NCT Number: NCT02489344

AMENDED CLINICAL TRIAL PROTOCOL 04

COMPOUND: GZ/SAR402671

TITLE: 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

STUDY NUMBER: LTS14116

VERSION DATE / STATUS: 10-Nov-2017/ Approved

CLINICAL STUDY DIRECTOR: [redacted]

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NAMES AND ADDRESSES OF

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CLINICAL TRIAL SUMMARY

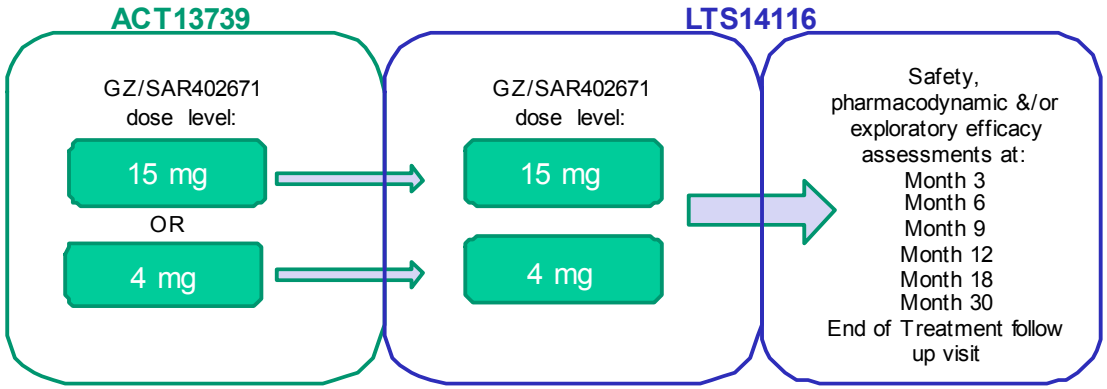
COMPOUND: GZ/SAR402671	**STUDY No: GZ402671/LTS14116**
TITLE	An open-label, multicenter, multinational extension study of the long-term safety, pharmacodynamics, and exploratory efficacy of GZ/SAR402671 in adult male patients diagnosed with Fabry disease
INVESTIGATOR/TRIAL LOCATION	Sites that participated in study ACT13739
PHASE OF DEVELOPMENT	2
STUDY OBJECTIVE(S)	**Primary objective:** To assess the long-term safety of GZ/SAR402671 in adult male patients with Fabry disease who previously completed study ACT13739. **Secondary objective(s):** To assess the long-term effect of GZ/SAR402671 on pharmacodynamic and exploratory efficacy endpoints in adult male patients with Fabry disease who previously completed study ACT13739.
STUDY DESIGN	Open-label, multicenter, multinational extension study of the long-term safety, pharmacodynamics and exploratory efficacy of daily, oral GZ/SAR402671 administration in adult male patients with Fabry disease who have completed study ACT13739.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria** • Male patient with Fabry disease who previously completed study ACT13739. • The patient is willing and able to provide signed informed consent. • Sexually active patient is willing to practice true abstinence in line with their preferred and usual lifestyle or use two acceptable effective methods of contraception. **Exclusion criteria** • The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study.
Total expected number of patients	This is an extension study, and therefore, the number of patients will be determined by patients completing study ACT13739.
STUDY TREATMENT(s)	
Investigational medicinal product(s)	GZ/SAR402671
Formulation	GZ/SAR402671 is provided in capsule formulations containing 15 mg or 4 mg of GZ/SAR402671
Route(s) of administration	Oral
Dose regimen	Patients will continue to receive once daily, oral GZ/SAR402671 at the same dose level administered at the end of study ACT13739 (ie, 15 mg or 4 mg in the event the GZ/SAR402671 dose was reduced in ACT13739).

ENDPOINT(S)	**Primary endpoint** Safety as measured by: • Assessment of adverse events (AEs)/ treatment-emergent AEs (TEAEs) • Physical examination • Neurological examination • Clinical laboratory evaluations including hematology, biochemistry, and urinalysis • Vital signs and body weight • Ophthalmology exam • 12-lead electrocardiogram (ECG) **Secondary Endpoint(s):** 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 • Patient reported outcomes • 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)
ASSESSMENT SCHEDULE	See Study Flow Chart. When possible, demographic, medical/surgical history, Fabry disease history including *GLA* (αGAL gene) mutations as well as safety, pharmacodynamic and exploratory efficacy assessments collected prior to first GZ/SAR402671 administration in ACT13739 will be imported from the ACT13739 study database into the LTS14116 database. LTS14116 study entry visit may occur at the same time as the ACT13739 week 26 clinical visits.
STATISTICAL CONSIDERATIONS	**Sample size determination:** The maximum enrollment possible for this study will be determined by the final number of patients who completed study ACT13739. **Analysis population:** The Full Analysis Set (FAS) and the Safety Set will include all patients who receive at least 1 dose of study treatment in this study. **Analysis of primary endpoints:** Safety: Out of range laboratory values, vital signs, and ECGs will be flagged by the investigator as clinically significant or non-clinically significant abnormalities. The clinically significant abnormalities will be recorded as AEs

	and included in the TEAE counts. TEAEs and SAEs will be tabulated (counts and percentages). Discontinuations due to AEs will be summarized. Descriptive statistics for actual values and changes from baseline will be generated by time point for selected safety parameters of interest. Data may also be plotted. For the purpose of analysis, baseline will be prior to the first dose GZ/SAR402671 in study ACT13739. **Analysis of secondary endpoints** Pharmacodynamics and exploratory efficacy: Descriptive statistics for actual values and change from treatment baseline will be generated by time point for selected pharmacodynamic and exploratory efficacy endpoints as appropriate. For the purpose of analysis, treatment baseline will be prior to the first dose GZ/SAR402671 in study ACT13739. Pharmacokinetics: GZ/SAR402671 plasma concentrations will be reported including patient number, visit and time relative to GZ/SAR402671 administration.
DURATION OF STUDY PERIOD (per patient)	The maximum duration per patient is approximately 31 months as follows: Treatment period: up to 30 months Post-treatment follow up: 1 month (± 7 days)

1 FLOW CHART

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

		Treatment period						Post-treatment observations	
	Study entry[a]	3 Month (± 14 days)	6 Month (± 14 days)	9 Month (± 14 days)	12 Month (± 14 days)	18 Month (± 14 days)	30 Month (± 14 days)	Early withdrawal	End of treatment follow up[b] (1 month ± 7 days)
Informed consent for extension	X								
Inclusion/exclusion criteria	X								
Visit at clinical site	X	X[f]	X[f]	X[f]	X[f]	X[f]	X	X	X
Study treatment administration									
GZ/SAR402671		Once daily oral dosing							
Distribution of patient diary	X								
Review of patient diary		X	X	X	X	X	X	X	
Collection of patient diary							X	X	
Safety Assessments									
Vital signs and weight		X	X	X	X	X	X	X	X
Physical examination		X	X	X	X	X	X	X	
Neurological examination		X	X	X	X	X	X	X	
Ophthalmology exam		X	X[c]	X	X	X[c]	X[c]	X[c]	
Electrocardiogram		X	X	X	X	X	X	X	
Biochemistry, hematology & urinalysis		X	X	X	X	X	X	X	
Concomitant medications/therapies	<	-	-	-	-	-	-	-	>
Adverse event recording	<	-	-	-	-	-	-	-	>
Pharmacokinetics									
Plasma sample[d]			X			X	X	X	X
Pharmacodynamics									
Plasma samples for GL-3, lyso GL-3, GM3, GL-1			X			X	X	X	X
High sensitivity cardiac troponin T			X			X	X	X	
Urine GL-3			X			X	X	X	X
Exploratory biomarkers – blood and plasma			X			X	X	X	X

		Treatment period						Post-treatment observations	
	Study entry[a]	**3 Month (± 14 days)**	**6 Month (± 14 days)**	**9 Month (± 14 days)**	**12 Month (± 14 days)**	**18 Month (± 14 days)**	**30 Month (± 14 days)**	**Early withdrawal**	**End of treatment follow up**[b] **(1 month ± 7 days)**
Exploratory biomarkers – urine			X			X	X	X	X
Podocyturia							X		
Exploratory efficacy									
GL-3 in skin biopsy			X[g]				X	X	
Patient reported outcomes			X[h]			X[h]	X[h]	X[h]	
Urinary albumin and protein : ACR & PCR[e]			X, X, X			X, X, X	X, X, X		
Echocardiogram			X			X	X	X	
Brain MRI							X	X	
eGFR			X			X	X		

Abbreviations: ACR, albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; GL 1, glucosylceramide; GL 3, globotriaosylceramide; GM3, monosialodihexosylganglioside; IMP, investigational medicinal product; MRI, magnetic resonance imaging; PCR, protein to creatinine ratio.

a When possible, demographic, medical/surgical history, Fabry disease history including *GLA* (αGAL gene) mutations as well as safety, pharmacodynamic and exploratory efficacy assessments collected prior to first GZ/SAR402671 administration in ACT13739 will be imported from the ACT13739 study database into the LTS14116 database. LTS14116 study entry visit may occur at the same time as the ACT13739 week 26 clinical visit.

b End of treatment follow up on site visit 1 month (± 7 days) after the last GZ/SAR402671 administration.

c Eye dilation required for examination.

d One pharmacokinetic sample to be collected at each visit indicated within 1 to 8 hours following oral administration of GZ/SAR402671. Pharmacokinetic sample during the early withdrawal (if applicable) and post treatment follow up visit will be collected at any time during the visit.

e Urine ACR/PCR: 3 overnight urine samples to be collected with 4 to 7 days between each collection. All urine samples are to be collected within a 16-day period.

f IMP kits will be supplied to patients at site visits or may also be supplied directly to patient's home (Direct To Patient)

g Skin biopsy at month 6 is optional- to be performed on the day of month 6 visit or at any other day during the following 30 days

h BDI-II is part of protocol amendment #3 and will be conducted starting at the first patient visit after amendment approval and thereafter in subsequent visits

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3 LIST OF ABBREVIATIONS

ACR:	albumin to creatinine ratio
AE:	adverse event
AESI:	adverse event of special interest
BDI:	Beck Depression Inventory
BDI-II:	Beck Depression Inventory- Second Edition
CL1:	claudin
CS:	clinically significant
CTCAE:	Common Terminology Criteria for Adverse Events
DMC:	data monitoring committee
ECG:	electrocardiogram
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
ERT:	enzyme replacement therapy
GCP:	good clinical practice
GL-1:	glucosylceramide
GL-3:	globotriaosylceramide
GM3:	monosialodihexosylganglioside
ICH:	International Conference on Harmonisation
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
LC-MS/MS:	liquid chromatography tandem mass spectrometry
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
NCI:	National Cancer Institute
NCS:	not clinically significant
PCR:	protein to creatinine ratio
PCX:	podocalyxin
PRO:	patient reported outcome
SAE:	serious adverse event
SAP:	statistical analysis plan
SF-36:	Short Form-36
TEAEs:	treatment-emergent adverse events

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Fabry disease is a rare, X-linked, genetic disorder caused by mutations in the gene that encodes the lysosomal enzyme, αGAL. This enzymatic deficiency leads to the progressive accumulation of glycosphingolipids, most notably globotriaosylceramide (GL-3), in lysosomes of a variety of cell types and tissues. Although multiple organ-specific cell types accumulate GL-3 and are important to consider, the systemic accumulation in capillary endothelial cells is believed to play a major role in the general pathological process that leads to the devastating renal, cardiac, and cerebrovascular clinical manifestations of the disease and to substantially decreased life expectancy (1, 2).

Fabry disease is a progressive disorder that takes years to advance to end stage organ failure mainly in hemizygous male patients. Although *GLA* (αGAL gene) mutations are carried by the X chromosome, female patients exhibit a variable phenotype, ranging from oligosymptomatic to a presentation as severe as that observed in male patients (3, 4, 5, 6). The initial signs and symptoms of Fabry disease often begin during childhood and frequently include neuropathic pain in the extremities, hypohidrosis, angiokeratomas, and gastrointestinal discomfort (7, 8, 9). Over a period of decades, the progressive accumulation of GL-3 impairs vital organ function, putting patients with Fabry disease at risk of developing renal failure, cardiovascular dysfunction, and stroke (10, 11, 12). However, it is now clear that tissue damage, such as fibrosis in heart and kidney, starts well before the onset of organ failure (13, 14, 15).

Because Fabry disease patients have deficient αGAL enzymatic activity, one therapeutic approach is enzyme replacement therapy (ERT). There are currently two approved recombinant forms of human αGAL for Fabry disease, both administered as biweekly intravenous infusions. Agalsidase beta, manufactured by Sanofi Genzyme is marketed under the brand name Fabrazyme. Agalsidase alfa, manufactured by Shire is marketed under the brand name Replagal.

4.2 GZ/SAR402671

GZ/SAR402671 is a small molecule, a second generation glucosylceramide synthase inhibitor that blocks the first step in glycosphingolipids biosynthesis, the enzymatic conversion of ceramide, to glucosylceramide (GL-1). By reducing the amount of GL-1, the central building block for the synthesis of more complex glycosphingolipids including GL-3, this substrate reduction therapy with GZ/SAR402671 offers a potential therapeutic strategy for Fabry disease and other glycosphingolipidosis disorders, as already demonstrated with eliglustat for Gaucher disease (16).

Refer to the Investigator's brochure for a complete summary of nonclinical experience with GZ/SAR402671 (17).

4.3 RATIONALE

This open-label, 30 month (2.5 years) treatment study is being conducted to allow male Fabry disease patients who have previously completed study ACT13739 to continue receiving GZ/SAR402671. The primary objective of LTS14116 is to evaluate the long term safety of GZ/SAR402671 in this patient population; secondary endpoints include further evaluating GZ/SAR402671 pharmacodynamics and exploratory efficacy.

5 STUDY OBJECTIVES

5.1 PRIMARY

To assess the long-term safety of GZ/SAR402671 in adult male patients with Fabry disease who previously completed study ACT13739.

5.2 SECONDARY

To assess the long-term effect of GZ/SAR402671 on pharmacodynamic and exploratory efficacy endpoints in adult male patients with Fabry disease who previously completed study ACT13739.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

LTS14116 is an open-label, multicenter, multinational extension study of the long-term safety, pharmacodynamics and exploratory efficacy of daily, oral GZ/SAR402671 administration in adult male patients with Fabry disease that completed ACT13739.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The maximum duration per patient is approximately 31 months as follows:

- Treatment period: up to 30 months
- Post-treatment follow up: 1 month (± 7 days). Patients who start commercial ERT, investigational or any other Fabry disease treatment within the 1-month (±7 days) follow up period will not be considered for follow up assessments.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial will be determined by last patient last visit.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEES

A data monitoring committee (DMC) will be established to provide independent review of safety data and to ensure that risk to patients is minimized. The DMC will periodically review all available data including laboratory results, physical and clinical examination findings, radiology, AEs, and serious adverse events (SAEs) for any safety trends that could impact the treatment of patients. The DMC will also review data on an ad hoc basis to assist in determining if AEs should preclude continued treatment with GZ/SAR402671.

The specific responsibilities of the DMC will be described in the DMC Charter.

6.5 SPECIFIC PARAMETERS

6.5.1 Safety

Safety assessments include adverse event (AE) reporting, physical, neurological and ophthalmic examinations, body weight, vital signs, hematology, biochemistry, urinalysis, and electrocardiograms (ECG).

6.5.2 Pharmacodynamics

GZ/SAR402671 pharmacodynamics will be further evaluated in this long term study. Blood and/or plasma samples will be collected to evaluate GL-3, lyso GL-3, GM3, and GL-1. Urine samples will be collected to evaluate GL-3 levels. Blood and/or plasma and urine samples will also be collected to evaluate exploratory biomarkers including but not limited to high sensitivity cardiac troponin T, Chitotriosidase activity (via plasma) and podocyturia (via urine).

6.5.3 Exploratory efficacy

The exploratory efficacy of GZ/SAR402671 will be further evaluated in this long term study through changes in GL-3 scores as evaluated by light microscopy in skin biopsy, patient reported outcome (PRO) questionnaires, and urinary albumin and protein [albumin to creatinine ratio (ACR) and protein to creatinine ratio (PCR)]. In addition, given the 36 month total treatment duration of ACT13739 and in LTS14116 combined, exploratory efficacy of GZ/SAR402671 will also be evaluated through changes in echocardiograms, brain magnetic resonance imaging (MRI) and estimated glomerular filtration rate (eGFR).

6.5.4 Pharmacokinetics

Single pharmacokinetic samples are to be collected at clinical visits. Resulting data will be used as part of the GZ/SAR402671 clinical development program in population-based modeling to identify common factors that contribute to GZ/SAR402671 pharmacokinetics.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patient with Fabry disease who previously completed study ACT13739.

I 02. The patient is willing and able to provide informed consent.

I 03. Sexually active patient is willing to practice true abstinence in line with their preferred and usual lifestyle or use two acceptable effective methods of contraception, including a barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be evaluated for the following exclusion criteria:

E 01. The patient, in the opinion of the investigator, is unable to adhere to the requirements of the study.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

GZ/SAR402671 hard gelatin capsules will be supplied for once daily oral administration, containing 4 mg or 15 mg of GZ/SAR402671 (calculated with reference to the active moiety), and the following excipients: croscarmellose sodium, colloidal silicon dioxide, sodium stearyl fumarate, and microcrystalline cellulose. Throughout this document, these doses will be referred to as 4 mg and 15 mg, respectively.

GZ/SAR402671 can be administered without restriction to food.

Between the protocol scheduled on site visits interim visits may be required for investigational medicinal product (IMP) dispensing. As an alternative to between clinical visits, GZ/SAR402671 may be supplied from the site to the patient via a sponsor-approved courier company where allowed by local regulations and approved by ethics committee, sponsor and the subject.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Not applicable.

8.3 BLINDING PROCEDURES

This study has an open-label design.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

All patients will receive GZ/SAR402671at the same dose level at the end of study ACT13739 (ie, 15 mg or 4 mg in the event the GZ/SAR402671 dose was reduced in ACT13739).

8.5 PACKAGING AND LABELING

GZ/SAR402671 is packaged according to good manufacturing practices and local regulatory specifications and requirements.

The capsules are packaged in blister packs. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

GZ/SAR402671 must be stored between 15 to 25°C. Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP provided by the sponsor in a secure and safe place in accordance with local regulations, labeling specifications, policies and procedures.

8.7 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 protocol 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 the sponsor. 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 the sponsor. In this case, the investigator will be responsible for promptly addressing any request made by the sponsor, 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 study protocol, or dispose of IMP in any other manner not approved of by the sponsor.

8.7.1 Treatment accountability and compliance

The investigator or designee will keep an accurate record of all IMP that is received, dispensed, and returned on a per patient basis using a IMP accountability log.

A patient diary will be issued to the patient at the entry visit with instructions to record each dose received. The patient should bring their diary and any remaining capsules to each clinic visit. The site staff will review the patient diary during each clinic visit and record excursions from treatment into the case report form (CRF). The patient diary will be collected at the end of the treatment period or when GZ/SAR402671 treatment is permanently discontinued (whichever occurs first).

8.7.2 Return and/or destruction of treatments

Reconciliation of all used, partially-used or unused treatments must be performed at the site by the investigator or designee and the monitoring team using treatment log forms.

Authorization for destruction will be given by the sponsor once the reconciliation has been completed. This destruction can be performed at the site depending on local regulations and site specific capabilities; alternatively, study drug may be returned to the sponsor or designee for destruction.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment administered concurrently with the IMP to or by the patient concomitantly to any IMP(s).

8.8.1 CYP3A4 inducers or inhibitors

GZ/SAR402671 should not be administered concomitantly with any strong or moderate inducers or inhibitors of CYP3A4 per FDA classification (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling).

If a patient is inadvertently administered a strong or moderate CYP3A4 inducer or inhibitor, the investigator should contact the sponsor as soon as possible. The investigator or physician should switch the patient to an alternative medication that is not a CYP3A4 inducer or inhibitor.

8.8.2 Renin-Angiotensin-Aldosterone System (RAAS) blockers, pain medication and/or antidepressants

If the patient is on RAAS blockers, pain medication and/or antidepressants, the investigator should maintain the dose recorded at screening through the duration of the study, except for safety reasons.

8.8.3 Forbidden cataractogenic medications

Given the preclinical lens findings (17), a chronic regimen (ie, more frequent than once every 2 weeks) of any dose or route of the following medications are forbidden during the treatment period:

- Corticosteroids

However, corticosteroids may be used on a restricted basis in patients who require temporary use (≤1 week) for the treatment of any acute illness. Such medications must not be used on more than a total of 2 occasions (ie, up to 1 week per occasion) during the 30-month treatment period.

- Psoralens used in dermatology with ultraviolet light therapy (also known as PUVA)
- Typical antipsychotics
  - Atypical antipsychotics are allowed.
- Glaucoma medications

The investigator should consider substituting medications listed above for non-cataractogenic treatments, as appropriate.

8.8.4 Contraceptives

Each patient will be required to either practice true abstinence consistent with his preferred and usual lifestyle or use double-contraceptive methods with their female partner for the entire duration of the treatment period until 90 days after last treatment with IMP:

1. A barrier method such as a condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/suppository, and
2. An established non-barrier method such as oral, injected, or implanted hormonal methods, an intrauterine device or intrauterine system

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT- SAFETY

The primary endpoint of this study is safety. The following safety assessments will be collected and analyzed:

- Assessment of adverse events (AEs)/treatment emergent AEs(TEAEs)
- Physical examination
- Neurological exam
- Clinical laboratory evaluations, including hematology, biochemistry, and urinalysis
- Vital signs and body weight
- Ophthalmology exam
- 12-lead ECG

9.1.1 Adverse events

Adverse events, spontaneously reported by the patient or observed by the investigator, will be monitored throughout the study. The safety profile will be based on incidence, severity, and cumulative nature of TEAEs. TEAEs are defined as AEs that develop or worsen during the on-treatment period. For this study, the on-treatment period will be defined as the period from the time of first dose of IMP to at least 1 month after the last administration of the IMP. For the purposes of the study, status of ongoing and new AEs will be assessed 1 month after the last study drug administration, or for patients who discontinue early, after their last completed study visit. Any new AE or SAE that occurs during the 1 month follow-up period and is assessed as related to the drug or study procedures will be reported/collected in the clinical database.

Definitions of AEs, SAEs, and AEs of special interest (AESIs), including reporting procedures, can be found in Section 10.4 and Section 10.5.

At each study visit, patients will be evaluated for new AEs and the status of existing AEs. The investigator may elicit symptoms using an open-ended question, followed by appropriate questions that clarify the patient's verbatim description of AEs or change in concomitant medications.

Adverse events will be summarized with respect to the type, frequency, severity, seriousness, and relatedness. Pretreatment and TEAEs will be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" using the Medical Dictionary for Regulatory Activities (MedDRA). All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

9.1.2 Physical exam

Whenever possible, the same physician should perform the physical examination at all study visits. The findings of each examination will be recorded. Each physical examination will include the following physical observations/measurements:

General appearance	Mental status	Peripheral arterial pulses
Heart	Head, eyes, ears, nose and throat	Lymph nodes
Skin	Extremities/joints	Abdomen
Respiratory auscultation	External genitalia	

A site physician will assess the physical examination findings as normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS).

9.1.3 Neurological exam

Each neurological examination will include, but not be limited to, assessments of the patient's mental, cranial nerves, motor system, deep tendon reflex, sensation, and cerebellum, and evaluations of pain. The examination should be performed by the same neurologist throughout the study, if possible.

9.1.4 Laboratory safety variables

The following hematology, chemistry, and urinalysis samples will be obtained prior to administration of GZ/SAR402671:

- Blood hematology: Complete blood count, including white blood cell count, platelet count, hemoglobin, and hematocrit with absolute (not percentage) differential cell counts of lymphocytes, monocytes, neutrophils, basophils, eosinophils, and (if applicable) abnormal cells.
- Blood chemistry: sodium, potassium, chloride, blood urea nitrogen, glucose, uric acid, calcium, phosphorus, magnesium, albumin, total protein, creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, lipase, alkaline phosphatase, and C reactive protein.
- Urine biochemistry: Routine urinalysis (including but not limited to urine microscopy, metered pH, specific gravity), creatinine, total protein, and albumin.

Analysis of all safety laboratory parameters will be conducted by a central laboratory. Procedures for handling and shipment of all central laboratory samples will be included in the information provided by the central laboratory. Specimens will be processed appropriately by the central laboratory facility and laboratory reports will be made available to the investigator in a timely manner to assure appropriate clinical review.

The investigator must score all abnormal laboratory values as either CS or NCS. Because some laboratory values may be outside of the normal value range due to the underlying disease, the investigator should use clinical judgment when considering clinical significance. Clinical significance is defined as any change in laboratory parameters from baseline, which has medical relevance. If CS worsening of laboratory values from baseline levels is noted, the changes will be documented as an AE, scored according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and documented on the electronic case report form (eCRF).

The investigator will continue to monitor the patient with additional laboratory assessments until (1) values have reached normal range and/or baseline levels, or, (2) in the judgment of the investigator, abnormal values are not related to the administration of IMP or other protocol-specific procedures.

9.1.5 Vital signs and weight

Vital signs including weight (in kg), respiratory rate, heart rate (in bpm), blood pressure (systolic/diastolic in mmHg), and temperature (in Celsius °C). Heart rate, systolic and diastolic blood pressure measured after 10 minutes in supine resting position and after 3 minutes in standing position.

If a change from baseline is noted that meets the definition of an AE (see Section 10.4.1), the AE should be documented on the eCRF.

9.1.6 Ophthalmology Examination

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. For month 6, month 18 and month 30 examinations, dilation of the pupils is required. 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.

9.1.7 Electrocardiogram variables

Standard 12-lead ECGs will be recorded using an electrocardiographic device after at least 5 minutes in supine position.

Electrocardiograms will be recorded in triplicate within 5 minutes with at least 1 minute between 2 replicates.

Each ECG consists of a 10-second recording of the 12 leads simultaneously, leading to:

- A single 12-lead ECG (25 mm/s, 10 mm/mV) printout with heart rate, PR, QRS, QT, QTc automatic correction evaluation, including date, time, initials, and number of the patient, signature of the research physician, and at least 3 complexes for each lead. This printout will be retained at the site.
- A digital storage that enables eventual further reading by an ECG reading center: each digital file will be identified by theoretical day and time, real date and real time (recorder time), sponsor study code, patient number (ie, 3 digits), date of birth, and site and country numbers, if relevant. The digital recording, data storage, and transmission (whenever requested) need to comply with all applicable regulatory requirements (ie, FDA 21 CFR, part 11). The central reading findings will be used for statistical analyses.

9.2 SECONDARY ENDPOINT – PHARMACODYNAMICS

A secondary endpoint of this study is pharmacodynamics. The following pharmacodynamic endpoints will be collected and analyzed:

- 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

9.2.1 Plasma samples for GL-3, lyso GL-3, GL-1, and GM3

Plasma samples for GL-3, lyso GL-3, GL-1, and GM3 will be analyzed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method at a central laboratory. Refer to the study manual for details on the collection, processing, storage, and shipment of these samples.

9.2.2 High sensitivity cardiac troponin T

Plasma samples to explore changes in high sensitivity cardiac troponin T will be analyzed at a central laboratory. Refer to the study manual for details on the collection, processing, storage, and shipment of these samples.

9.2.3 Urine samples for GL-3

Urine samples for GL-3 will be analyzed using a validated LC-MS/MS method at a central laboratory. Refer to the study manual for details on the collection, processing, storage, and shipment of these samples.

9.2.4 Exploratory biomarkers in blood and urine

Blood (plasma) and urine samples for exploratory biomarkers related to Fabry disease will be collected and analyzed later using appropriate platforms. Refer to the study manual for details on the collection, processing, storage, and shipment of these samples.

9.2.5 Podocyturia

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. Cells with small/apoptotic and normal size nuclei will be counted separately. Terminal deoxynucleotidyl transferase dUTP nick end labeling staining will be performed for apoptosis. All counts will be corrected for urine creatinine.

9.3 SECONDARY ENDPOINT – EXPLORATORY EFFICACY

A secondary endpoint of this study is exploratory efficacy. The following exploratory efficacy endpoints will be collected and analyzed:

- GL-3 in skin biopsy
- PRO questionnaires
- Urinary albumin and protein (ACR and PCR)
- Echocardiogram
- Brain MRI
- eGFR

9.3.1 Globotriaosylceramide in skin biopsy

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. For superficial capillary endothelium, discrepant scoring will be resolved by an adjudication process in which the slide will be reread 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.

9.3.2 Patient reported outcome questionnaires

Upon arrival at applicable study visits, the patient will complete PRO questionnaires first. PROs will be completed before dosing, before completing any other health data forms, and before participating in any clinical assessments by the investigator or other healthcare provider(s). These questionnaires will be administered by individuals trained in the administration of standardized questionnaires. Specific instructions for the administration of PRO questionnaires are provided in study manual.

9.3.2.1 Short Form-36

The Short Form-36 (SF-36) health survey is a patient-reported survey of patient health. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score, the more the disability. The higher the score the less disability i.e. a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health.

9.3.2.2 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 (18).

9.3.2.3 Beck Depression Inventory- Second Edition (BDI-II)

The Beck Depression Inventory 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) (19). Details of BDI-II will be described in the study manual.

9.3.3 Protein excretion from urine

Protein excretion will be evaluated from the median of 3 timed overnight urine samples collected between 4 to 7 days of each other. 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.

9.3.4 Echocardiogram

A 2-dimensional and M-mode echocardiograph with Doppler 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 in an overall conclusion as normal, abnormal but not CS, or abnormal and CS. Wherever possible, the same physician should review all echocardiographs for a given patient. If the investigator determines the echocardiograph 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. Specific procedures for these tests are supplied in the study manual.

9.3.5 Brain magnetic resonance imaging

A brain MRI (without contrast agent) will include, but not be limited to assessments of 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. 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 not CS, or abnormal and CS. If the investigator determines the MRI is abnormal and CS and a change from baseline, 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 prevail and be used for statistical analyses.

See the study imaging manual for procedures for sending assessments to the central analysis laboratory. Brain MRI results will be reported to the investigator.

9.3.6 Estimated glomerular filtration rate

Estimated GFR will be calculated by the central laboratory using an isotope dilution mass spectrometry-calibrated serum creatinine assay and the Chronic Kidney Disease Epidemiology Collaboration equation (20).

9.4 OTHER ENDPOINTS – PHARMACOKINETICS

9.4.1 Sampling time

One pharmacokinetic sample to be collected at each visit indicated in Section 1.2 within 1 to 8 hours following oral administration of GZ/SAR402671. The time of GZ/SAR402671 administration on the day of the PK sample collection as well as the time of the PK sample collection is to be recorded in the eCRF. PK sample during the early withdrawal (if applicable) and post treatment follow up visit will be collected at any time during the visit.

9.4.2 Pharmacokinetics handling procedure

Table 1 - Summary of plasma sample handling procedures

	GZ/SAR402671
Blood sample volume	4 mL
Anticoagulant	K_2EDTA
Handling procedures	See study specific laboratory manual
Plasma aliquot split	Yes, 3 aliquots
Plasma storage conditions	Keep in upright position at -70°C
Plasma shipment conditions	Frozen, on dry ice

9.4.3 Bioanalytical method

GZ/SAR402671 plasma concentrations will be determined using a validated LC-MS/MS method (DMPK15-R012) with a lower limit of quantification of 0.5 ng/mL under the responsibility of QPS, Newark, Delaware, USA.

9.4.3.1 Pharmacokinetics parameters

Given that single pharmacokinetic samples will be collected at clinical visits, no pharmacokinetic parameters will be generated. Plasma concentration data will be used as part of the GZ/SAR402671 clinical development program in population-based modeling to identify common factors that contribute to GZ/SAR402671 pharmacokinetics.

9.5 ESTIMATED SAMPLED BLOOD VOLUME

Table 2 - Estimated sample blood volume

Type	Volume per sample	Sample number	Volume per study
Hematology	2 mL	6	12 mL
Biochemistry (includes eGFR)	10 mL	6	60 mL
High sensitivity cardiac troponin T	2 mL	3	6 mL
Plasma GL-3, lyso GL-3, GM3	10 mL	4	40 mL
Exploratory biomarkers	10 mL	4	40 mL
Pharmacokinetics	4 mL	4	16 mL
Total			**174 mL**

9.6 FUTURE USE OF SAMPLES

For patients who have consented to it, left over samples following testing may be used for other research purposes (excluding genetic analysis) related to Fabry disease and/or to GZ/SAR402671.

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

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

10 STUDY PROCEDURES

This section describes the evaluations that are to take place during the study according to the schedule for the study procedures (Section 1.2).

10.1 VISIT SCHEDULE

See Section 1.2 for the schedule study visits and study assessments.

10.1.1 Study entry visit

Patients enrolled in the study will have the following procedures performed at study entry.

- The patient will receive information on the study objectives and procedures from the investigator.
- The patient will have to sign the informed consent prior to any action related to the study.

Patients who meet all the inclusion criteria and none of the exclusion criteria will be eligible for inclusion in the study. The study entry visit may occur at the same time as the ACT13739 week 26 clinical visit. For the purposes of analysis in this study, data collected at screening and prior to first GZ/SAR402671 treatment in ACT13739 will be imported from the patient's prior study file in the ACT13739 database. Items to be imported into the LTS14116 database include demographic, medical/surgical history, Fabry disease history, including *GLA* mutations, as well as results from safety, pharmacodynamics, and exploratory efficacy assessments.

10.1.2 Treatment period

A patient diary will be issued to the patient 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 eCRF.

For all clinical visits during the treatment period (as indicated in Section 1.2):

- the patient will take GZ/SAR402671 in the clinic;
- Blood and urine samples are to be collected before the oral administration of GZ/SAR402671.

10.1.2.1 Month 6, month 18 and month 30 visits

On the scheduled visiting days, upon arrival, the patient will complete PRO questionnaires first. PROs are to be completed before dosing, before completing any other health data forms, and before participating in any clinical assessments by the investigator or other healthcare provider(s).

One pharmacokinetic sample is to be collected at each visit indicated in Section 1.2 within 1 to 8 hours following oral administration of GZ/SAR402671.

10.1.3 Post treatment follow-up

Patients will be followed-up during a site visit that takes place 1 month (± 7 days) after the last GZ/SAR402671 administration.

This visit is to evaluate the Fabry disease biomarkers and pharmacokinetics. Patient is required to give blood and urine samples for analysis of these biomarkers as described in Section 1.2.

Patients who start commercial ERT, investigational or any other FD treatment within the 1-month (±7 days) follow up period will not be considered for follow up assessments.

During the follow up period TEAE will continue to be collected up to the end of the period the date of start of new treatment.

10.2 DEFINITION OF SOURCE DATA

Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records (eg, hospital records, clinical and office charts, laboratory reports and notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcripts certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments) involved in the clinical study. Source documentation must be maintained to support information provided in the eCRF.

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

The IMP should be continued whenever possible. If the IMP is stopped, then it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation because of suspected AEs may be considered by the investigator after discussions with the sponsor. After close and appropriate clinical/and or laboratory monitoring, once the investigator considers, according to his/her best medical judgment that the occurrence of the concerned event was unlikely due to the IMP, the safety of the patient is not affected, and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2). Treatment with the IMP may be re-initiated after discussion with the sponsor. For all temporary treatment discontinuations, the duration should be recorded by the investigator in the appropriate eCRF pages.

10.3.2 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 at any time.

10.3.3 List of 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 eCRF.

The following may be justifiable reasons for the investigator or sponsor to discontinue a patient from treatment:

- The patient was erroneously included in the study (ie, was found to not have met the inclusion/exclusion criterion).
- The patient experiences an intolerable or unacceptable AE.
- The patient is unable to comply with the requirements of the protocol, including failure to appear at study visits or refusal of clinical study material administration.
- The study is terminated by the sponsor.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

If a patient decides to discontinue participation in the study, he should be contacted by the investigator in order to obtain information about the reason(s) for discontinuation and collection of information regarding any potential AEs.

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion including follow up phone calls at 1 month ±7 days after the last GZ/SAR402671 administration, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. Patients who discontinue GZ/SAR402671 and start commercial ERT, investigational or any other Fabry disease treatment within the 1-month (±7 days) follow up period will not be contacted for follow up.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the early withdrawal visit.

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

10.3.5 Procedure and consequence for patient withdrawal from study

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

Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up (eg, medical records check). Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patient is to complete the procedures planned for early withdrawal visit.

For patients who fail to return to the site, the investigator should make the best effort to contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his health status, including at least his 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 (SAP) 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 retreated in the study. Their treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An 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.

10.4.1.2 Serious adverse event

A 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:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence seizures, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- 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).

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and immediate notification by the investigator to the sponsor 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.

Adverse events of special interest for this study include:

- Symptomatic overdose (serious or non-serious) with IMP
  - An 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 any dose of IMP that exceeds the prescribed amount.
  - Of note, asymptomatic overdose has to be reported as a standard AE.
- New or worsening lens opacities and cataracts

- Increase in ALT (see the "Increase in ALT" flow diagram in Section 17 (Appendix A) of the protocol)
- Pregnancy of a female partner of a male patient enrolled in LTS14116.

10.4.2 Evaluation of adverse events/serious adverse events

10.4.2.1 Relationship to Study Treatment

Assessment of the association between the AE and study exposure is important for regulatory reporting. For each AE the investigator determines whether there is a reasonable possibility that the AE may have been caused by the study treatment according to the categories below:

- Not Related: There is no suspicion of a causal relationship between exposure and the AE.
- Unlikely Related: There is no evidence for a causal relationship between exposure and the AE; however, such a relationship cannot be ruled out.
- Possibly Related: There is some evidence supporting the possibility of a causal relationship between exposure and the AE.
- Related: There is strong evidence that there is a causal relationship between exposure and the AE.

A relationship to the IMP must be given for each AE recorded, even if there is only limited information at the time.

The investigator may change his/her opinion of causality in light of follow-up information, amending the AE report accordingly.

10.4.2.2 Severity grading

Adverse events and laboratory abnormalities will be assessed according to the NCI CTCAE v4.03, which will be provided in the study manual and may be accessed through the NCI website at http://ctep.info.nih.gov/reporting/ctc.html.

Note that severity grading is not the same as "seriousness," which is defined in Section 10.4.1. Seriousness serves as a guide for regulatory reporting obligations.

10.4.2.3 Outcome

Outcome describes the status of the AE. The investigator will provide information regarding the patient outcome of each AE.

Definitions for possible results of an AE outcome:

- Fatal: The termination of life as a result of an AE.
- Not recovered/not resolved: The patient has not recuperated or the AE has not improved.
- Recovering/resolving: The patient is recuperating or the AE is improving.

- Recovered/resolved: The patient has recuperated or the AE has resolved.
- Recovered with sequelae/resolved with sequelae: The AE has resolved, but the patient has been left with symptoms or pathology.
- Unknown: Not known, not observed, not recorded, or refused.

10.4.2.4 Action taken regarding investigational medicinal product

The investigator will be required to provide the action taken regarding IMP in response to the AE. Options include:

- Dose not changed: No change in administration of the IMP.
- Dose reduced: Reduction in the frequency, strength or amount of IMP administered.
- Drug (IMP) interrupted: Temporary interruption (termination) in administration of the IMP.
- Drug (IMP) withdrawn: Administration of the IMP terminated (no further dosing).
- Not applicable: Determination of a value is not relevant in the current context.
- Unknown: Not known, not observed, not recorded, or refused.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- 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 the sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities 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

Instructions for AE reporting are summarized in Table 3.

10.4.4 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 eCRF; the system will automatically send a notification to the monitoring team after approval of the investigator within the eCRF 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 the sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF 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 eCRF system does not work.

Any SAE brought to the attention of the investigator at any time after the end of the study by the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the eCRF. Instructions for AE reporting are summarized in Table 3.

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by the sponsor are provided in Section 17.

Table 3 - 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 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Symptomatic overdose	Yes	Yes	No
		ALT ≥ 3 ULN or ALT ≥ 2X treatment baseline value	Yes	Yes	Yes
		Lens opacities and cataracts	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes

AE: adverse event; AESI: adverse event of special interest; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SAE: serious adverse event; ULN: upper limit of normal.

10.5 PREGNANCY REPORTING

Male patients will be instructed to notify the investigator immediately if they discover that their female 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 10.4.4 to contact the sponsor within 24 hours; however, the investigator will be asked to complete the Pregnancy forms in addition to AE forms. The pregnancy 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.

If not otherwise established, the investigator will inform the patient that the sponsor is required to gather information regarding the course and outcome of the pregnancy after exposure to a study product. The progress of the pregnancy must be followed until the outcome of the pregnancy is known (ie, delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested.

The investigator will be asked to obtain follow-up information no later than 2 months after the gestational period to obtain maternal/fetal/neonatal outcome and any other relevant information.

Follow-up information may be requested at additional time points. All study related visits/contacts involving a known pregnancy should include pregnancy status assessment until pregnancy outcome is known.

10.6 OBLIGATIONS OF THE SPONSOR

During the course of the study, the sponsor 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, independent ethics committees (IECs)/institutional review boards (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 or in this protocol will be considered unexpected.

The sponsor 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

The data collected in this study represents an additional 30 months of extended treatment in patients who completed their first 6 months of treatment in study ACT13739. As the intention is to evaluate up to 36 months of GZ/SAR402671, baseline for this study will represent the GZ/SAR402671 treatment baseline and will be defined as the last assessment prior to the first GZ/SAR402671 administration. Therefore all baseline assessment values used in the calculations for this study will be those imported from ACT13739 study database.

A SAP will be written and finalized prior to database lock to give guidance to the statistical analysis. It will be in compliance with the International Conference on Harmonisation (ICH) and Food and Drug Administration's Guidance for Industry: Statistical Principles for Clinical Trials.

The sponsor or its designee will perform the statistical analysis of the data from this study. The analysis will be performed using the SAS® statistical software system Version 9.1 3 or higher.

All eCRF data, as well as any outcomes derived from the data, will be displayed in patient data listings. Patient data listings will be presented for all patients enrolled into the study. Categorical variables will be summarized using frequencies and percentages, and continuous variables will be summarized using descriptive statistics (number of patients with observation, mean, standard deviation, median, minimum, and maximum). Graphical displays will be presented as appropriate.

11.1 DETERMINATION OF SAMPLE SIZE

The maximum enrollment possible for this study will be determined by the final number of patients completing study ACT13739.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who signed the informed consent.

All screened patients will be included in a summary of patient accountability for this study, including patient disposition. Patient enrollment and disposition will be summarized for the overall patient set. Summary of patient disposition will include the frequency and percentages of patients who enrolled, received study treatment, completed/discontinued study treatment (including reasons for discontinuation), and completed/discontinued the post-treatment safety follow-up.

11.3 ANALYSIS POPULATIONS

The full analysis set and the Safety Set will include all patients who receive at least 1 dose of study treatment in this study. No Per-Protocol Set (PPS) will be defined for this study; however, selected outcomes may be summarized for the ACT13739 PPS, as defined in the SAP of that study, if applicable.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure will be assessed and summarized will be presented for all patients as detailed in the SAP.

11.4.2 Analyses of primary endpoints – safety

The safety evaluation will be based upon the review of the individual values (clinically significant abnormalities), descriptive statistics (summary tables, graphics) and if needed on statistical analysis (appropriate estimations, confidence intervals). See Section 9.1 for additional details on safety assessments.

All the safety analyses will be performed using the safety population.

11.4.2.1 Adverse events

11.4.2.1.1 Definitions

AEs will be coded according to MedDRA.

The AEs will be classified into pre-defined standard categories according to chronological criteria:

- Treatment-emergent AEs (TEAEs): AEs that occurred or worsened during the on-treatment period of this study;
- Post-treatment AEs: AEs that occurred or worsened during the post-treatment period.

If the start date of an AE is incomplete or missing, then the AE will be considered as a TEAE unless a partial date shows it as a post-treatment event.

All AEs reported in the study will be listed, sorted by subject, onset date.

11.4.2.1.2 Treatment-emergent adverse events

Subjects presenting TEAEs will be listed sorted by treatment group, system-organ class and preferred term.

The number and the percentage of subjects with at least one TEAE, severe TEAE, serious TEAE and TEAE leading to treatment discontinuation will be summarized by treatment.

Treatment-emergent AEs will be summarized by treatment, tabulating:

- The number and percent of subjects with at least one TEAE within each and overall system organ class(es);
- The number and percent of subjects experiencing each preferred term in each system organ class;
- The number of occurrences of all preferred terms within each and overall system-organ class(es);
- The number of occurrences of each preferred term in each system-organ class.

11.4.2.1.3 Deaths, serious, and other significant adverse events

Any deaths and SAEs will be listed.

11.4.2.1.4 Adverse events leading to treatment discontinuation

Any AEs leading to treatment discontinuation will be listed.

11.4.2.1.5 Adverse events of special interest

Adverse events of special interest will be listed.

11.4.2.2 Clinical laboratory tests

Observed values and changes from treatment baseline to study time points will be summarized descriptively. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. Frequencies of clinically significant abnormal values and shifts from baseline to study time points will be summarized. Patient listings will be provided.

11.4.2.3 Physical examinations, neurological examinations, and ophthalmology examinations

The frequencies and percent of patients with normal/abnormal findings at clinical visits will be summarized.

11.4.2.4 Vital signs

For vital signs, descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be presented for temperature (°C), blood pressure, heart rate, respiratory rate, and weight (kg) at each visit. Changes from treatment baseline to each visit will also be presented.

11.4.2.5 Electrocardiograms

Electrocardiogram variables as well as changes from treatment baseline in these variables, using descriptive statistics (N, mean, standard deviation, median, minimum and maximum); will be presented for appropriate visits. Likewise, ECGs variables will be summarized using frequencies and percents at appropriate visits.

11.4.3 Analyses of secondary endpoints – pharmacodynamics

Pharmacodynamic parameters will be summarized for each visit using descriptive statistics. Change from treatment baseline will be calculated and summarized. See Section 9.2 for additional information on pharmacodynamic assessments.

11.4.4 Analyses of secondary endpoints - exploratory efficacy

Change from treatment baseline and 95% CIs for exploratory endpoints will be summarized using descriptive statistics as appropriate. See Section 9.3 for additional information exploratory efficacy assessments.

11.4.4.1 Echocardiograms

Continuous echocardiogram variables as well as changes from treatment baseline in these variables, using descriptive statistics (N, mean, standard deviation, median, minimum and maximum); will be presented for appropriate visits. Likewise, categorical echocardiogram variables will be summarized using frequencies and percents at appropriate visits.

11.4.4.2 Analyses of Patient Reported Outcomes

All quality of life data will be summarized by questionnaire, relevant scale or summary scores, and time point. No statistical inference will be performed.

11.4.5 Multiplicity considerations

No adjustments for multiple testing will be utilized.

11.5 INTERIM ANALYSIS

No interim analysis is planned.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the sponsor, the investigator, delegated investigator staff and subinvestigator, 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 (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 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 the sponsor 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 the sponsor.

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 the sponsor (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 subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All subinvestigators shall be appointed and listed in a timely manner. The subinvestigators 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

The sponsor 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 the sponsor 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, except for the pre-identified source data directly recorded in the CRF. 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 in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF 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 eCRF.

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 eCRF.

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 curriculum vitae describing the experience, qualification and training of each investigator and subinvestigator 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 subinvestigators shall be bound by the same obligation as the investigator. The investigator shall inform the subinvestigators of the confidential nature of the clinical trial.

The investigator and the subinvestigators 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 /subinvestigator 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 subinvestigators 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.
- Patient race or ethnicity (ethnicity: not Hispanic or Latino; race: American Indian or Alaska native, Asian, Black, Native Hawaiian or other Pacific Islander, White and ‘not reported’) will be collected in this study because these data are required by several health authorities.

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, Good Clinical Practice 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 subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.

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

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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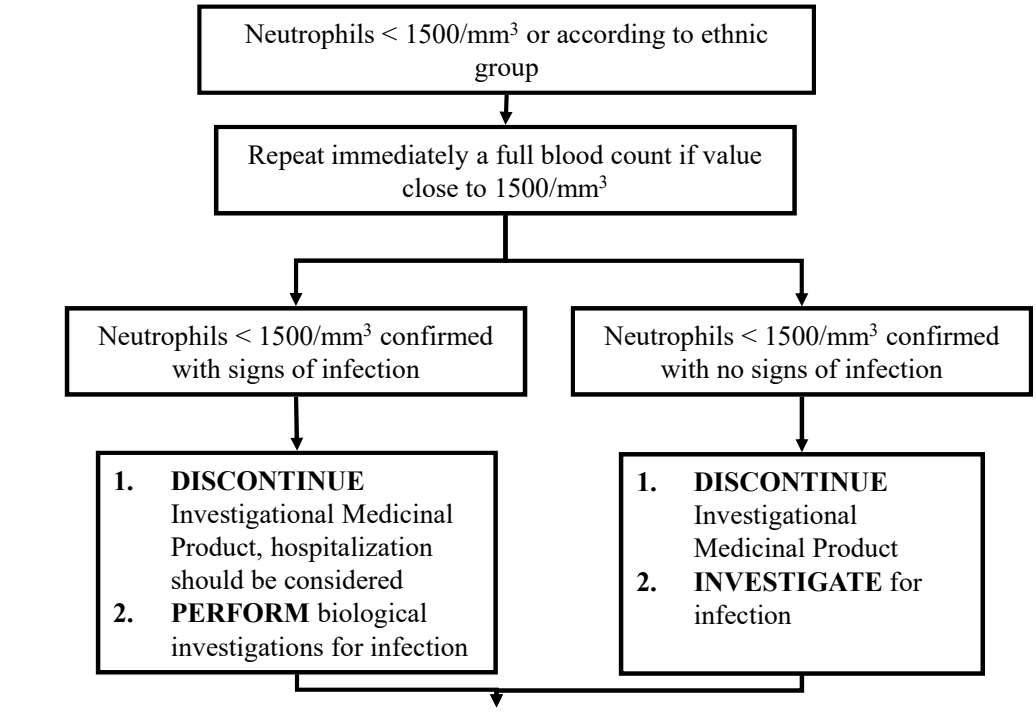
17 APPENDICES

General Guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

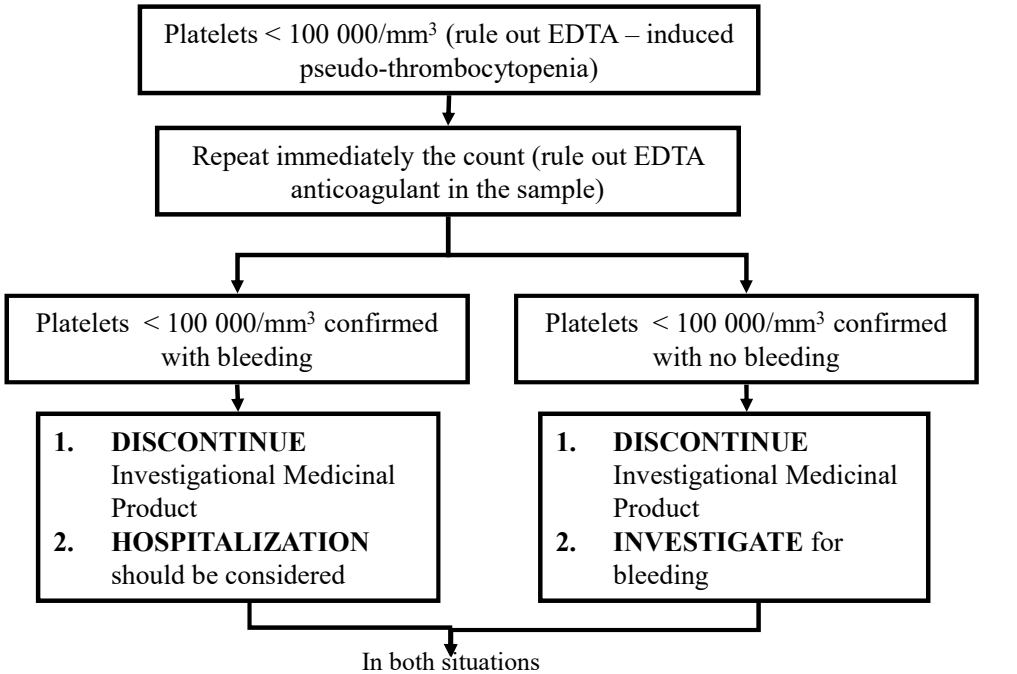


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

THROMBOCYTOPENIA

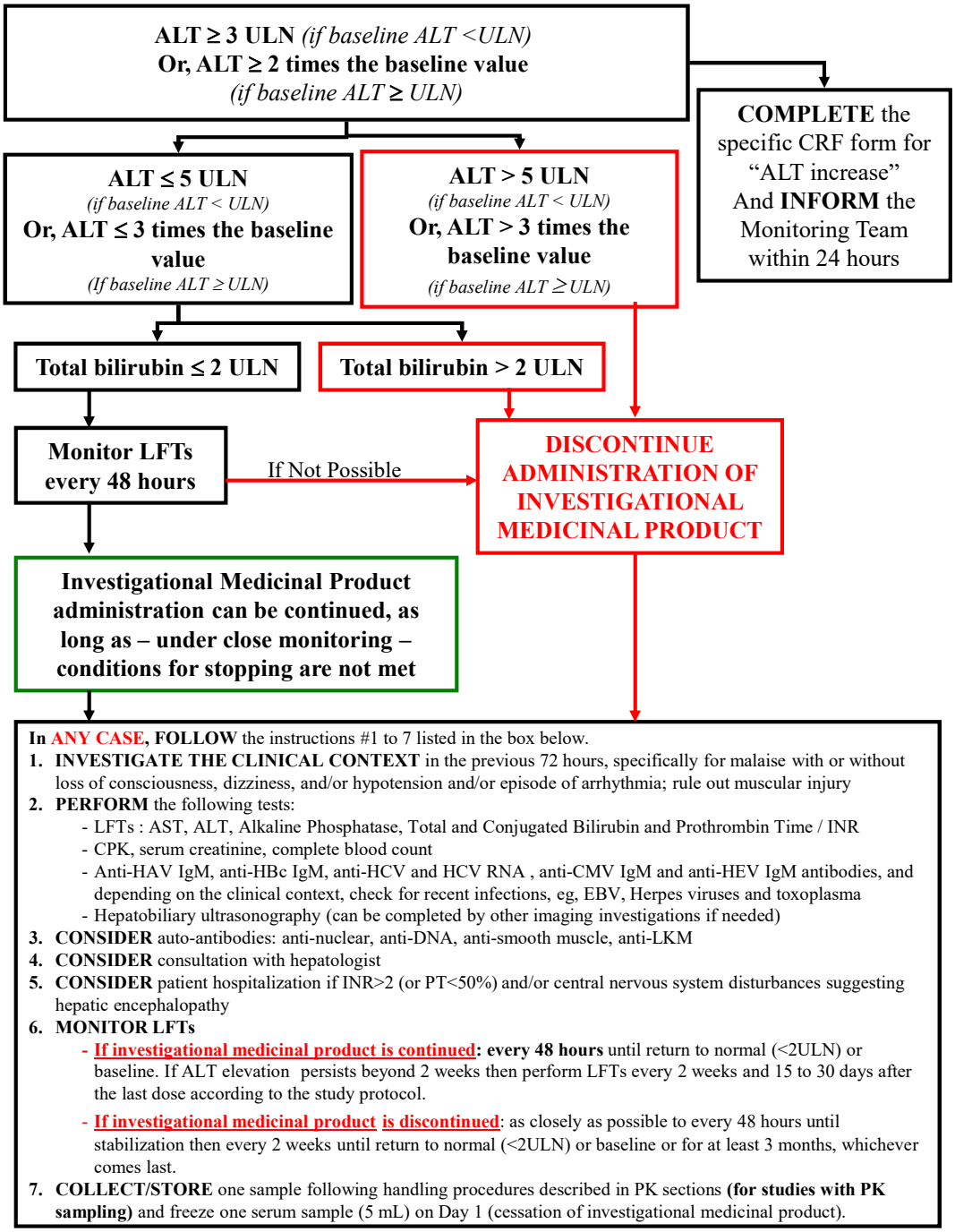


3. **INFORM** the local Monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if platelets remain < 50 000/mm3
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

INCREASE IN ALT

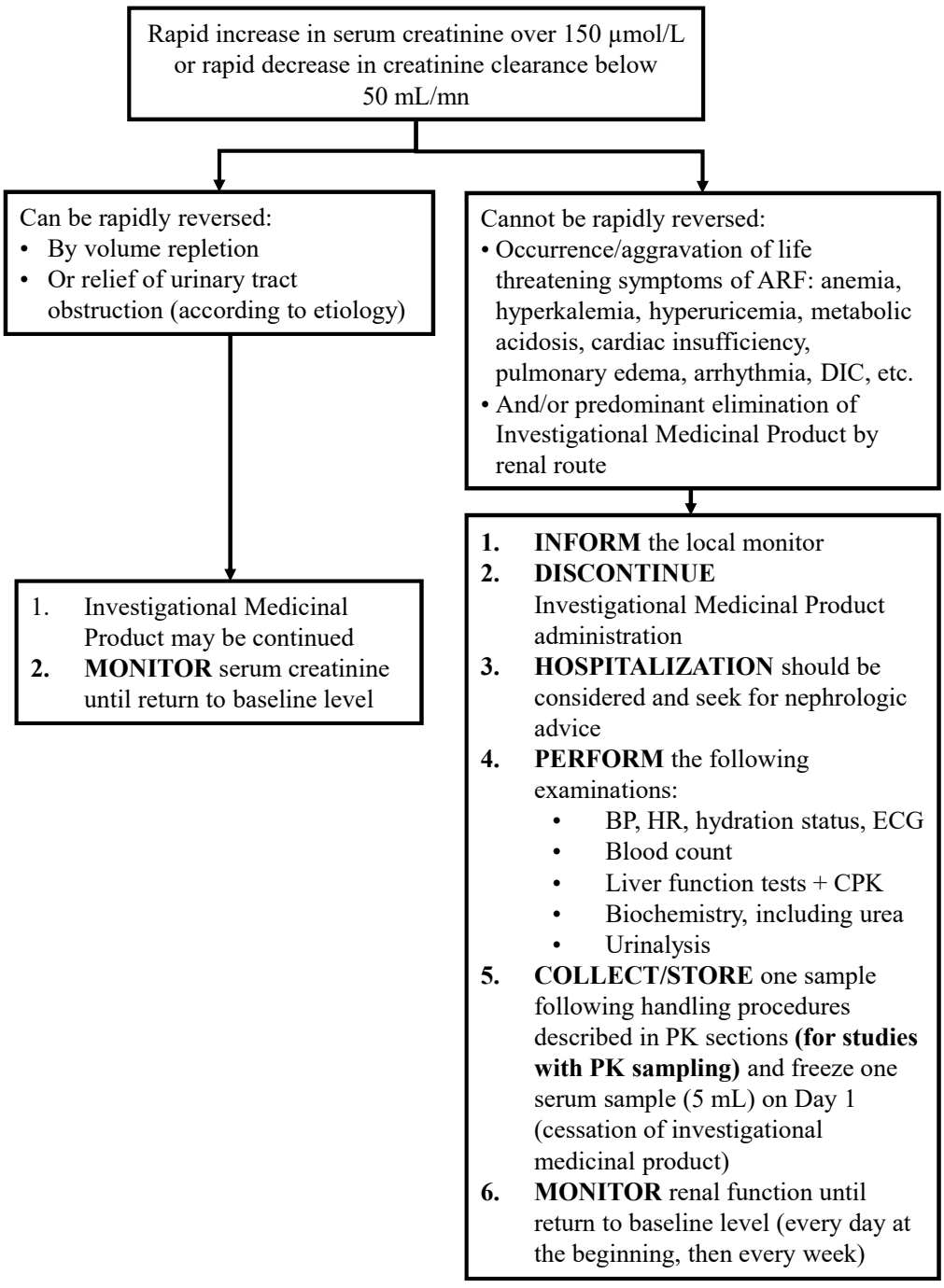


In ANY CASE, FOLLOW the instructions #1 to 7 listed in the box below.

1. **INVESTIGATE THE CLINICAL CONTEXT** in the previous 72 hours, specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia; rule out muscular injury
2. **PERFORM** the following tests:
   - LFTs : AST, ALT, Alkaline Phosphatase, Total and Conjugated Bilirubin and Prothrombin Time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA , anti-CMV IgM and anti-HEV IgM antibodies, and depending on the clinical context, check for recent infections, eg, EBV, Herpes viruses and toxoplasma
   - Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed)
3. **CONSIDER** auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, anti-LKM
4. **CONSIDER** consultation with hepatologist
5. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
6. **MONITOR LFTs**
   - **If investigational medicinal product is continued: every 48 hours** until return to normal (<2ULN) or baseline. If ALT elevation persists beyond 2 weeks then perform LFTs every 2 weeks and 15 to 30 days after the last dose according to the study protocol.
   - **If investigational medicinal product is discontinued**: as closely as possible to every 48 hours until stabilization then every 2 weeks until return to normal (<2ULN) or baseline or for at least 3 months, whichever comes last.
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product).

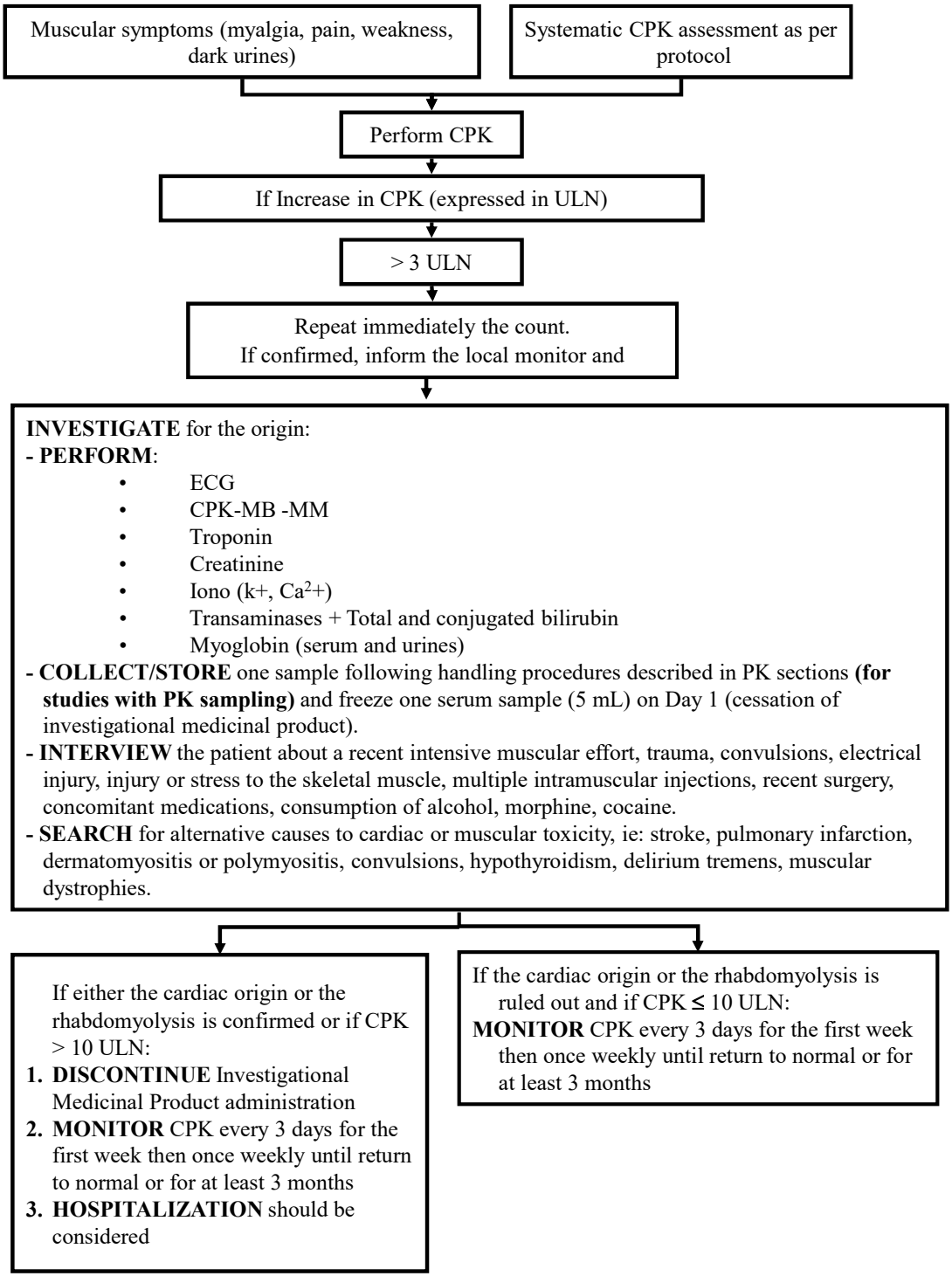
NOTE: ALT ≥ 3 ULN (IF BASELINE ALT < ULN) OR ALT ≥ 2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE SECTIONS 10.4.1.3, 10.4.5, AND 10.4.6). IN ADDITION, IF ALT < 3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

LTS14116 Amended Protocol 04

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	10-Nov-2017 17:32 GMT+0100
[redacted]	Regulatory Approval	10-Nov-2017 17:44 GMT+0100
[redacted]	Clinical Approval	14-Nov-2017 14:04 GMT+0100