NCT Number: NCT02489344

STATISTICAL ANALYSIS PLAN

An open-label, multicenter, multinational extension study of the long-term safety, pharmacodynamics and exploratory efficacy of GZ/SAR402671 in adult male patients diagnosed with Fabry disease

GZ/SAR402671-ACT13739-LTS14116

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR:	albumin/creatinine ratio
AE:	adverse event(s)
AESI:	adverse event(s) of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	anatomic Therapeutic Chemical Classification System
BDI:	Beck Depression Inventory
BMI:	body mass index
BQL:	below quantifiable limit
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
CRF:	case report form
CS:	clinically significant
CSR:	clinical study report
DMC:	data monitoring committee
eCRF:	electronic case report form
ECG:	electrocardiogram
eGFR:	estimated glomerular filtration rate
EM:	electron microscopy
ERT:	enzyme replacement therapy
GL-1:	glucosylceramide
GL-3:	globotriaosylceramide
GM3:	monosialodihexosylganglioside
HEENT:	head, eyes, ears, nose, throat
HLGT:	high-level group term
HLT:	high-level term
IDMS:	isotope dilution mass spectrometry
IMP:	investigational medicinal product
LC-MS/MS:	liquid chromatography tandem mass spectrometry
LLT:	lower-level term
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
NA:	not applicable
NCS:	not clinically significant
PCR:	protein/creatinine ratio
PK:	pharmacokinetic
PRO:	patient reported outcome
PT:	preferred term

SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	standard deviation
SF36:	short Form-36
SOC:	system organ class
TEAE:	treatment emergent adverse event
WBC:	white blood cell
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

LTS14116 is an open-label, multicenter, multinational extension study of GZ/SAR402671 in adult male Fabry disease patients who previously completed study ACT13739 and satisfy the eligibility criteria. In this extension study, patient will continue to receive once daily, oral GZ/SAR402671 at the same dose level administered at the end of study ACT13739.

This extension study consists of an enrollment visit, where study entry in the extension should occur at the same time as the ACT13739 week 26 clinical visit, followed by a treatment period up to 30 months (2.5 years) and 1 month follow-up for all patients completing or discontinuing the study medication. Patients who start commercial enzyme replacement therapy (ERT) within the 1-month follow up period will not be considered for follow up. The maximum duration of participation per patient in the extension study will be approximately 31 months.

The safety data and the results of the study will be periodically reviewed by Data Monitoring Committee (DMC).

Eleven (11) adult male Fabry disease patients from 5 sites were enrolled into the ACT13739 study, of which 8 entered the extension study LTS14116.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of the LTS14116 extension study is to assess the long-term safety of GZ/SAR402671 in adult male Fabry disease patients who previously completed study ACT13739.

1.2.2 Secondary objectives

The secondary objective of the LTS14116 extension study is to assess the long-term effect of GZ/SAR402671 on pharmacodynamic and exploratory efficacy endpoints in adult male Fabry disease patients who previously completed study ACT13739.

Pharmacodynamics as measured by:

- Plasma globotriaosylceramide (GL-3), lyso GL-3, glucosylceramide (GL-1) and monosialodihexosylganglioside (GM3)
- Exploratory blood and urine biomarkers including, but not limited to, high sensitivity cardiac troponin T, plasma chitotriosidase assay (plus chitotriosidase genotyping for interpretation) and podocyturia
- Urine GL-3

Exploratory efficacy as measured by:

- GL-3 in skin biopsy
- Urinary albumin and protein [albumin to creatinine ratio (ACR) and protein to creatinine ratio (PCR)]
- Echocardiogram
- Brain magnetic resonance imaging (MRI)
- Estimated glomerular filtration rate (eGFR)
- Health-related quality of life, a measure of the impact of the patient's health on his well-being as assessed by the patient reported Short Form generic health survey (36 items) (SF-36) questionnaire, Gastrointestinal questionnaire, Beck Depression Inventory- Second Edition (BDI-II)

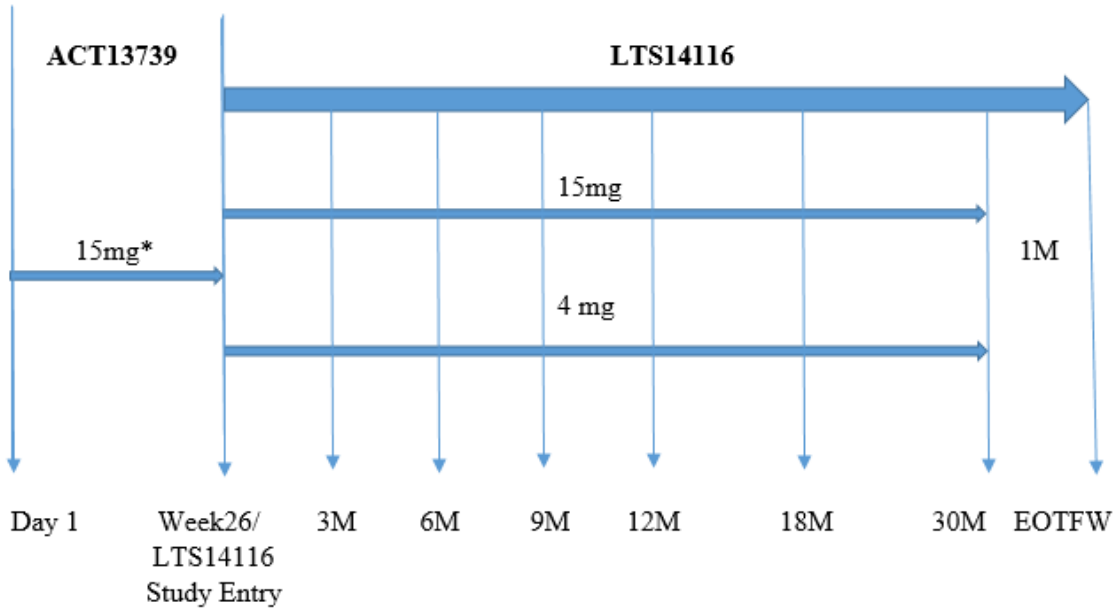
1.3 DETERMINATION OF SAMPLE SIZE

Eleven (11) patients were enrolled in ACT13739 study of which 9 patients completed. Therefore, 9 is the maximum number of patients available to participate in the extension period. In total, 8 patients gave informed consent and entered the extension study LTS14116.

1.4 STUDY PLAN

The following figure describes an overview of the study design.

Figure 1 – Overview of the study design



* For safety concerns, a dose reduction of IMP to 4mg may occur
M: Month
EOTFW: End of treatment follow up

The LTS14116 study comprises of the following timepoints/periods:

- The study entry visit may occur at the same time as the week 26 clinical visit of the core study (ACT13739). The patients who complete study ACT13739 will sign the informed consent prior to any action related to the study. For the purpose of analysis in this study, data collected at screening and prior to the first GZ/SAR402671 administration in ACT13739 (including demographic, medical/surgical history, Fabry disease history, GLA mutations, results from safety, pharmacodynamics, and exploratory efficacy assessments) will be imported into the extension study (LTS14116) database.
- A treatment period of 30 months. During this treatment period, the patient will take once daily oral dose of 15 mg or 4 mg of GZ/SAR402671 treatment on scheduled site visits (Months 3, 6, 9, 12, 18, and 30) as well as daily self-administer at home. A patient diary will be issued to patients with instructions to record each dose that will be self-administered, and to bring their diary and any remaining capsules to subsequent clinic visits. At each visit, the patient diary and remaining capsules will be reviewed and dosing

information will be recorded in the electronic case report form (eCRF). The study assessment clinical visits are scheduled based on the study entry day and have a ±14 day window period. All clinical data will be collected at specific time points according to the study procedure and schedule of assessments. On the clinical visits during the treatment period, the patient will complete any PROs before completing any other health data forms, and before participating in any clinical assessments. Blood and urine samples will also be collected before taking the treatment dose of GZ/SAR402671. An independent DMC will oversee safety in this study through periodic and ad-hoc reviews of study data.

- A follow-up visit with a site visit 1 month (±7 days) after the last GZ/SAR402671 administration. Patients who start commercial ERT within the 1-month follow up period will not be considered for follow up.

The protocol Section 10 and the protocol Section 1.2 (Study Flow Chart) provide further details on the conduct and timing of study assessments.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was never changed in an amendment.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

NA

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

As LTS14116 is the extension study of the ACT13739 study, the baseline values from the ACT13739 study will be utilized in the analysis of the collected data from the combined ACT13739 and LTS14116 study periods. Therefore, in the planned analysis the baseline value is defined as the last available value before the first investigational medicinal product (IMP) intake in ACT13739 study, unless otherwise specified. Data collected in the ACT13739 study will be imported into the LTS14116 database, and all 11 patients who received IMP treatment in the ACT13739 study, regardless of whether the patient entered the LTS14116 extension study, will be presented in the analysis, in order to have a more complete picture of the responses over time of the GZ/SAR403671 treated Fabry patients..

All baseline safety and efficacy parameters (apart from those listed below) will be presented along with the summary statistics in the efficacy and safety sections (Section 2.4.4 and Section 2.4.5).

Demographic characteristics

Demographic variables are age in years, sex (Male), race (Caucasian/White, Black, Asian/Oriental, Other). The demographic data collected in ACT13739 will be imported into the LTS14116 database.

Medical or surgical history

Medical/surgical parameters include body system, system/condition/diagnosis, start and stop dates, and ongoing status. In addition, Fabry medical history collected from the ACT13739 study for prespecified abnormalities, including the diagnosis date, Fabry medical history abnormality, description of abnormality, start and stop dates, and ongoing status, will be imported into the LTS14116 database.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of LTS14116 database lock.

Disease characteristics at baseline

Specific disease history includes age at Fabry diagnosis in years, Leukocyte αGAL activity (<4.0, ≥4.0 nmol/hr/mg), Plasma αGAL activity (<1.5, ≥1.5 nmol/hr/mL), and Genotyping will be imported from the ACT13739 study.

Vital signs

Vital signs parameters include weight, height, and body mass index (BMI) at baseline.

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

2.1.2 Prior or concomitant medications

Concomitant medications taken during the LTS14116 study are to be reported in the LTS14116 case report form (CRF) pages. All medications collected for the 11 patients who participated in the ACT13739 study will be imported into the LTS14116 database in order to show an overall profile of the patients' long term medication use.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD), using the version in effect at Sanofi at the time of LTS14116 database lock.

- Prior medications are those medications which the patient used prior (within 30 days before screening) to the first IMP intake in ACT13739 study. Prior medications could be discontinued before the first administration of IMP or could be ongoing during the treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly with the IMP, i.e., from the first IMP intake in the ACT13739 study through the day of last IMP intake in the LTS14116 study. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the residual treatment epoch or the posttreatment epoch in LTS14116 (as defined in the observation period in Section 2.1.4).
- Posttreatment medications are those the patients took during the period starting from the day after the last IMP intake in the combined ACT13739/LTS14116 study period up through the end of follow-up phase. Medications started during the residual treatment or posttreatment epoch are not concomitant medications, though medications that started during the treatment epoch and continued into the residual epoch and posttreatment epoch may be classified as both concomitant and posttreatment medications.

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

2.1.3 Efficacy endpoints

Evaluation schedule for efficacy variables is presented in protocol Section 1.2.

All efficacy evaluations up to study closeout measurement (visit) will be included for analysis unless otherwise specified. Baseline for the efficacy variable is defined as the last non-missing value on or before the first IMP intake in ACT13739 study.

2.1.3.1 Primary efficacy endpoint(s)

LTS14116 is an extension study of ACT13739. The primary objective is to evaluate the long-term safety of GZ/SAR402671; therefore, no primary efficacy endpoint is defined.

2.1.3.2 Secondary efficacy endpoint(s)

Secondary endpoint - pharmacodynamics

The following pharmacodynamic endpoints will be collected and analyzed (see study flowchart in protocol Section 1.2).

- Plasma GL-3, lyso GL-3, GL-1 and GM3
- Urine GL-3
- Exploratory blood/plasma and urine biomarkers including, but not limited to plasma high sensitivity cardiac troponin T, plasma Chitotriosidase assay (plus chitotriosidase genotyping for interpretation) and podocyturia

Plasma samples for GL-3, lyso GL-3, GL-1, and GM3 and urine sample for GL-3 levels will be analyzed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method at a central laboratory.

Plasma samples will be collected to explore changes in high sensitivity cardiac troponin T analyzed at a central laboratory. Blood (plasma) and urine samples for exploratory biomarkers related to Fabry disease will be collected and analyzed later using appropriate platforms.

Urine samples will be processed to prepare cytospin slides, which will be stained for podocyte (podocalyxin, PCX) and parietal cell (claudin 1, CL1) markers. PCX +/CL1 − cells will be identified as podocytes and PCX +/CL1 + cells as parietal cells with podocyte phenotype.

Secondary endpoints - exploratory efficacy

The secondary exploratory efficacy endpoints are as follows:

GL-3 clearance from skin

A skin biopsy will be performed for the scoring of GL-3 as evaluated by light microscopy optionally at month 6 and mandatorily at month 30 of the treatment period. Quantification of cellular GL-3 by histomorphometry through electron microscopy (EM) may also be evaluated. For each study site, a physician experienced in skin biopsy technique will be identified to ensure all tissue samples are correctly obtained and are appropriately processed for shipment. Sample processing, storage, and shipment guidelines are provided in the study manual. Masked biopsy samples will be reviewed and scored by 3 independent pathologists using light microscopy. GL-3 clearance is scored as none/trace (0), mild (1), moderate (2), or severe (3) GL-3 accumulation/inclusions.

A majority score will be determined for each slide and cell type based on the individual scores of each pathologist. If there is a difference >1 between any 2 of the 3 pathologist's scores, this will be considered as a discrepant scoring. For the evaluation of superficial skin capillary endothelium, the discrepant scoring of a slide will be resolved by an adjudication process in which the slide will be re-read by the original independent pathology reviewers. If a majority score cannot be derived from the adjudication process, then the median adjudicated score will be used. For other skin cell types evaluated, the discrepant scoring will be resolved by using the median score. In some instances, scores may not be available from all 3 pathologists for a given slide and cell type. If scores are provided by 2 of the 3 pathologists, the majority score is the score given by each pathologist (if they agree) or the higher of the two individual scores (if they disagree). If only one pathologist provides a score, the value for the majority score is set to missing.

Protein excretion

Protein excretion will be evaluated from the median of 3 timed overnight urine samples, that will be collected with 4 to 7 days between each collection (see study flowchart in protocol Section 1.2). All urine samples must be collected within a 16-day period. All 3 samples must be collected regardless of the results. Specific parameters that will be measured and reported include ACR and PCR.

Echocardiogram

A 2-dimensional and M-mode echocardiograph with Doppler will be performed at the study visits specified in study flowchart in protocol Section 1.2. The variables will include, but not be limited to, ventricular cavity size, valve characterization, ejection fraction, ventricular wall thickness, regional wall motion, diastolic function, and pericardium characterization, pulmonary blood pressure and blood flow will be determined by Doppler ultrasound.

Two copies of the echocardiograph recording will be generated for each study time point. One copy will be kept at the study site with a site physician interpretation. A site physician will assess the echocardiograph and provide an overall conclusion as normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS).

The second copy will be sent to the central laboratory for analysis. The central laboratory findings will be used for statistical analyses. Specific procedures for these tests are supplied to each study investigator in the study manual.

Brain MRI

Brain MRI (without contrast agent) assessments include: number and volume of white matter lesions, stroke, pulvinar sign, and other significant abnormalities.

Two copies of the MRI recording will be generated for each requested timepoint (see study flowchart in protocol Section 1.2). One copy will be kept at the study site with the interpretation of a site physician. A site physician will assess the MRI and record an overall conclusion as normal, abnormal but NCS, or abnormal and CS. If the study investigator determines the MRI is abnormal and CS and a change from screening, the result will be documented as an AE.

The second copy will be sent to the central laboratory for analysis. The central laboratory findings will be used for statistical analyses.

eGFR

eGFR will be calculated by the central laboratory using an isotope dilution mass spectrometry(IDMS)-calibrated serum creatinine assay and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see Section 2.5.1 for CKD-EPI formula).

2.1.4 Safety endpoints

The primary endpoint of this study is safety. The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, electrocardiograms (ECGs), physical examinations, neurological examination and ophthalmologic examination. The LTS14116 study represents an additional 30 months of treatment of GZ/SAR402671 in patients who completed their 6 months of treatment of in the ACT13739 study. As the intention is to evaluate data of up to 36 months of GZ/SAR402671 treatment, the safety data from the ACT13739 study will be imported into the LTS14116 database. In order to have a fuller picture of the treatment effect, data from all 11 patients who participated in the ACT13739 study, regardless of time of study termination, will be included in the safety analysis.

Observation period

The observation period of the analysis combining the ACT13739 and LTS14116 will be divided into 4 epochs:

- The **pre-treatment** epoch is defined as the time from the signed informed consent date up to the day prior to the first IMP administration in the ACT13739 study.
- The **on-treatment** epoch is defined as the time from the first administration of the IMP in the ACT13739 study to the last administration of the IMP in the combined ACT13739/LTS14116 treatment period, including any temporary treatment discontinuation period, if any.
- The **residual treatment** epoch is defined as the time from the day after the last IMP administration, whether during the ACT13739 or the LTS14116 study, plus 30 days or last study visit, whichever occurs first.

The treatment-emergent adverse event (TEAE) period will include both the on-treatment and the residual treatment epochs.

- The **posttreatment** epoch is defined as the period of time starting the day after the end of the TEAE period up to the end of the study (defined as either the last study visit for patients who start commercial ERT within 1 month after the last IMP treatment, or the 1 month (±7 days) follow-up site visit for the rest of the patients).

The on-study observation period includes the pre-treatment, on-treatment, residual treatment, and the posttreatment epochs.

2.1.4.1 Adverse events variables

Adverse event observation period

In the case of an AE that worsened or became serious, each part of the event is considered in the Study Data Tabulation Model (SDTM) as a separate record, with the date the AE worsened or became serious as the start date of the new record and linked by the initial AE reference number. (A single end date/time and outcome will be used for both records.)

The emergence is determined for each record of the AEs as follows:

- Pre-treatment AEs are defined as AEs that developed, worsened, or became serious from the signed informed consent date up to first administration of IMP
- Treatment-emergent adverse events (TEAEs) are adverse events that developed, worsened, or became serious during the TEAE period (as defined in Section 2.1.4)
- Posttreatment adverse events are adverse events that developed, worsened, or became serious during the posttreatment period

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

Adverse events (including serious adverse events) will be recorded from the time of signed informed consent in the ACT13739 until the completion of the LTS14116 study.

AESIs include the following categories listed in the Adverse Event Log form in the eCRF:

- Symptomatic overdose
- Alanine aminotransferase (ALT) increase
- New or worsening lens opacities and cataracts
- Pregnancy of a female partner of a male patient enrolled in ACT13739/LTS14116

AEs that fall into any AESI category will be checked off on the Adverse Event Log form in the eCRF by the site investigator, and flagged in the database.

2.1.4.2 Deaths

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

- Death on-treatment: deaths occurring during the TEAE period (as defined in Section 2.1.4)
- Death posttreatment: deaths occurring after the end of the TEAE period

2.1.4.3 Laboratory safety variables

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

Blood samples for clinical laboratories will be taken at the scheduled visits listed in study flowchart in protocol Section 1.2. The laboratory parameters will be classified as follows:

- Hematology
  - Complete blood count, including hematocrit with absolute (not percentage) differential cell counts of lymphocytes, hemoglobin, platelets, erythrocytes, basophils, eosinophils, lymphocytes, monocytes, neutrophils, leukocytes, and (if applicable) abnormal cells
- Blood chemistry
  - albumin, alkaline phosphatase (ALP), alanine aminotransferase, aspartate aminotransferase, direct bilirubin, total bilirubin, blood urea nitrogen, calcium, chloride, creatinine, glucose, potassium, lipase, magnesium, phosphorus, total protein, sodium, uric acide, C-reactive protein

Urine samples will be collected as follows

- Urine biochemistry: albumin, creatinine, total protein, and routine urinalysis (including but not limited to sediment examination, specific gravity, metered pH.)

2.1.4.4 Vital signs variables

Vital signs taken include: heart rate (supine, standing), systolic and diastolic blood pressure (supine, standing), temperature (supine), respiratory rate (supine). In addition, height at the baseline visit and weight at every visit will be taken (see study flowchart in protocol Section 1.2).

2.1.4.5 Electrocardiogram variables

Standard 12-lead ECGs will be recorded using an electrocardiographic device after at least 5 minutes in the supine position at the investigator site (see study flowchart in protocol Section 1.2). Triplicate ECG will be recorded within 5 minutes with at least 1 minute between 2 replicates.

The printout of the recording will be retained at the site and manually read by the study site cardiologist or qualified investigator to determine whether the result is normal, abnormal but NCS, or abnormal and CS.

The ECG recordings will also be digitally transmitted to ECG reading center for the central reading of the ECG parameters. ECG parameters include RR interval, PR interval, QT interval, QTc (according to Bazett and Fridericia formulae) interval, QRS duration, and HR.

2.1.4.6 Physical examination variables

Physical examination will be performed at study visits specified in study flowchart in protocol Section 1.2 The findings of each examination will be recorded. Each physical examination will include the following physical observations/measurements:

- General appearance
- Heart
- Skin
- Respiratory auscultation
- Mental status
- HEENT (head, eyes, ears, nose, throat)
- Extremities/Joints
- External genitalia
- Peripheral atrial pulses
- Lymph nodes
- Abdomen

A site physician will assess the physical examination findings as normal, abnormal but NCS, or abnormal and CS.

2.1.4.7 Neurological examination variables

Neurological examination variables will include: mental, cranial nerves, motor system, deep tendon reflex, sensation, and cerebellum, and evaluations of pain. It will be performed at study visits specified in study flowchart in protocol Section 1.2.

2.1.4.8 Ophthalmology examination variables

A standard ophthalmology examination will be performed at the scheduled visits specified in study flowchart in protocol Section 1.2. The examination should be performed by the same ophthalmologist throughout the study, if possible, and will include but not be limited to, visual acuity, slit-lamp examination and examination of the cornea, lens, and retina. At Month 6, Month 18, Month 30, and in cases of Early Withdrawal, dilation of the pupils is required for examination. Photography of the lens with broad beam and red reflex, and cornea with the broad beam should be done at Month 30 for all patients.

2.1.5 Pharmacokinetic variables

Single pharmacokinetic samples will be collected at clinical visits (see study flowchart in protocol Section 1.2). As a result, no pharmacokinetic parameters will be generated.

2.1.6 Pharmacodynamic/genomics endpoints

The pharmacodynamic endpoints (plasma GL-3, lyso GL-3, GL-1 and GM3, urine GL-3 and exploratory blood and urine biomarkers, high sensitivity cardiac troponin T, plasma chitotriosidase assay, and podocyturia) are considered as secondary endpoints in this study (see Section 2.1.3.2).

2.1.7 Quality-of-life endpoints

SF-36

The SF-36v2® Health Status Survey (standard 4-week recall period) consists 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 scales and the items constituting the scales are as follows:

- Physical Functioning (PF) – Items 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
- Role Limitations Due to Physical Health (RP) – Items 4a, 4b, 4c, 4d
- Bodily Pain (BP) – Items 7, 8
- General Health Perceptions (GH) – Items 1, 11a, 11b, 11c, 11d
- Vitality (VT) – Items 9a, 9e, 9g, 9i
- Social Functioning (SF) – Items 6, 10
- Role Limitations Due to Emotional Problems (RE) – Items 5a, 5b, 5c
- Mental Health (MH) – Items 9b, 9c, 9d, 9f, 9h

Note: Item 2, a general health item formerly referred to as Reported Health Transition (Self-Evaluated Transition (SET) in the current version of the health survey), is not used to score any of the eight health domain scales or component summary measures .

Prior to any summary scores being calculated, values outside the range of acceptable item response values will be converted to missing scores. Next, ten items in the questionnaire (items 1, 6, 7, 8, 9a, 9d, 9e, 9h, 11b, and 11d) will be reverse scored. Reverse scoring of these items is required so that a higher item response value indicates better health for all SF -36v2® Healthy Survey items and summary measures. In addition, items 1, 7, and 8 require further recalibration of the items scores according to the developer's recommendation as follows:

Table 1 - Scoring for Item 1

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

Table 2 - Scoring for Item 7

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

Table 3 – Scoring for Item 8 if Both Item 7 and Item 8 are answered

Response Choices	If Item 8 Pre-coded Item Value	& Item 7 Pre-coded Item Value	Then Final Item Value
Not at all	1	1	6
Not at all	1	2 through 6	5
A little bit	2	1 through 6	4
Moderately	3	1 through 6	3
Quite a bit	4	1 through 6	2
Extremely	5	1 through 1	1

Table 4 – Scoring for Item 8 if Item 7 is not Answered

Response Choices	Pre-coded Item Value	Final Item Value
Not at all	1	6.0
A little bit	2	4.75
Moderately	3	3.5
Quite a bit	4	2.25
Extremely	5	1.0

Table 5 – Scoring for Item 6

Response Choices	Pre-coded Item Value	Final Item Value
Not at all	1	5
Slightly	2	4
Moderately	3	3
Quite a bit	4	2
Extremely	5	1

Table 6 – Scoring for Items 9a, 9d, 9e, 9h

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

Table 7 – Scoring for Items 11b and 11d

Response Choices	Pre-coded Item Value	Final Item Value
Definitely true	1	5
Mostly true	2	4
Don’t know	3	3
Mostly false	4	2
Definitely false	5	1

Raw scale scores are calculated using final item values only. A respondent has to have answered at least 50% of the items contributing to a particular scale for a raw scale score to be computed. If the respondent did not answer at least 50% of the items contributing to a particular scale, the raw scale score will be set to missing for that scale for that respondent for a particular timepoint. If a respondent has answered at least 50% of the items contributing to a particular scale but some of the items were not answered, the missing items will be estimated by the average score across the items that were answered.

The raw scale scores will be computed by taking the sum of the items for that particular scale. Each raw scale score will then be transformed to a 0 to 100 scale using the following formula:

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

This information is listed in Table 8.

Table 8 - Lowest and highest possible raw scores and score range of the scales

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

The two overall summary scores will be calculated by first determining the standard deviation scores (also called z-scores) for the eight scales as follows:

$$\text{z-score} = \frac{(\text{transformed scale score} - \text{mean from the 1998 general U.S. population})}{\text{standard deviation from the 1998 general U.S. population}}$$

$$\text{z-score} = \frac{(\text{transformed scale score} - \text{mean from the 1998 general U.S. population})}{\text{standard deviation from the 1998 general U.S. population}}$$

Specifically, the following numbers (Table 9) are used in the calculation of the eight z-scores:

Table 9 – Means and standard deviations used for the z-score calculations

Scale	Mean from the 1998 general population	Standard deviation from the 1998 general population
Physical functioning	83.29094	23.75883
Role-Physical	82.50964	25.52028
Bodily Pain	71.32527	23.66224
General Health	70.84570	20.97821
Vitality	58.31411	20.01923
Social Functioning	84.30250	22.91921
Role-Emotional	87.39733	21.43778
Mental Health	74.98685	17.75604

The SF36v2 then utilizes a linear T-score transformation method so that scores for each of the health domain scales has a mean of 50 and a standard deviation of 10. For example:

Physical functioning (PF) T-score = 50 + (PF z_score * 10)

The z-scores for the raw scales will be combined to form the two aggregate raw summary scores by multiplying each one by its corresponding scoring coefficient derived from the 1990 general U.S. population and taking the sum of those values. If any of the component scale scores are missing, then the associated aggregate summary score is not computed.

The following scoring coefficients (Table 10) are used in calculating the aggregate raw summary scores:

Table 10 – Scoring coefficients used in calculating the aggregate raw summary scores

Scale	Coefficients used for raw PCS	Coefficients used for raw MCS
Physical functioning	0.42402	-0.22999
Role-Physical	0.35119	-0.12329
Bodily Pain	0.31754	-0.09731
General Health	0.24954	-0.01571
Vitality	0.02877	0.23534
Social Functioning	-0.00753	0.26876
Role-Emotional	-0.19206	0.43407
Mental Health	-0.22069	0.48581

The physical component summary (PCS) and mental component summary (MCS) are then standardized:

PCS = (raw PCS x 10) +50

MCS = (raw MCS x 10) +50

Gastrointestinal questionnaire

Gastrointestinal symptoms (degree and frequency of abdominal pain, bowel movements and stool consistency) of Fabry disease will be captured using a modified version of the inflammatory bowel severity scoring system.

BDI-II

The BDI second edition is a 21-item self-report inventory intended to assess the existence and severity of symptoms of depression as listed in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV; 1994).

The scale for the BDI was originally created by using descriptions of patient symptoms including mood, pessimism, sense of failure, self-dissatisfaction, guilt, suicidal ideas, crying, irritability, social withdrawal, insomnia, fatigue, appetite, weight loss, and self-accusation. In the first portion of the test, psychological symptoms are assessed whereas the second portion assesses physical symptoms. Each question has a four-point scale ranging which ranges from 0 (symptom not present) to 3 (symptom very intense). The overall score constitutes the sum of all BDI item score, disregarding any missing item score.

2.1.8 Health economic endpoints

NA

2.1.9 Further therapy after discontinuation of investigational medicinal product administration during the study

NA

2.2 DISPOSITION OF PATIENTS

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

Enrolled patients are defined as patients who signed the informed consent and enrolled in the ACT13739 study whether or not the said patients continue in the LTS14116 study.

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

- Patient treated in ACT13739 study
- Patients who completed ACT13739 study and did not enter LTS14116 study
- Patients who enrolled in LTS14116
- LTS14116 patients who completed the study treatment period as per protocol
- LTS14116 patients who did not complete the study treatment period as per protocol
  - Breakdown of reasons for permanent treatment discontinuation in the LTS14116 study
- LTS14116 patients who completed/discontinued the posttreatment safety follow-up visits

Percentages will be calculated using the number of enrolled patients in the ACT13739 or LTS14116 as the denominator for milestones occurred in the respective studies, eg, number of patients completed the ACT13739 study will be based on the number of patients enrolled in the ACT13739. Reasons for treatment discontinuations will be supplied in table format giving numbers and percentages. A listing for all ACT13739/LTS14116 enrolled patients will also be provided.

All major deviations, as recorded through standard Sanofi procedure, will be summarized in tables giving numbers and percentages of deviations.

Additionally, the analysis populations (see Section 2.3.1) for safety and efficacy will be summarized in a table by number of patients on the enrolled population.

- Efficacy population: full analysis set (FAS)
- Safety population

Patient disposition and patient populations will be summarized for all patients enrolled in ACT13739/LTS14116.

2.2.1 Randomization and drug dispensing irregularities

Inclusion and drug-dispensing irregularities occur whenever:

1. An inclusion is not in accordance with the protocol-defined method, such as an ineligible patient is included;

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined method, such as a non-included patient is treated with IMP reserved for included patients.

Inclusion and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All inclusion and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among enrolled patients (number and percentages).

2.3 ANALYSIS POPULATIONS

2.3.1 Efficacy populations

Patients treated without informed consent will not be included in the full analysis set (FAS).

Full analysis set (FAS)

The FAS includes all patients who receive at least 1 dose of IMP in the ACT13739 study.

2.3.2 Safety population

The safety population is defined as: all patients who received at least 1 dose of the IMP during the ACT13739 study.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

All patients who enrolled in ACT13739 and the subgroup who also enrolled in LTS14116 will be summarized separately on demographic and baseline characteristic data.

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

Parameters described in Section 2.1.1 will be summarized using descriptive statistics and displayed in listings on the FAS.

Medical/surgical and Fabry history will be summarized by primary SOC and PT for treatment group. The table will be sorted by SOC internationally agreed order followed by PT decreasing order based on the overall incidence in the treatment group.

P-values on demographic and baseline characteristic data will not be calculated.

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

2.4.2 Prior or concomitant medications

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

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and generic name. All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC anatomic category and generic name linked to the medication. Therefore patients may be counted more than once for the same medication.

The tables for prior medications, concomitant medications and posttreatment medications will be sorted by decreasing frequency of ATC followed by all encompassed generic names based on the incidence in the treatment group. In case of equal frequency regarding ATCs (anatomic or generic names), alphabetical order will be used.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure will be assessed and summarized within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure, and recorded dose information.

Duration of IMP exposure is defined as last dose date – first dose date (in ACT13739) + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.1 for calculation in case of missing or incomplete data).

Duration of IMP exposure from start of ACT13739 will be summarized (in weeks) descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories: up to 3months, >3 to 6 months, >6 to 9 months, >9 to 12 months, >12 to 18 months, >18 to 30 months, >30 to 36 months, and >36 months.

Additionally, the cumulative duration of treatment exposure in the on-treatment epoch will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

The total IMP per patient will be defined as the sum of the actual dose in mg received at all site visits and the actual dose in mg*(stop date – start date + 1) of each recorded week of at home administration. The total IMP per patient during the on-treatment epoch will be summarized descriptively (number, mean, SD, median, minimum, and maximum).

The treatment exposure to IMP from the start of ACT13739 study through the end of the LTS14116 study will be displayed in listings as recorded on the CRF.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data. Differences between the planned (intended) dose and the actual dose administered during a site visit may be shown in a listing along with the exposure data, or in a separate listing, depending on number of cases. Due to the design of the patient diary, a calculation of percentage of planned doses taken within a home administration period is not possible.

Cases of overdose are reported in the AE e-CRF pages and will be described in the AE analysis.

2.4.4 Analyses of efficacy endpoints

The primary objective of this LTS14116 study is to assess long-term safety. Efficacy data will be summarized with appropriate measures of variability. All efficacy analyses will be performed using the FAS.

2.4.4.1 Analysis of primary efficacy endpoint(s)

No primary efficacy endpoint is defined for the LTS14116 study; therefore, no primary efficacy analysis is planned.

2.4.4.2 Analyses of secondary efficacy endpoints

The full analysis set will be used in the analysis of all secondary efficacy endpoints. The on-study observation period as defined in Section 2.1.4 will be used in the presentation of the data.

Pharmacodynamics and biomarkers

The result and change from baseline in pharmacodynamics and biomarkers data will be summarized using descriptive statistics (including number, mean, SD, median, minimum, and maximum) and 95% confidence intervals for each visit. Spaghetti plots of measured values over time will be provided for all pharmacodynamic parameters and biomarkers. In addition, mean with SD graph will be produced. The pharmacodynamic and biomarker results for each patient will also be listed.

Skin GL-3

The skin biopsy at all visit assessments will be summarized. Shifts from baseline in skin GL-3 scores as assessed by light microscopy (LM) will be summarized by frequencies and percentages.

In addition, the skin score will be categorized into the following groups: 0 to <2, 2 to 3. Shifts from baseline in grouped skin GL-3 scores will be summarized by frequencies and percentages at all visits.

A listing of skin GL-3 accumulation scores as assessed by LM will be produced.

ACR and PCR

Urinary protein excretion is assessed by examining the albumin to creatinine ratio (ACR) and protein to creatinine ratio (PCR). The median value of the 3 measurements at each scheduled visit will be used for the statistical analysis. The results and change from baseline will be summarized using descriptive statistics and 95% confidence intervals at each scheduled visit. The spaghetti plot of ACR and PCR over time and the mean with SD graph will be provided. In addition, the results will be provided in a listing.

Echocardiogram

The summary statistics of all continuous echocardiogram variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point). The overall interpretation will be summarized by frequencies and percentages for normal, abnormal but NCS, or abnormal and CS categories. The spaghetti plot and mean with SD graph will be provided for important echocardiogram parameters. A listing of echocardiogram results will be presented by patient.

MRI

All continuous MRI variables will be summarized using descriptive statistics for each visit or study assessment (baseline, each post-baseline time point). The overall interpretation will be summarized by frequencies and percentages for normal, abnormal but NCS, or abnormal and CS categories. The MRI data listing will be provided by patient.

eGFR

The result and change from baseline will be summarized using descriptive statistics and 95% confidence intervals (t-distribution assumed) for each visit. Spaghetti plots of measured values over time and the mean with SD graph will be provided to illustrate trends over time. A listing will be provided by patient for eGFR data.

2.4.4.3 Multiplicity issues

Since the primary objective is to evaluate the long-term safety, no multiplicity adjustment will be made for testing multiple efficacy endpoints.

2.4.4.4 Additional efficacy analysis(es)

NA

2.4.5 Analyses of safety data

General common rules

The safety analysis will be conducted according to the Sanofi quality document BTD-009536 v3.0 "Analysis and reporting of safety data from Clinical Trials through the Clinical Study Report."

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

- Safety data in patients who do not belong to the safety population (eg, exposed but not enrolled) will be listed separately
- The baseline value is defined in Section 2.1.1
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated 24 May 2014 [Appendix A])
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage. PCSA flags will be determined after rounded values according to Sanofi quality document BTD-009536 version 3.0.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE period by treatment group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit.
- Unscheduled measurements will not be summarized in the safety analysis, instead it will be listed in data listings.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Pretreatment and posttreatment adverse events, if any, will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify

an AE as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.5.3.

AE incidence tables will present the number (n) and percentage (%) of patients experiencing an AE, as well as event counts, if specified. Patients with multiple occurrences of the same AE (eg, same preferred term) will be counted only once in the tables within a treatment phase, but all associated events will be counted, if events are presented in the table. The denominator for computation of percentages is the safety population.

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the tables of adverse events summarized by SOC and PT categories will be sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs unless otherwise specified.

The handling of intensity of AE is specified in Section 2.5.1.

Analysis of all TEAEs

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAEs
  - Serious TEAEs
  - Severe or life-threatening TEAEs
  - Related TEAEs
  - TEAEs leading to death
  - TEAEs leading to permanent treatment discontinuation
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE and number of events, sorted by the internationally agreed SOC order, with PT presented in alphabetical order within each SOC
- All TEAEs regardless of relationship and related by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE and number of events, sorted by the internationally agreed SOC order, with PT presented in alphabetical order within each SOC
- All TEAEs by maximal intensity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE by intensity (ie, mild, moderate, severe, life-threatening, death), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. Patients experiencing multiple events of the same AE (eg, same preferred term) of different intensities will be counted only once under the category of the highest intensity experienced.

Listings of all TEAEs showing patient identifier, IMP first dose date, SOC decode, PT decode, diagnosis (verbatim), date and day of onset, end date, AESI with immediate notification, category of AESI, intensity, corrective treatment/therapy, action taken with study treatment, relationship to study treatment, outcome, date of death if any, AE seriousness criteria will be produced.

Analysis of all treatment emergent SAE(s)

- All treatment-emergent SAEs by primary SOC and PT, showing the number (%) of patients with at least 1 serious TEAE and number of events, sorted by the internationally agreed SOC order, with PT presented in alphabetical order within each SOC
- All treatment-emergent SAEs regardless of relationship and related by primary SOC and PT, showing the number (%) of patients with at least 1 serious TEAE and number of events, sorted by the internationally agreed SOC order, with PT presented in alphabetical order within each SOC

Listings of all SAEs showing patient identifier, IMP first dose date, SOC decode, PT decode, diagnosis (verbatim), date and day of onset, end date, AESI with immediate notification, category of AESI, intensity, corrective treatment/therapy, action taken with study treatment, relationship to study treatment, outcome, date of death if any, AE seriousness criteria will be produced.

Analysis of all TEAE(s) leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE and number of events, sorted by the internationally agreed SOC order, with PT presented in alphabetical order within each SOC

Listings of all AEs leading to treatment discontinuation showing patient identifier, IMP first dose date, SOC decode, PT decode, diagnosis (verbatim), date and day of onset, end date, AESI with immediate notification, category of AESI, intensity, corrective treatment/therapy, action taken with study treatment, relationship to study treatment, outcome, date of death if any, AE seriousness criteria will be produced.

Analysis of AEs of special interest (AESI)

- All AESIs by AESI category and PT, showing the number (%) of patients with at least 1 treatment-emergent AESI and number of events, sorted by decreasing incidence of PT within each AESI category

Listings of all AESIs showing patient identifier, IMP first dose date, SOC decode, PT decode, diagnosis (verbatim), date and day of onset, end date, AESI with immediate notification, category of AESI, intensity, corrective treatment/therapy, action taken with study treatment, relationship to study treatment, outcome, date of death if any, AE seriousness criteria will be produced.

Analysis of posttreatment AEs

- All posttreatment AEs by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment AE and number of events, sorted by the internationally agreed SOC order, with PT presented in alphabetical order within each SOC

Listings of all posttreatment AEs showing patient identifier, IMP first dose date, SOC decode, PT decode, diagnosis (verbatim), date and day of onset, end date, AESI with immediate notification, category of AESI, intensity, corrective treatment/therapy, action taken with study treatment, relationship to study treatment, outcome, date of death if any, AE seriousness criteria will be produced.

2.4.5.2 Deaths

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

- Number (%) of patients who died by study period (on-study, on-treatment, posttreatment)
- TEAE leading to death (death as an outcome on the AE case report form page as reported by the Investigator) by primary SOC and PT showing number (%) of patients sorted by internationally agreed SOC order, with PT presented in alphabetical order within each SOC

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point). Spaghetti plots will be plotted over time (at same time points) for some special interest parameters like aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) etc.

The incidence of PCSAs (list provided in Appendix A) at any time during the TEAE period will be summarized by biological function (red blood cells and platelets, white blood cells, metabolism, electrolytes, renal function, and liver function) whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

A listing of patients with at least 1 postbaseline PCSA will be provided and will display the whole profile over time of all parameters of the corresponding biological function.

For parameters for which no PCSA criterion is defined, similar table(s) using the normal range will be provided. All laboratory values will be classified as normal ('Normal'), below normal ('Low'), or above normal ('High') based on normal ranges supplied by the central laboratory. Frequencies of clinically abnormal values and shift tables comparing the baseline classification (Normal, Low, High) to the classification at each postbaseline visit will be presented. All clinical laboratory data will be presented in listings.

The handling of <BQL values is specified in Section 2.5.1.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all vital signs variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point). All vital sign data will be presented in listings.

The incidence of PCSAs at any time during the TEAE period will be summarized by vital sign parameters irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

A listing of patients with at least 1 postbaseline PCSA will be provided and will display the whole profile over time of all parameters

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, SD, minimum, and maximum) of all continuous ECG variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point). The mean of the triplicate ECG measurements at each visit will be used for the descriptive statistics. The handling of triplicate ECG interpretation is described in Section 2.5.1. Categorical variables will be summarized by frequencies and percentages. A listing of ECG results will be presented by patient.

The incidence of PCSAs at any time during the TEAE period will be summarized by ECG parameters irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

A listing of patients with at least 1 postbaseline PCSA will be provided and will display the whole profile over time of all parameters.

2.4.5.6 Analysis of physical examination variables

Frequencies and percentages of patients with normal or abnormal findings and CS change from baseline of physical examinations will be summarized by body system. A listing will be provided for physical examination results.

2.4.5.7 Analysis of neurological examination variables

The frequencies and percentages of patients with normal/abnormal findings at baseline and succeeding visits will be summarized by site/system. In addition, listings will be provided for the same.

2.4.5.8 Analysis of ophthalmology examination variables

The ophthalmology examination results will be presented by frequencies and percentages. A listing will be provided for examination results

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Plasma concentrations of GZ/ GZ/SAR402671 will be summarized for using descriptive statistics (including number, arithmetic mean, SD, geometric mean, coefficient of variation (CV %), minimum, median, and maximum) for each visit. Listing and graph of plasma concentration will be provided.

Pharmacodynamic variables that are included in the secondary endpoints specified in Section 2.1.3.2 will be analyzed as described in Section 2.4.4.2.

2.4.7 Analyses of quality of life/health economics variables

SF-36

Eight scales (range between 0 and 100) and the two component summaries (PCS and MCS) will be analyzed. Results and change from baseline will be summarized using descriptive statistics (including number, mean, median, SD, minimum, and maximum) for each visit. Boxplots of the standardized scores over time for the 8 function scale scores and the 2 aggregate summary scores of SF-36 will be produced.

GI

The summary statistics (including number, mean, median, SD, minimum, and maximum) of questionnaire results will be calculated for each visit or study assessment (baseline, each postbaseline time point). Categorical variables will be summarized by frequencies and percentages. The bowel movement results will be derived as described in Section 2.5.1. Boxplots and bar graphs will be used to illustrate GI responses over time, as appropriate.

BDI

Baseline and change from baseline in BDI overall score will be summarized descriptively (including number, mean, median, SD, minimum, and maximum) for each visit (baseline, each postbaseline time point). Boxplots of the BDI overall score over time will be provided.

The quality of life data will be listed by patient for SF-36, GI & BDI.

2.5 DATA HANDLING CONVENTIONS

The data handling conventions for the variables used in the statistical analysis are included in this section.

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age in years = integer part of ((date of informed consent – date of birth)/365.25)

$$\text{BMI} = \frac{\text{weight(kg)}}{\text{height(m)}^2}$$

Renal function formulas

CKD-EPI equation (1):

eGFR (mL/min/1.73 m2) = 141 * min(sCr/κ,1)α * max(sCr/κ,1)-1.209 * 0.993Age * 1.018 [if

female] * 1.159 [if black]

For the above, sCr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of sCr/κ or 1, and max indicates the maximum of sCr/κ or 1. All patients are males so the 1.018 correction factor will not be used.

Handling of triplicate ECG interpretation

If the ECG interpretation is recorded in triplicate, the derived categorical values will be used for statistical analysis. For example, the ECG interpretation results reported as ‘normal’, ‘abnormal’ and ‘abnormal ECG, clinically significant’, then the derived values will be ‘only normal’, ‘ at least one abnormal but only non-clinically significant’ and ‘at least one abnormal and clinically significant’ respectively.

Handling of <BQL laboratory values

If the laboratory values are recorded as less than a quantifiable limit, the value halfway between 0 and the BQL will be used for statistical analysis. For example, if the value is reported as <6.2, then the value 3.1 will be used. In cases of ratios, such as PCR and ACR, if one or both of the assayed parameters used to calculate a ratio has <BQL value, then the above mentioned imputation should be performed prior to the calculation of the ratio.

Handling of GI questionnaire

If 'Most number of times of bowel movement' and "Least number of times of bowel movement' results are recorded per week/month, then derived the results with per day frequency for the same. The per day frequency results for the above parameters will be used for statistical analysis.

Handling of intensity of AEs

If the intensity is 'Severe' or 'Life-Threatening', then combine these intensity categories into a single category as 'Severe and/or Life-Threatening' for the analysis purpose..

2.5.2 Data handling conventions for secondary efficacy variables

NA

2.5.3 Missing data

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

For data listings, the character date will always be used to present the date collected in the CRF.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

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

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

Handling of medication missing/partial dates

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

Handling of AEs with missing or partial date/time of onset

Missing or partial AE onset dates and times will not be imputed. If the partial AE onset date/time information does not indicate that the AE started prior to treatment or after the treatment-emergent AE period, the AE will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. This data categorization will be used for presenting treatment-emergent AE summary tables or listings. No imputation is planned for date/time of AE resolution.

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

When the date and time of the first IMP administration is missing, all AEs that occurred on or after the day of randomization will be considered as TEAEs. The exposure duration will be kept as missing in such cases.

The last dose intake will be determined according to IMP administration dates collected in the case report form and will not be approximated by the last returned package date.

Handling of missing assessment of relationship of AEs to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP will be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation will be done at the data level.

Handling of missing intensity of AEs

If the intensity is missing for 1 of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

NA

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries, but will be used for computation of baseline, as well as presented in listings.

2.5.6 Pooling of centers for statistical analyses

NA

2.5.7 Statistical technical issues

NA

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database is planned to be locked at approximately 70 days after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

1. Levey AS, Steven LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)
(From BTD-009536 – Version 3.0 –24-MAY-2014)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
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Parameter	PCSA	Comments
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	

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Parameter	PCSA	Comments
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	

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Parameter	PCSA	Comments
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

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Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

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Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	