 days prior to enrollment.

E 03. The patient has received miglustat within the 6 months prior to enrollment.

E 04. The patient has documented prior esophageal varices or liver infarction or current liver enzymes (alanine transaminase [ALT]/aspartate aminotransferase [AST]) or Total

Bilirubin >2 times the upper limit of normal (ULN), unless the patient has a diagnosis of Gilbert Syndrome.

E 05. The patient has any clinically significant disease other than Gaucher disease, including cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic (eg, hypokalemia, hypomagnesemia), psychiatric disease, other medical conditions, or serious intercurrent illnesses that may preclude participation in the study.

E 06. The patient is known to have any of the following: cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, or current treatment with Class IA or Class III antiarrhythmic medicinal products.

E 07. The patient has tested positive for the human immunodeficiency virus (HIV) antibody, hepatitis C antibody, or hepatitis B surface antigen.

E 08. The patient has a history of cancer within 6 months of enrolment, with the exception of basal cell carcinoma.

7.2.2 Exclusion criteria related to eliglustat

E 09. The patient is a CYP2D6 IM, EM and URM and is taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor.

E 10. The patient is a CYP2D6 PM having taken a strong CYP3A inhibitor within 2 weeks prior to enrolment.

7.2.3 Exclusion criteria related to the current knowledge of eliglustat

E 11. If a female patient of childbearing potential has a positive pregnancy test blood β-Human Chorionic Gonadotropin (blood β-hCG) or is breastfeeding prior to first dosing of eliglustat in this study, the patient cannot enroll in the study at this time, but may be rescreened after the end of the pregnancy, and/or when she is no longer breast feeding, provided rescreening takes place before the end of the enrollment period.

E 12. Women of childbearing potential who are unwilling or unable to be tested for pregnancy.

Rescreening will be allowed for patients who have failed screening because they met a temporary exclusion criterion such as concomitant medication. Patients will be allowed to rescreen only once and within 2 weeks of the 1st screening, except for pregnant or breast feeding patients who may be rescreened later, as described in E11 above.

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 Sanofi Genzyme. The Investigator will contact Sanofi Genzyme Clinical Study Director if a patient meets any of the withdrawal criteria. The following may be justifiable reasons for the Investigator or Sanofi 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.
- Sanofi Genzyme terminates the study.
- If a female patient of childbearing potential has a positive pregnancy test blood β-hCG or is lactating after first dosing with eliglustat in this study, the patient may remain in the study, but must suspend eliglustat till delivery and while breast feeding. The maximum duration of such an IMP suspension is 12 months. During the IMP suspension the patient must maintain compliance with all the other study requirements, except for the radiological examinations that are prohibited in pregnant women.

If a patient meets at least 1 of the following criteria, the Investigator must notify the Sanofi Genzyme Clinical Study Director. The Investigator and Sanofi Genzyme will review the clinical status of the patient and will determine if the patient should be withdrawn from the study.

- The patient’s hemoglobin level falls below 80 g/L and remains below 80 g/L when the test is repeated within approximately 2 weeks.
- The patient’s platelet count falls below 50 x 10^9/L and remains below 50 x 10^9/L when the test is repeated within approximately 2 weeks,
- The patient experiences a clinically significant bleeding episode assessed by the Investigator as related to a low platelet count.
- The patient experiences a decline in Gaucher disease status that, in the opinion of the Investigator, warrants discontinuation from the study (eg, repeated bone crises, clinically significant increases in liver or spleen volumes).

Patient who discontinue or withdraw from participation in the study will be contacted in order to obtain information about the reason(s) for discontinuation/withdrawal and for collection of AEs, if any. The patient will be asked to return to the clinic to complete all study discontinuation/withdrawal assessments. The Investigator will describe the reason for

discontinuation on the Completion/Discontinuation case report form. Patients who discontinue/withdraw participation from the study will not be replaced. A summary of all discontinuations will be included in the final study report.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

Eliglustat is supplied as 84 mg hard gelatin capsules for oral administration. Each 84 mg capsule contains 100 mg of eliglustat tartrate, which is equivalent to 84 mg of eliglustat free base.

CYP2D6 IM, EM and URM patients will receive 84 mg BID. CYP2D6 PM will receive 84 mg QD.

Given the rarity of the CYP2D6 URM phenotype, experience on treating these patients is limited. To make sure they are properly treated, additional monitoring will be performed in this patients (see Section 10.2.3.3).

Eliglustat will be taken orally with water.

For patients on BID dosing regimen, doses should be taken roughly every 12 hours (one capsule in the morning and one capsule in the evening). For patients on QD dosing regimen, doses should be taken at about the same time every day.

Eliglustat absorption is not affected by food. Therefore, it can be taken with or without food at the convenience of the patient.

8.1.1 IMP dose reduction

Certain concomitant medications require a reduction in the dose of eliglustat (see Section 8.5.1.2).

8.1.2 IMP temporary suspension

Treatment with eliglustat should be suspended in patients who require short-term treatment with

- A strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor in CYP2D6 EMs and IMs.
- A strong or moderate CYP3A inhibitor in CYP2D6 PMs.

These medications can be used for up to 2 weeks at a time.

All IMP temporary suspension should be documented in the IMP distribution CRF.

Up to 2 episodes of eliglustat suspension are allowed per year.

If these medications are required for longer treatment periods, the investigator should consult with the Clinical Study Director.

If a patient becomes pregnant during her participation in the study she may remain in the study, but must suspend eliglustat until delivery and while breast feeding. The maximum duration of such an IMP suspension is 12 months. During the IMP suspension the patient must maintain compliance with all the other study requirements, except for the radiological examinations that are prohibited in pregnant women.

8.2 PACKAGING AND LABELING

Each bottle of IMP 84 mg capsules will contain 60 capsules and will be labeled with a single panel label. This will be provided in induction-sealed, high density polyethylene bottles with child resistant closure caps. Label text will include, at a minimum, the study protocol number, the contents of the bottle, lot number, use-by date, storage conditions and Genzyme name and address. Also included on the label will be any required cautionary statements and any other requirements, in accordance with regulations specific to each country where this study is conducted.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.3 STORAGE CONDITIONS AND SHELF LIFE

The IMP must be stored at a controlled room temperature of 20°C-25°C, with excursions permitted from 15°C - 30°C, in a secured location.

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (eg, controlled room temperature storage) and information on in-use stability and instructions for handling the IMP should be managed according to the rules provided by Sanofi Genzyme.

8.4 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly notified to Genzyme. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by Genzyme. In this case, the Investigator will be responsible for promptly addressing any request made by Genzyme, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.4.1 Treatment accountability and compliance

At each visit the Investigator or his/her delegate will question patients to assess treatment compliance and will remind patient of the importance of excellent treatment compliance.

IMP accountability:

- Treatment units are returned by the patient at each visit;
- The Investigator or delegate records the dosing information on the appropriate page(s) of the CRF;
- The monitor in charge of the study then checks the CRF data by comparing them with the IMP that he/she has retrieved and the treatment log forms.

8.4.2 Return and/or destruction of treatments

All used, partially-used or unused treatment bottles will be retrieved from each patient at each site visit. A detailed treatment log of the patient returned bottles (used, partially used, or unused) to the site will be established. Any IMP destroyed on site or returned to Genzyme will be documented in the treatment log and associated Sponsor form(s). The Investigator will not destroy any IMP unless Genzyme provides written authorization. Please refer to the study Pharmacy Manual for further details.

8.5 CONCOMITANT MEDICATION

Patients will be monitored continuously for changes in the use of concomitant medications (introduction of new medications and changes in the dose or regimen of preexisting medications).

Patients will be instructed to report to the Investigator any changes in concomitant medications before these changes are made, or, in the case of changes made in emergency situations, as soon as possible.

8.5.1 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

8.5.1.1 ANTIARRHYTHMICS

Because eliglustat is predicted to cause mild increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations, use of eliglustat is prohibited in combination with Class IA and Class III antiarrhythmic medications. Patients who require long term treatment with any of these medications should be removed from the study.

8.5.1.2 EFFECT OF OTHER DRUGS ON ELIGLUSTAT

Eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A4. Concomitant administration of substances affecting CYP2D6 or CYP3A4 activity (ie, CYP2D6/CYP3A inhibitors and CYP3A strong inducer) may alter Genz-99067 plasma concentrations. Grapefruit products contain one or more components that inhibit CYP3A and can increase plasma concentrations of eliglustat. Grapefruit and grapefruit products including grapefruit juice, but not grapefruit seeds, are prohibited at any time during the study.

Table 1 provides an overview of allowed and prohibited inhibitors and inducers for chronic use, as determined by the patient's CYP2D6 phenotype.

Table 1 - Concomitant Medications Recommendations for Use with Eliglustat

CYP2D6 Phenotype	Category of Inducer / Inhibitor							
	Strong CYP3A Inducer	Weak CYP3A Inhibitor ALONE	Moderate CYP3A Inhibitor ALONE	Strong CYP3A Inhibitor ALONE	Moderate CYP2D6 Inhibitor ALONE	Strong CYP2D6 Inhibitor ALONE	Moderate or Strong CYP3A Inhibitor and Moderate or Strong CYP2D6 Inhibitor COMBINED	
Poor Metabolizer	Not recommended	Use with caution	Not recommended	Contraindicated	Allowed	Allowed	Moderate CYP3A Inhibitor and Moderate or Strong CYP2D6 Inhibitor COMBINED As moderate CYP3A inhibitor alone (Not recommended)	Strong CYP3A Inhibitor and Moderate or Strong CYP2D6 Inhibitor COMBINED As Strong CYP3A alone (Contraindicated)
Intermediate and Extensive Metabolizer	Not recommended	Allowed at usual dose of 84 mg BID	Use with caution	Use with caution	Use with caution	84 mg once daily	Contraindicated	
Ultra-Rapid Metabolizer	Not recommended	Allowed	Allowed	Allowed	84 mg once daily	84 mg once daily	Contraindicated	

8.5.1.3 EFFECT OF ELIGLUSTAT ON OTHER DRUGS

In vivo eliglustat was found to be an inhibitor of P-glycoprotein (P-gp; 1.5-fold increase in digoxin area under the plasma concentration versus time curve from 0 to the real time corresponding to the last concentration above the lower limit of quantification) and an inhibitor of CYP2D6 (2.1-fold in metoprolol area under the plasma concentration versus time curve extrapolated to infinity [area under the concentration-time curve (AUC)]), consistent with in vitro data showing eliglustat to be an inhibitor of CYP2D6 and of P-gp. Eliglustat may increase the plasma concentration of those substances and should be used with caution in combination with a P-gp or a CYP2D6 substrate. Lower doses of such drugs may be required.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The main purpose of this extended treatment study is to evaluate long term skeletal responses to eliglustat after 2 additional years of treatment with eliglustat. Five common skeletal manifestations of Gaucher disease will be assessed:

1) Mobility, bone pain and bone crisis, as assessed by the Gaucher Disease clinical assessments; 2) bone marrow infiltration; 3) BMD; 4) Lytic lesions, osteonecrosis, fractures and infarcts; 5) bone biomarkers

9.1.1 Gaucher disease clinical assessments (mobility, bone pain, bone crisis).

Patients will be asked to rate

- 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.

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

9.1.2 Bone marrow infiltration

Will be assessed on sagittal T1 and T2 weighted MRI views of the lumbar spine and coronal T1 and T2 weighted MRI views of the entire bilateral femurs. A categorical bone marrow infiltration score will be calculated based on the amount of fat in the basivertebral vein region and the T1 and the T2 signals (18).

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.

9.1.3 Bone mineral density (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.

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

9.1.4 Lytic lesions, osteonecrosis, fractures and infarcts

Lytic lesions, osteonecrosis, infarcts and fractures will be assessed on bone MRI and bone X-Ray.

9.1.5 Bone biomarkers

Will 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.

9.2 SECONDARY ENDPOINT(S)

9.2.1 Efficacy endpoints

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.

9.2.2 Safety endpoints

9.2.2.1 Adverse events

Refer to Section 10.5 to 10.7 for details.

Continuous monitoring will be performed for (S)AEs and concomitant medications.

Results of pregnancy testing for female patients of childbearing potential will be collected.

9.2.2.2 Laboratory safety variables

The clinical laboratory data consist of hematology analyses. These analyses will be conducted by local laboratories at each site. Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

9.2.2.3 Physical examination

Complete physical exam will be performed including complete neurological exam with ocular motility test.

9.2.3 Patient Reported Outcomes

Patients' quality of life (Short Form-36 Health survey) will be evaluated at baseline and twice-yearly.

The SF-36 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 is a multi-purpose, short-form health survey with 36 questions. Accordingly, the SF-36 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 (19). A recall period of 1 week will be used.

9.3 PHARMACOKINETICS

Although PK samples are not scheduled, unscheduled PK samples may be collected in individual cases after discussion between the investigator and Genzyme.

9.3.1 Sampling time

Sampling times will be decided in each case after discussion between the investigator and Genzyme.

9.3.2 Pharmacokinetics handling procedure

Special procedures for collection, storage and shipping of plasma will be described in the operational manual for handling samples.

9.3.3 Bioanalytical method

Plasma Genz-99067 will be measured with a validated liquid chromatography coupled to tandem mass spectrometry method with a lower limit of quantification of 0.2 ng/mL.

9.3.4 Pharmacokinetics parameters

Not applicable.

9.4 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For subjects who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (excluding genetic analysis) related to lysosomal storage disorders than those defined in the present protocol.

These other research analyses will help to understand either disease subtypes or drug response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers.

These samples will remain labelled with the same identifiers than the one used during the study (ie, subject ID). They will be transferred to a Sponsor site (or a subcontractor site), which can be located outside of the country where the study is conducted. Genzyme has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.5 APPROPRIATENESS OF MEASUREMENTS

9.5.1 Primary endpoint

The primary endpoint, bone disease, will be assessed using measurements that have been validated for Gaucher disease or for other more common bone conditions.

Gaucher disease clinical assessments (mobility, bone pain and bone crisis) are established clinical parameters of bone lesions in Gaucher disease (8).

Magnetic Resonance Imaging is an established procedure to evaluate bone marrow not only for Gaucher disease, but also in oncology (20). It avoids the exposure to ionizing radiations observed with computerized tomography. A semi-quantitative method of measuring bone marrow infiltration by MRI has been developed and validated (18). It requires only standard equipment. Therefore, it can be implemented in study sites worldwide. Central reading of the images by trained readers will increase the quality and decrease the variability of the results.

Bone MRI also allows detecting lytic lesions, osteonecrosis, infarction and fractures.

Bone MRI will be performed yearly, a standard frequency in patients who are expected to be stable after multiple years of eliglustat treatment.

Dual-energy X-ray absorptiometry is the gold standard to measure BMD. A yearly frequency has been established as the time necessary to see significant changes in BMD.

Femur and spine X-Ray will serve mainly as references for additional follow up of the patients once they have left the study, when MRI may not been widely available or traditionally used to follow patients.

Bone biomarkers

Total procollagen type 1 N-terminal propeptide (P1NP), a marker of bone formation, and C-terminal telopeptide of type 1 collagen (CTx), a marker of bone resorption, have been recommended as reference markers of fracture risk assessment in age related osteoporosis by a working group of the International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine (21).

MIP1β has been shown to display moderate sensitivity and specificity to detect osteonecrosis in Gaucher disease (22).

9.5.2 Secondary endpoints

The use of patient reported outcomes as provided by quality of life questionnaires is encouraged by health authorities and entities paying for health care. In the absence of a validated tool to specifically assess disease burden in Gaucher disease type I patients, SF-36 has been selected because it is validated in multiple diseases and is available in multiple languages.

Chitotriosidase is an established biomarker in Gaucher disease and is thought to reflect the total body burden in Gaucher cells, except in patients who carry 1 or 2 null allele. Its level is related to the amount of GL-1, the substrate that accumulates as a result of the decreased activity of mutated acid β-glucosidase. Its level is elevated in untreated patients, especially the more severely affected ones, and decreases when patients improve on ERT or SRT (see for example (23)(24).

10 STUDY PROCEDURES

10.1 GENERAL CONSIDERATIONS

Imaging:

Central reading will be set up for liver and spleen MRI and bone imaging. All imaging procedures will be performed locally and the images copied onto an electronic support and shipped to a central facility for interpretation. Interpretation by local specialists will be used for the usual care of the patients, but its results will not be entered in the clinical database.

Urine Pregnancy test:

In addition to the blood pregnancy tests performed at every visit, prior to performing any radiologic study assessment (imaging), a urine pregnancy test must be performed and the result reviewed by the radiologist/technician who will document that the patient has a negative pregnancy test result by signing, dating, and noting the time of the review on the pregnancy result report. In case of a positive pregnancy test, radiologic study assessments will not be performed.

In addition female patients must perform a urine pregnancy test at home every 4 weeks while receiving eliglustat treatment.

Any positive urine pregnancy test will be verified with a blood pregnancy test. All pregnancy tests results must be documented in the patient file.

Laboratory tests:

All laboratory tests will be done at the local laboratory at the exception of those for biomarkers, which will be done in central laboratories.

10.2 VISIT SCHEDULE

All visits will be outpatient visits. However, for patients who have to travel long distances to come to a site, overnight stay in the hospital or in a lodging facility nearby may be used.

10.2.1 Screening period

Screening will be performed between 45 and 1 day before Day 1 of the study. Screening can be performed at the time of the EOS visit of the previous study the patient was enrolled in.

Final GZGD00304, GZGD02507, GZGD02607 and GZGD03109 study assessments may serve as entry evaluation for this study if performed less than 3 month for laboratory testing, 1 year for bone imaging and 6 months for other assessments.

However, safety (S)AE, concomitant medication and prior medication history, physical examinations, HIV antibody, hepatitis C antibody, or hepatitis B surface antigen, blood pregnancy test, height will have to be performed in all cases.

Patients will be assigned a unique ID number. This new ID number as well as the number of the previous study the patient was enrolled in and his/her ID number in that study will appear in the clinical database.

For some assessments it will be possible to use results from the end of study visit of the previous eliglustat study the patient was enrolled in. For others they will need to be performed anew. See detail below.

The screening procedures do not have to be performed over 2 visits. Scheduling will be based on investigator, patient and resources availability.

After completion of all the screening assessments, the investigator will review their results to confirm that each patient meets all the inclusion criteria and none of the exclusion criteria before scheduling the patient for the Day 1 visit.

10.2.1.1 Clinical information

- Demographic data will be entered in the corresponding CRF.
- Previous medical/surgical history entered in the CRF of the previous study should not be re-entered in the Medical history CRF of this study, but will be used in the analysis of this study.
- The following categories of medico/surgical events are considered part of the medical/surgical history of the patient and should be entered in the Medical/surgical history CRF:
  - AEs started during the previous study, which are closed at the time of the screening visit and are still considered clinically significant by the investigator at the time of the screening visit.
  - Medical/surgical events started after the follow-up phone call of the previous study and before the ICF signing in the current study, whether ongoing or closed, if they are considered clinically significant by the investigator.
  - Clinically significant abnormal laboratory test results at Visits 1 and 2 (Screening period)
- AEs started during the previous study, which are ongoing at the time of the screening visit should be entered in the AE CRF regardless of whether the patient had a gap in eliglustat treatment after the end of the previous study, or the end of study visit of the previous study and the screening visit of this study are concomitant.
- Concomitant medications: Any concomitant medication the patient is taking at the time of screening or took during the previous 30 days. This should include eliglustat if the last dose of eliglustat in the previous study was taken 30 days or less prior to the screening

visit. ERT should be included if the patient was on ERT during the period between the end of the previous study and the screening visit.

- Complete physical exam including weight and height
- Gaucher disease clinical assessments
- SF-36, to be completed at the study site by the patient before any other study assessment.

10.2.1.2 Imaging

- X-Rays of both femurs and lumbar spine, unless the same exams were performed as part of the previous study 1 year or less prior.
- DXA of both hips and the lumbar spine, unless the same exams were performed as part of the previous study 1 year or less prior.
- MRI of both femurs and lumbar spine, unless the same exams were performed as part of the previous study 1 year or less prior,
- Spleen and liver MRI, unless the same exams were performed as part of the previous study 6 months or less prior.

Details on technical specifications and quality control for these procedures will be provided in the vendor manual and must be strictly followed.

10.2.1.3 Laboratory tests

To be collected only if there were performed more than 3 months ago as part of the previous study the patient was enrolled in and the results are available, except for the viral serologies and the blood pregnancy test (only for female of child bearing potential), which will need to be performed in all cases.

- Viral serologies: human immunodeficiency virus antibody, and hepatitis C antibody or hepatitis B surface antigen.
- Complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, platelet count, red blood cell parameters, reticulocytes)
- Liver functions tests: AST, ALT, Alkaline phosphatase (AP), total bilirubin, albumin, GGT.
- Biomarkers: serum chitotriosidase; plasma MIP1-β; serum P1NP; serum CTX that must be collected after overnight fasting; plasma GL-1; plasma lyso-GL-1.
- For women of child bearing potential: blood pregnancy test.

10.2.2 Day 1 visit

- Complete physical exam
- For women of child bearing potential: blood pregnancy test

10.2.3 Semiannual visits

Semiannual visits will be performed at 6 month intervals (+/-14 days) in reference to the Day 1 visit.

10.2.3.1 Clinical assessments

- Complete physical exam.
- IMP compliance.
- AE
- Concomitant medications
- SF-36

10.2.3.2 Laboratory tests

- CBC (includes red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, white blood cell count and differential, platelet count).
- Biomarkers: serum chitotriosidase; plasma MIP1-β; serum P1NP; serum CTX that must be collected after overnight fasting; plasma GL-1; plasma lyso-GL-1.
- For women of child bearing potential: blood pregnancy test

10.2.3.3 Special provision for URM patients

CYP2D6 URM patients will have liver and spleen MRI and hematology performed every 6 month till week 52. However, the frequency of liver and spleen MRI and hematology can be increased to every 3 month till week 52 at the discretion of the Investigator. After week 52 CYP2D6 URMs patients will follow the standard schedule.

10.2.4 Annual visits

Annual visits will be performed once a year (+/-14 days) in reference to the Day 1 visit.

In addition to the assessments of the semiannual visits the following assessments will be performed.

10.2.4.1 Clinical assessments

- Gaucher assessments

10.2.4.2 Imaging

- DXA of both hips and the lumbar spine
- MRI of entire bilateral femur and lumbar spine

- Liver and spleen MRI
- At the 2nd and 4th anniversaries only, X-Ray of femur and lumbar spine.

10.2.5 Study completion or patient discontinuation/withdrawal

10.2.5.1 Clinical assessments

- Complete physical exam including weight
- Gaucher disease clinical assessments
- SF-36
- IMP compliance.
- AE
- Concomitant medications

10.2.5.2 Laboratory assessments

- CBC
- Biomarkers

10.2.5.3 Imaging

- X-Ray femur and spine, unless it was performed less than 2 years prior
- DXA hip and spine, unless it was performed less than 1 year prior
- Bone MRI, unless it was performed less than 1 year prior
- Liver and spleen MRI, unless it was performed less than 1 year prior

10.3 DEFINITION OF SOURCE DATA

Source Data are defined as original documents, data and records. This includes but is not limited to hospital records, clinic and office charts, study-specific source document worksheets, phone logs, memoranda, evaluation checklists, laboratory requisitions and reports, MRI, DXA, X-Ray reports, local laboratory reports, medication dispensing reports and any other documents regarding the patient.

10.4 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is discontinued, it should be determined whether the discontinuation can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the patient's

medical file and the IMP Accountability CRF. In any case, the patient should remain in the study as long as possible.

10.4.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiating of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met, and after discussion with Genzyme (refer to Section 7.1 and 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the IMP administration CRF.

If a patient becomes pregnant during her participation in the study she may remain in the study, but must suspend the IMP till delivery and while breast feeding. The maximum duration of such an IMP suspension is 12 months. During the IMP suspension the patient must maintain compliance with all the other study requirements, except for the radiological examinations that are prohibited in pregnant women.

10.4.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP during the duration of the study.

10.4.3 Criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

The use of eliglustat is prohibited in combination with Class IA and Class III antiarrhythmic medications. See Section 8.5.1.1 for detail.

Patients requiring medications incompatible with eliglustat because of drug-drug interaction for longer than 2 weeks should be discontinued from the study. See Section 8.5.1.2 for detail.
Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up, whichever comes last, unless the patient is lost to follow up.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last visit at study completion or patient discontinuation/withdrawal.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.4.4 Procedure and consequence for patient withdrawal from study.

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

If possible, the patients are assessed using the procedure normally planned for the visit at study completion or patient discontinuation/withdrawal.

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient, and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be enrolled again in the study. Their inclusion and treatment numbers must not be reused.

10.5 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.5.1 Definitions of adverse events

10.5.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.5.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

- Is a medically important event

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive nor indicative of expected AEs:

- Any reason for intensive treatment in an emergency room or at home
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.5.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to Genzyme product or program, for which ongoing monitoring and immediate notification by the Investigator to Genzyme is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

For this study the following AEs will be considered as AESI and should be reported as such to GPE:

- Clinically significant cardiac arrhythmias detected by ECG or Holter monitoring that do not meet criteria for an SAE.
- Syncope from any cause.
- Pregnancy of a female patient as well as pregnancy occurring in a female partner of a male patient.
- Pregnancy will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.5.1.2).

In the event of pregnancy in a female patient, IMP should be suspended. See Section 10.4.3 for detail.

Female patients will be instructed to notify the investigator immediately if they discover they are pregnant. Pregnant female patients will be discontinued from the study.

Male patients will be instructed to notify the investigator immediately if they discover that their sexual partner is pregnant.

If the investigator learns of a report of pregnancy at any time after signing the informed consent, the investigator should follow the instructions in Section 10.5.4 to contact the sponsor within 24 hours; however, the investigator will be asked to complete the Pregnancy forms rather than SAE forms. The patient will be followed until the outcome of the pregnancy is known (eg, live birth or stillbirth). The investigator will be responsible for this follow-up.

Follow-up of the pregnancy in a female patient or in a female partner of a male patient is mandatory until the pregnancy outcome has been determined, unless prohibited by local regulations.

- Symptomatic overdose (serious or non-serious) with IMP
  - A symptomatic overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as administration of a quantity of IMP per administration or per day, which is above the maximum recommended dose according to the authorized product information

    If overdose is suspected, the patient will be asked to suspend the IMP immediately and come back to the site for appropriate monitoring.

    Asymptomatic overdose has to be reported as a standard AE.

10.5.2 General guidelines for reporting adverse events

- Patients for whom the screening visit of this study is done at the same time as the EOS visit of the previous eliglustat study they were enrolled in, the safety follow-up phone scheduled 30-37 days after the EOS visit of the previous study will not be done. Instead, these patients will be monitored according to the standard safety procedures of this study. The Ethics Committees (and Local Health Autority, if required) at the affected sites will be notified.
- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of study visit, or the last IMP administration for patient with early termination, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- The following categories of medico/surgical events are considered part of the medical/surgical history of the patient and should be entered in the Medical/surgical history CRF:
  - AEs started during the previous study, which are closed at the time of the screening visit and are still considered clinically significant by the investigator at the time of the screening visit.
  - Medical/surgical events started after the follow-up phone call of the previous study and before the ICF signing in the current study, whether ongoing or closed, if they are considered clinically significant by the investigator.
- AEs started during the previous study, which are ongoing at the time of the screening visit should be entered in the AE CRF regardless of whether the patient had a gap in eliglustat

treatment after the end of the previous study, or the end of study visit of the previous study and the screening visit of this study are concomitant.

- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by Genzyme. Patients who experience an ongoing SAE or an AESI at the prespecified study end-date, should be monitored until follow-up is no longer considered medically necessary or the patient is lost to follow-up.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study visit as defined by the protocol for that patient, unless the patient is lost to follow up.
- Clinically significant laboratory abnormalities after Visit 3 (Day 1) are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

10.5.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to Genzyme. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant

medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE 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 GPE.

10.5.4 Guidelines for reporting adverse events of special interest

For AESIs, Genzyme must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.5.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF. Instructions for AE reporting are summarized in Table 2.

Table 2 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.5.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Pregnancy and any AE listed in Section 10.5.1.3	Yes	Yes	Yes

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, Genzyme will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Any other AE not listed as an expected event in the Investigator's Brochure will be considered unexpected.

Genzyme will report all safety observations made during the conduct of the trial in the clinical study report.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 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 an 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.

11.2 DISPOSITION OF PATIENTS

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

11.3 ANALYSIS POPULATIONS

11.3.1 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.

11.3.2 Safety population

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

11.3.3 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.

11.4 STATISTICAL METHODS

All endpoints will be summarized descriptively; no hypothesis testing will be performed. Descriptive statistics include those for continuous (n, mean, median, minimum, maximum), categorical (n, percent), cumulative incidence (n, percent) or incidence rate (n/year) outcomes, as appropriate. Calculations and summaries will include all non-missing data at a given time point, imputation will not be performed.

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)
- When the study is complete

For the PAP, response 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; and
- Eliglustat baseline, defined at status at first dose of eliglustat in the previous Phase 2 or Phase 3 study.

In reference to the study period, skeletal response 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/cm2) and changes from baseline (eg, shift in category of bone pain or absolute and percent change from baseline in BMD g/cm2 or incidence over 2 years, as appropriate).

In reference to the period of eliglustat treatment, skeletal response 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, 6 yr., 7 yr., 8 yr. or 6-8 yr., 8-10 yr.

When the study has completed, summaries will be performed for both the total on-study period, and the eliglustat treatment period, as described above.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

Duration of IMP exposure is defined as: last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations.

A given period of administration will be considered noncompliant if the patient takes less than 90% or more than 105% of the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data. Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance categorized as <80%, 80%-90%, 90%-105%, >105% will be summarized.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

Five common skeletal manifestations of Gaucher disease will be summarized separately. A single composite endpoint will not be constructed.

1. Mobility, bone crisis and pain: Category of mobility status and bone pain, as well as number of new bone crises, will be summarized. Additionally shifts in category of mobility and pain from study and eliglustat baseline will be presented.
2. Bone marrow infiltration: Bone marrow infiltration score will be summarized both continuously and categorically. Reported values and changes from study and eliglustat baseline will be summarized as data is available.

   Category of infiltration score will be constructed and summarized:

   Mild: 0 to 4

   Moderate: 5 to 8

   Severe: 9-16

   Shifts in category from study and eliglustat baseline will be summarized.

1. BMD: Bone mineral density in (g/cm2), as well as T and Z scores, will be summarized by time point as well as absolute and percent changes from study and eliglustat baseline.
2. Lytic lesions, fractures, infarctions and osteonecrosis. Incidence of new or worsening lytic lesions, new or worsening AVN, new or worsening infarctions and new fractures will be summarized at the 2 year and end of study time points. Annual incidence rates may also be calculated and summarized.
3. Bone biomarkers: Levels of P1NP, CTx and MIP 1 β, as well as absolute and percent changes from study or eliglustat baseline will be summarized.

11.4.2.2 Analyses of secondary efficacy endpoints

Biomarker: Biomarkers will be summarized as measured values, absolute and percent change from eliglustat and study baseline.

11.4.3 Analyses of safety data

Adverse experience will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or higher; all adverse experiences will be summarized by body system and MedDRA preferred term overall, by relationship and severity and seriousness. All deaths will be summarized.

Physical examinations, routine laboratory assessments (chemistry and hematology), biomarkers and pregnancy testing for female patients of childbearing potential will be summarized at each

time point. Additionally, the change from study baseline and/or eliglustat baseline, as appropriate, may be summarized. Concomitant medications will be reported.

Observation period
The observation of safety data will be as follows:

- Screening is from signed informed consent to the day before the 1st dose of IMP is administered.
- TEAE observation period is from first to last dose of IMP in this study. Patients with an SAE or AESI should be followed until resolution or when follow-up is no longer considered medically necessary, or the patient is lost to follow-up.

All safety analyses will be performed on the Safety population using the following common rules:

The baseline value is defined generally as the last available value before first dose of IMP in this study.

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), preferred term (PT) sorted by decreasing frequency for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. 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 within each treatment group.

AE incidence tables for the AESIs below will be generated.

- Clinically significant cardiac arrhythmias detected by ECG or Holter monitoring that do not meet criteria for an SAE.
- Syncope from any cause.

Death: The following deaths summaries will be generated:

- Number (%) of patients who died and reasons for death if collected in death report form summarized on the safety population
- All AEs leading to death (death as an outcome on the AE CRF page as reported by the Investigator), by primary SOC and PT, showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of PT
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of PT.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

A listing of Genz-99067 plasma concentrations will be provided.

11.4.5 Analyses of Patient Reported Outcomes (Health-related Quality of Life/health economics variables

The SF-36 Health Status Survey Version 2 is made up of 36 questions, each of which has a weighted response associated with it. The 36 questions are combined into various groupings to form eight scales, which are then further combined to form two overall summary measures, the Physical Component Summary (PCS) and Mental Component Summary (MCS). These will be generated and summarized at each visit, as well as changes from eliglustat and study baseline, as described in the statistical analysis plan.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by Genzyme, the Investigator, delegated Investigator staff and Sub investigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sponsor public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (Institutional Review Board/Independent Ethics Committee (IRB/IEC)). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by Genzyme prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the informed consent form should be signed, name filled in and personally dated by the patient, and by the person who conducted the informed consent discussion.

The informed consent form and the assent form used by the Investigator for obtaining the Patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or Genzyme must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and Genzyme.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by Genzyme (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub investigators shall be appointed and listed in a timely manner. The Sub investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

Genzyme of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and Genzyme maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory

authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the CV describing the experience, qualification and training of each Investigator and Sub investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub investigators of the confidential nature of the clinical trial.

The Investigator and the Sub investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Sub investigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity (White, Black, Asian, American Indian or Alaska native, Native Hawaiian or Other Pacific Islander, Hispanic or Latino, Jewish descent –Ashkenazi or Sephardic, Japanese descent, Chinese descent) will be collected in this study because these data are required by several regulatory authorities (eg, on Japanese population for the Pharmaceuticals Medical Devices Agency (PMDA) in Japan, or on Chinese population for the China Food and drug administration (CFDA) in China).

Analyses of Subject genetic data will be conducted as described in the protocol as this is needed for pharmacogenetic analyses required for the purpose of the study or by regulatory authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;

- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Sub investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

It is anticipated that publications may result from this study. This will be specified at an appropriate time.

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed

90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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17 APPENDICES

Appendix A Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE

Male participants

No contraception requirements.

Female participants

Female patients of childbearing potential are eligible to participate if they are willing to practice true abstinence in line with their preferred and usual lifestyle, or if they agree to use a medically accepted form of contraception (either a barrier method, such as condom or diaphragm + spermicide, or a non-barrier method such as oral, injected, or implanted hormonal methods, or an intra-uterine device or system) consistently and correctly while receiving eliglustat.

COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

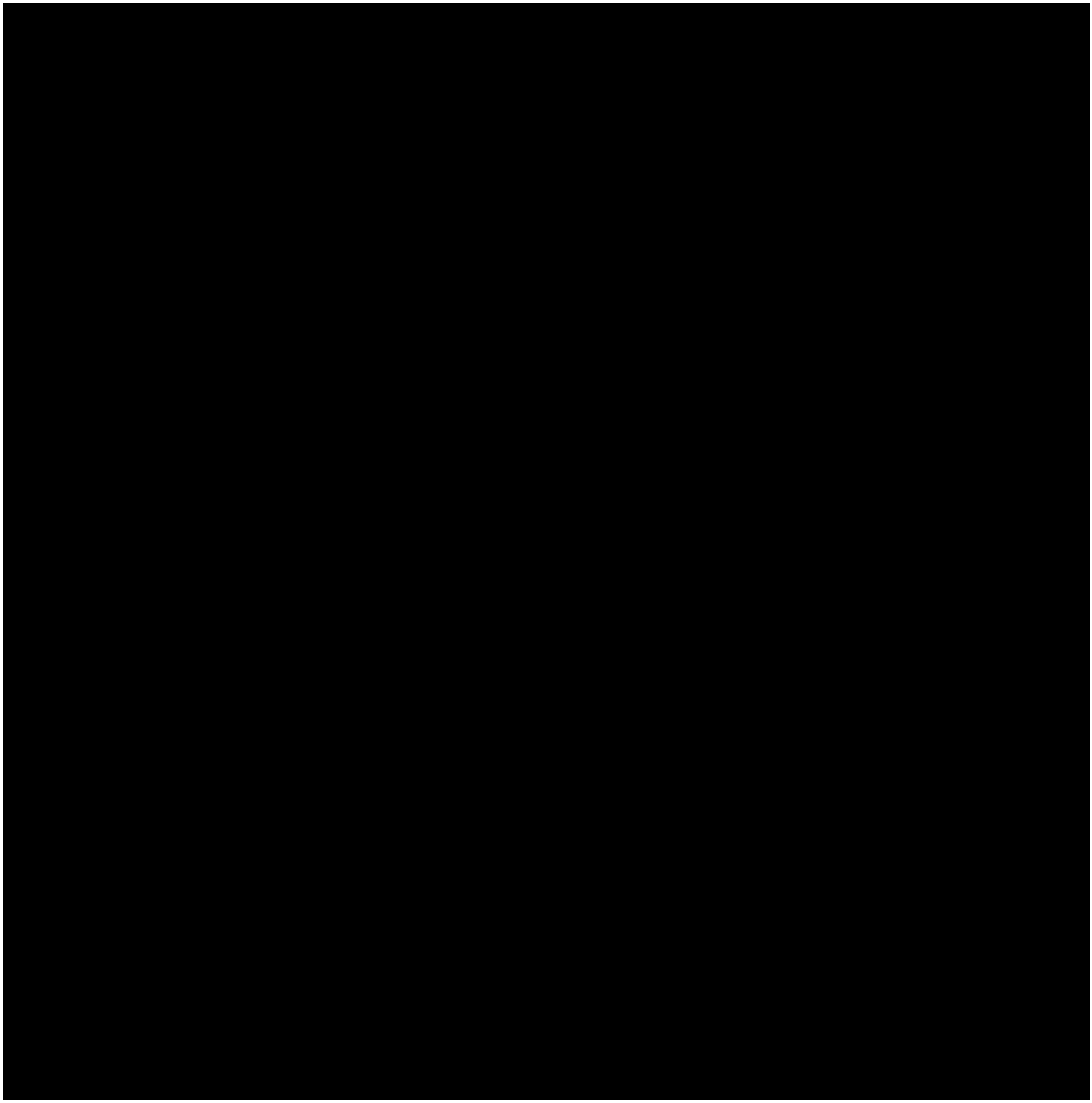
- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study must stop study treatment as soon as a pregnancy is confirmed and will be either withdrawn from the study or remain in the study. If a pregnant patient decides to remain in the study she must suspend the IMP till delivery and while breast feeding. The maximum duration of such an IMP suspension is 12 months. During the IMP suspension the patient must maintain compliance with all the other study requirements, except for the radiological examinations that are prohibited during pregnancy.

Appendix B Document(s) related to the assessment of 1 (or more) endpoint(s)

Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) Questionnaire



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Appendix C General guidance for the follow-up of laboratory abnormalities by Sanofi

Not applicable.

EFC13781 Amended protocol02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
	GPE Approval	
	Clinical Approval	