NCT04705051

AMENDED CLINICAL TRIAL PROTOCOL 01

Protocol title:	**Multicenter, open-label, extension study to characterize the long-term efficacy and safety of early versus delayed treatment with venglustat (GZ/SAR402671) in patients at risk of rapidly progressive autosomal dominant polycystic kidney disease (ADPKD)**
Protocol number:	**LTS15823**
Amendment number:	**01**
Compound number (INN/Trademark):	**GZ402671** **Venglustat**
Brief title:	**Long-term treatment of autosomal dominant polycystic kidney disease (ADPKD) with venglustat STAGED-PKD-EXT**
Study phase:	**Phase 3**
Sponsor name:	**Global Sponsor: Sanofi-Aventis Recherche & Développement**
Legal registered address:	**Sanofi-Aventis Recherche & Développement: 1 avenue Pierre Brossolette 91380 Chilly-Mazarin, France** **Manufacturer: Same as Sponsor**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	130913
EudraCT:	2020-004400-34
NCT:	Not available
WHO:	Not available
EUDAMED:	Not available
Other:	Not available

Date: 16-Mar-2021 Total number of pages: 102

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, and Spain	16 March 2021, version 1 (electronic 1.0)
Original Protocol	All	28 September 2020, version 1 (electronic 2.0)

Amended protocol 01 (16 March 2021)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to include country-specific requirements for patients in countries participating in the Voluntary Harmonisation Procedure (VHP) for multinational clinical trials in Europe (Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, and Spain).

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Overall Design; Section 4.1 Overall Design	Added reference for country-specific requirements for patients participating in Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, and Spain. These countries will follow instructions provided in Section 10.8.2.	To comply with the request raised during the European (EU) VHP review phase.
Section 10.8 (Appendix 8), Country-specific requirements	Inserted section heading 10.8.1 for Germany country-specific requirements. Inserted new Section 10.8.2 for Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, and Spain with country-specific requirements. All participants will be treated for the duration of 24 months. The protocol instruction "or until venglustat is commercially available for patients, whichever comes first" is not applicable to the countries listed above.	To comply with the request raised during the EU VHP review phase, study participants in these countries will receive venglustat (15 mg once daily) for the duration of 24 months.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

Multicenter, open-label, extension study to characterize the long-term efficacy and safety of early versus delayed treatment with venglustat (GZ/SAR402671) in patients at risk of rapidly progressive autosomal dominant polycystic kidney disease (ADPKD)

Brief title: Long-term treatment of autosomal dominant polycystic kidney disease (ADPKD) with venglustat

Rationale:

To obtain the long-term efficacy and safety of additional 24-month treatment with venglustat in patients with ADPKD who completed Study EFC15392.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the effect of early versus delayed treatment with venglustat on the total kidney volume (TKV) in participants at risk of rapidly progressive ADPKD.	• Percent change in TKV based on magnetic resonance imaging (MRI) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.
Secondary	
• To determine the effect of early versus delayed treatment with venglustat on the renal function (estimated glomerular filtration rate [eGFR]).	• Change in eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.
• To characterize the safety profile of venglustat.	• Safety in terms of treatment-emergent adverse events (TEAEs), adverse events (AEs), serious adverse events (SAEs), laboratory parameters, vital signs, electrocardiogram and findings from physical examination will be assessed through the study and will be reported in the electronic case report form (eCRF).
• To evaluate the effect of venglustat on the lens by ophthalmological examination.	• Change from EFC15392 study baseline in the lens clarity by ophthalmological examination during the open-label extension treatment-emergent period.
• To evaluate the effect of venglustat on mood using Beck Depression Inventory-II (BDI-II).	• Change from EFC15392 study baseline in BDI-II score during the open-label extension treatment-emergent period.

Overall design:

This will be an international, multicenter, open-label extension study rolling over adult participants at risk of rapidly progressive ADPKD who have previously completed Stage 1 or Stage 2 of Study EFC15392. All participants will be treated with venglustat 15 mg once daily (QD) for 24 months or until venglustat is commercially available for patients, whichever comes first. See Appendix 8 (Section 10.8) for definition applicable for patients participating in Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, and Spain (Section 10.8.2).

Brief summary:

This is a single group, treatment, Phase 3, open-label study to evaluate the efficacy and safety of venglustat in male and female participants at risk of rapidly progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Number of participants:

It is anticipated that a maximum of 640 participants who completed Stage 1 or Stage 2 of the EFC15392 study could be enrolled to participate in this study.

Intervention groups and duration:

This will be an interventional single arm study.

Duration period: 25.5 months at the maximum. Screening period (when applicable): up to 2 weeks. Core treatment period: 24 months. Follow-up: 30 days after final dose of the investigational medicinal product (IMP) (venglustat).

Enrollment in LTS15823 study must coincide with Visit 12 (Month 24; end-of-treatment visit) of the EFC15392 study. Patients who cannot be included in the extension study at the time of Visit 12 for administrative or logistical reasons, and provided they agree to participate in the LTS15823 study, will have a separate Screening visit (Visit 0) performed and must be enrolled in the LTS15823 within 2 months of the last dose of IMP (Visit 12 [Month 24]) administered in the EFC15392 study. This 2-month window can be further extended up to 6 months following review and approval from the Sponsor.

Study intervention(s)

Investigational medicinal product(s)

- Formulation: venglustat is provided in capsule formulation containing 15 mg of venglustat (active moiety). Venglustat is not approved in any territory.
- Route(s) of administration: oral.
- Dose regimen: 15 mg once daily.

Devices

Not applicable.

Posttrial access to study medication

Not applicable.

Statistical considerations:

- **Primary endpoint:** Percent change in TKV based on magnetic resonance imaging (MRI) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.

The primary estimand will be the difference (early venglustat versus delayed venglustat) in mean percent change in TKV from the EFC15392 study baseline to 24 months in the LTS15823 study, in all participants from the primary efficacy population, regardless of whether or not participants completed the LTS15823 study treatment period (treatment policy strategy).

Percent change from the EFC15392 study baseline in TKV will be analyzed using a mixed effect model with repeated measures (MMRM). The MMRM will include percent change in TKV at the following time points:

- Month 18 in the EFC15392 study.
- Baseline in the LTS15823 study.
- Month 24 in the LTS15823 study.

The MMRM will include fix effect of treatment group (early venglustat versus delayed venglustat), Mayo Imaging Classification (as per randomization stratification factor in the EFC15392 study: Class 1C versus 1D versus 1E), time point (as a categorical variable), treatment*time point interaction, Mayo Imaging Classification*time point interaction as well as the continuous fixed covariates of baseline TKV and the baseline-by-time point interaction.

The difference in baseline adjusted least-squares means will be used to compare the early venglustat group to the delayed venglustat group, at the 2-sided 0.05 level.

The primary analysis will include all observed TKV data in participants from the primary efficacy population, regardless of whether or not participants completed the treatment period. Participants who prematurely and permanently discontinue IMP in the LTS15823 study will be requested to obtain an MRI scan at 24-month visit and their data collected after treatment discontinuation will be included in the primary analysis. All efforts will be made to minimize the amount of missing data.

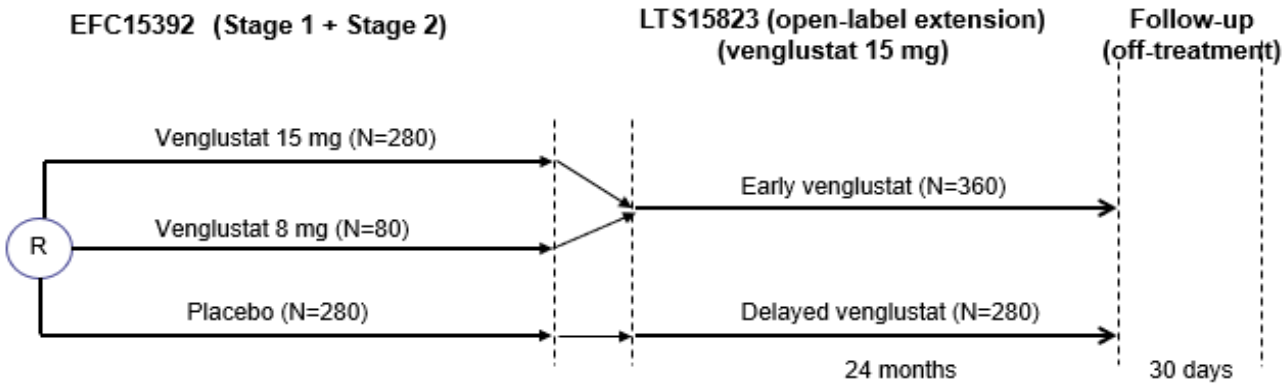
- **Main secondary endpoints:** Change in eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants

Change from the EFC15392 study baseline in eGFR will be analyzed using a MMRM similar to those used to analyze percent change in TKV. The MMRM will include change in eGFR at all time points in the EFC15392 and LTS15823 studies (change at Months 1, 3, 6, 9, 12, 15, 18, 21, and 24 in the EFC15392 study and at Baseline, Months 1, 6, 12, 18, and 24 in the LTS15823 study).

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 1 **- Graphical study design including the EFC15392 study**



In the open-label extension LTS15823 study:

- Early venglustat: participants who were randomized to venglustat (8 mg or 15 mg) in Stage 1 or Stage 2 of the EFC15392 study.
- Delayed venglustat: participants who were randomized to placebo in Stage 1 or Stage 2 of the EFC15392 study.

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Study flowchart for participants enrolled in LTS15823 study at Visit 12 (Month 24) of the EFC15392 study

Visit	1[a, b] Baseline	2	3	4	5	6	7	8	9	10[c] (EOT)	11[d] (Follow-up)
Month	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**1**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (±7)**
Informed consent	X										
Inclusion criteria	X										
Exclusion criteria	X										
Body weight, height[e]	X					X				X	
Vital signs[f]	X[b]	X	X	X	X	X	X	X	X	X	X
Physical examination - Complete (including full neurological examination)	X[b]					X				X	
Physical examination - Abbreviated[g]		X		X				X			X[h]
Chemistry[i]	X[b]	X		X		X		X		X	X[h]
Blood creatinine only (for eGFR calculation)[i]			X		X		X		X		
Hematology	X[b]	X		X		X		X		X	
Urine pregnancy test (WOCBP)[j]	X[b]	X	X	X	X	X	X	X	X	X	X

Visit	1[a, b] Baseline	2	3	4	5	6	7	8	9	10[c] (EOT)	11[d] (Follow-up)
Month	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**1**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (±7)**
Urinalysis with microscopy[k]	X[b]	X		X		X		X		X	X
GSL markers[l]	X[b]			X		X		X		X	
Serum/plasma biomarkers[h, l]	X[b]			X		X		X		X	
Urinary markers (24-hour)[m]	X[b]	X		X		X		X		X	
12-lead ECG[n]	X[b]			X						X	
MRI[o]	X[a]									X	
BDI-II	X[b]		X	X	X	X	X	X	X	X	X
Ophthalmological examination[p]	X[b]			X		X		X		X	
BPI-SF[q]	X[b]	X		X		X		X		X	
BFI[q]	X[b]	X		X		X		X		X	
EQ-5D-5L[q]	X[b]	X		X		X		X		X	
Call IxRS	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP	X	X	X	X	X	X	X	X	X		
IMP accounting and compliance		X	X	X	X	X	X	X	X	X	
Biobanking[l, r]	X[b]					X				X	
Concomitant medication[s]	X[b]	X	X	X	X	X	X	X	X	X	X

Visit	1[a, b] Baseline	2	3	4	5	6	7	8	9	10[c] (EOT)	11[d] (Follow-up)
Month	0	1	3	6	9	12	15	18	21	24	25
Day (window [days])	1	30 (±7)	90 (±7)	180 (±7)	270 (±7)	360 (±7)	450 (±7)	540 (±7)	630 (±7)	720 (±7)	750 (±7)
AEs/SAE[t]	X[b]	X	X	X	X	X	X	X	X	X	X

AEs = adverse events; AESIs = adverse events of special interest; BDI-II = Beck Depression Inventory II; BFI = Brief Fatigue Inventory; BP = blood pressure; BPI-SF = Brief Pain Inventory short form; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; EOT= end-of-treatment; EQ-5D-5L = EuroQoL 5 dimension 5 level; EW = early withdrawal; GSL = glycosphingolipid; IMP = investigational medicinal product; IxRS = interactive voice/web response system; MRI = magnetic resonance imaging; PRO = participant reported outcome; SAEs = serious AEs; WHO = World Health Organization; WOCBP = women of childbearing potential.

a Visit 12 (the end-of treatment, Month 24) of the EFC15392 study will correspond to Visit 1 (Day 1) of the LTS15823 study with all evaluations of Visit 12 of EFC15392 study and an additional MRI that will be performed in the time frame of Visit 1 of the LTS15823 study. Every effort shall be made to have MRI performed at Visit 1 of the LTS15823 study prior to the start of IMP. If for technical reasons MRI examination cannot be performed at Visit 1, it should be performed as soon as possible, within next 7 days.

b Clinical and instrumental assessments obtained at Visit 12 (Month 24) of the EFC15392 study will be used for both Visit 12 (Month 24) of EFC15392 study and Visit 1 of the LTS15823 study.

c If a participant discontinues treatment with IMP early during the core treatment period, the participant will have an end-of-treatment/early withdrawal (EOT/EW) Visit within 7 days and a Follow-up Visit 30 days after the last dose of IMP. Early EOT/EW visit will be performed without MRI. Participants who prematurely and permanently discontinue study medication in the LTS15823 study will be requested to obtain an MRI scan at Month 24 Visit.

d Follow-up assessments will be evaluated 30 days after the last dose of IMP.

e Height measured in the EFC15392 study will be recorded only at Visit 1.

f Vital sign measurements (sitting BP and heart rate): For all measurements, 3 separate seated BP measurements should be taken with at least 1 minute between readings, following at least 10-minute rest period and prior to phlebotomy. The arm with the higher pressure at the initial Screening visit of the EFC15392 study should be used for all subsequent BP measurements.

g The abbreviated physical examination should focus on areas important for assessment of AEs if necessary.

h Only for participants with abnormal laboratory results and/or AEs that will require follow up after Visit 10.

i Samples should be collected in fasting conditions.

j Any positive urine pregnancy test result must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations. Participants will perform monthly urine pregnancy test at home and report to the site.

k Urinalysis includes urine dipstick and microscopy. Dipstick includes assessment of specific gravity, pH, protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. Microscopy (central laboratory) includes detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment. Dipstick will be done locally; if any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement.

l Not applicable for Chinese participants.

m A 24-hour urine sample will be collected to evaluate exploratory biomarkers (not applicable for Chinese participants), albumin, total protein, creatinine, electrolytes, and osmolality. At the end of on-site visit, the participant should be given suitable containers in which to collect the 24-hour urine, required prior to the next on-site visit and to be returned at that visit.

n The 12-lead ECG recordings should be performed before blood samplings. The ECG will be evaluated as “normal” or “abnormal”.

o Using a central reader, liver volume and combined renal volume of both kidneys will be measured. Combined renal cyst volume and renal parenchyma may be determined at a later date for a subset of participants.

p The participant is required to have full ophthalmological examination at Visit 1, at Month 12 (Visit 6), and at Month 24 (Visit 10) (or upon withdrawal or discontinuation) with pupil dilation and WHO simplified cataract grading system evaluation of lens opacities. Best corrected visual acuity (BCVA) examination will be additionally performed at Month 6 (Visit 4) and Month 18 (Visit 8). If at any time during study participation, the participant experiences a decrease ≥2 lines in BCVA compared to baseline or previous assessment, full ophthalmological examination with pupil dilation and WHO simplified cataract grading system evaluation should be performed. If a new or worsening lens abnormality is found, documentation of finding with lens photography is recommended. Pupil dilation and full eye examination can be performed at any time if deemed medically necessary; WHO simplified cataract grading system evaluation should be performed if a change from baseline is observed during slit-lamp examination.

q The PROs will be administered to participants at study visit according to the listed schedule before dosing and before clinical assessments.

r Prior to the start of IMP at Baseline Visit. In participants who have consented to it, samples of serum will be collected and archived for future analysis.

s All ongoing or new medications from the end of the EFC15392 study should be reported in the LTS15823 study, even if reported prior to informed consent.

t All SAEs, AEs, and AEs of special interest (AESIs) will be collected starting with signing the informed consent and will continue until 30 days after the last dose of IMP or study end, whichever comes later. All AEs that occurred during treatment should be followed for at least 30 days following the last dose of IMP or until the event has resolved, the condition has stabilized, the etiology of the event is determined to be not related to IMP, or the participant is lost to follow-up. All participants will have a Follow-up visit 30 days after the last dose of IMP to collect safety information.

1.3.2 Study flowchart for participants enrolled in LTS15823 study after the end-of-treatment visit of the EFC15392 study

Visit	0[a, b] Screening	1[b, c] Baseline	2	3	4	5	6	7	8	9	10[d] (EOT)	11[e] (Follow-up)
Month		**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-7 days[f] (+3)**	**1 (+3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (±7)**
Informed consent	X											
Inclusion criteria	X	X										
Exclusion criteria	X	X										
Medical/surgical history[g]	X											
Medication history[g]	X											
Body weight, height[h]	X						X				X	
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination - Complete (including full neurological examination)	X						X				X	
Physical examination - Abbreviated[j]			X		X				X			X[k]
Chemistry[l]	X		X		X		X		X		X	X[k]
Blood creatinine only (for eGFR calculation)[l]				X		X		X		X		
Hematology	X		X		X		X		X		X	
Serum pregnancy test (WOCBP)[m]	X											

Visit	0[a, b] Screening	1[b, c] Baseline	2	3	4	5	6	7	8	9	10[d] (EOT)	11[e] (Follow-up)
Month		**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-7 days[f] (+3)**	**1 (+3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (±7)**
FSH and/or estradiol as needed[n]	X											
Urine pregnancy test (WOCBP)[o]	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis with microscopy[p]	X		X		X		X		X		X	X
GSL markers[q]	X				X		X		X		X	
Serum/plasma biomarkers[k, q]	X				X		X		X		X	
Urinary markers (24-hour)[r]		X	X		X		X		X		X	
Viral serology	X[s]											
12-lead ECG[t]	X				X						X	
MRI[u]	X										X	
BDI-II	X			X	X	X	X	X	X	X	X	X
Ophthalmological examination[v]	X				X		X		X		X	
BPI-SF[w]		X	X		X		X		X		X	
BFI[w]		X	X		X		X		X		X	
EQ-5D-5L[w]		X	X		X		X		X		X	
Call IxRS		X	X	X	X	X	X	X	X	X	X	X
Dispense IMP		X[b, c]	X	X	X	X	X	X	X	X		

Visit	0[a, b] Screening	1[b, c] Baseline	2	3	4	5	6	7	8	9	10[d] (EOT)	11[e] (Follow-up)
Month		**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-7 days[f] (+3)**	**1 (+3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (±7)**
IMP accounting and compliance			X	X	X	X	X	X	X	X	X	
Biobanking[q, x]	X						X				X	
Concomitant medication[y]	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAE[z]	X	X	X	X	X	X	X	X	X	X	X	X

AB = antibody; AEs = adverse events; AESI = adverse events of special interest; BCVA = best corrected visual acuity; BDI-II = Beck Depression Inventory II; BFI = Brief Fatigue Inventory; BP = blood pressure; BPI-SF = Brief Pain Inventory short form; DNA = deoxyribonucleic acid; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; EOT= end-of-treatment; EQ-5D-5L = EuroQoL 5 dimension 5 level; EW = early withdrawal; FSH = follicle-stimulating hormone; GSL = glycosphingolipid; HBV = hepatitis B virus; IMP = investigational medicinal product; IxRS = interactive voice/web response system; MRI = magnetic resonance imaging; PRO = participant reported outcome; SAEs = serious AEs; WHO = World Health Organization; WOCBP = women of childbearing potential.

a Patients who cannot be included in the extension study at the time of the end-of-treatment visit of the EFC15392 study for administrative or logistical reasons must have a separate Screening visit (Visit 0) in the LTS15823 study. Neurological and ophthalmic examination results obtained at Visit 12 (Month 24) of the EFC15392 study can be used for Visit 1 of the LTS15823 study in these participants if Visit 0 of LTS15823 is performed within 2 months after the Visit 12 in the EFC15392 study. All other assessments required at Visit 0 of LTS15823 study must be performed in the time frame of the LTS15823 study. Patients screened in more than 2 months after Visit 12 of the EFC15392 study will have as well as a separate Screening visit (Visit 0) and all Visit 0 assessments performed.

b All Visit 0 and Visit 1 assessments, including MRI, must be performed prior to the first IMP administration in the LTS15823 study.

c The IMP will be dispensed at Visit 1 after confirmation of Visit 0 eGFR >30 mL/min/1.73 m^2, after review of Visit 0 blood chemistry and hematology results, Visit 0 ECG central reading, blood pregnancy test (if done at Visit 0) and Visit 1 urinary pregnancy test.

d If a participant discontinues treatment with IMP early during the core treatment period, the participant will have an end-of-treatment/Early Withdrawal (EOT/EW) Visit within 7 days and a Follow-up Visit 30 days after the last dose of IMP. Early EOT/EW visit will be performed without MRI. Participants who prematurely and permanently discontinue IMP in the LTS15823 study will be requested to obtain an MRI scan at the Month 24 Visit.

e Follow-up assessments will be evaluated 30 days after the last dose of IMP.

f If necessary, a second pretreatment eGFR value can be obtained for confirmation of eligibility to account for potential eGFR variability. Duration of screening period can be increased up to 2 weeks if a second pretreatment eGFR value will be required or if any test has to be repeated due to indeterminate result or technical issue. Other reasons have to be discussed with the Sponsor.

g Only medical events that occurred between the end-of-study visit of the EFC15392 study and Visit 1 in LTS15823 study. Ongoing medications at the time of the end-of-study visit of the EFC15392 or new medications and changes in dose of ongoing medications that occurred between the end-of-treatment visit of the EFC15392 study and Visit 0 in LTS15823 study. All medical events will be reported in AE eCRF forms.

h Height measured in the EFC15392 study will be recorded only at Visit 0.

i Vital sign measurements (sitting BP and heart rate): For all measurements 3 separate seated BP measurements should be taken with at least 1 minute between readings, following at least 10-minute rest period and prior to phlebotomy. The arm with the higher pressure at the Screening visit (Visit 0) should be used for all subsequent BP measurements.

j The abbreviated physical examination should focus on areas important for assessment of AEs if necessary.

k Only for participants with abnormal laboratory results and/or AEs that will require follow up after Visit 10.

l Samples should be collected in fasting conditions.

m Serum pregnancy testing at Visit 0 only for female participants who stopped using contraception after the end of the EFC15392 study (no urine pregnancy test will be required at Visit 0 for these participants). If serum pregnancy test was performed at Visit 0, test result must be reviewed prior to the start of IMP at Visit 1.

n FSH and estradiol will be tested at screening at the discretion of Investigator if participant progressed into menopause and will require confirmation of menopause status.

o No urine pregnancy test will be required at Visit 0 for participants who will have a blood urine pregnancy test performed at Visit 0. Any positive urine pregnancy test result must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations. Participants will perform monthly urine pregnancy test at home and report to the site.

p Urinalysis includes urine dipstick and microscopy. Dipstick includes assessment of specific gravity, pH, protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. Microscopy (central laboratory) includes detection of formed cellular elements, casts, bacteria, yeast, parasites, and crystals in centrifuged urine sediment. Dipstick will be done locally, if any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement.

q Not applicable for Chinese participants.

r 24-hour urine sample will be collected to evaluate exploratory biomarkers (not applicable for Chinese participants), albumin, total protein, creatinine, electrolytes, and osmolality. At the end of Visit 1 and other on-site visits, the participant should be given suitable containers in which to collect the 24-hour urine, required prior to the next on-site visit and to be returned at that visit.

s At the discretion of Investigator if a new medical (viral hepatitis or HIV infection) condition is suspected. If Investigator will decide that viral serology test is warranted at Visit 1, patient will be excluded in case of positive result of any of the following tests: hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti HIV 1 and anti HIV 2 Ab). Patients with a positive hepatitis B surface antibody (HBsAb) test are eligible if other criteria are met (ie, negative tests for: HBsAg, hepatitis B core antibody [HBcAb]). Patients who are immune due to natural infection (positive HBsAb, negative HBsAg, and positive HBcAb) are eligible if they have a negative HBV DNA test.

t The 12-lead ECG recordings should be performed before blood samplings. Visit 0 ECG central reader assessment should be evaluated prior to IMP administration at Visit 1. The ECG will be evaluated as “normal” or “abnormal”.

u Baseline MRI should be performed prior to first IMP administration in the LTS15823 study. Using a central reader, liver volume and combined renal volume of both kidneys will be measured. Combined renal cyst volume and renal parenchyma may be determined at a later date for a subset of participants.

v The participant is required to have full ophthalmological examination at Visit 0 or Visit 1, at Month 12 (Visit 6), and at Month 24 (Visit 10) (or upon withdrawal or discontinuation) with pupil dilation and WHO simplified cataract grading system evaluation of lens opacities. Best corrected visual acuity (BCVA) examination will be additionally performed at visits Month 6 (Visit 4) and Month 18 (Visit 8). If at any time during study participation, the participant experiences a decrease ≥2 lines in BCVA compared to baseline or previous assessment, full ophthalmological examination with pupil dilation and WHO simplified cataract grading system evaluation should be performed. If a new or worsening lens abnormality is found, documentation of finding with lens photography is recommended. Pupil dilation and full eye examination can be performed at any time if deemed medically necessary; WHO simplified cataract grading system evaluation should be performed if a change from baseline is observed during slit-lamp examination.

w The PROs will be administered to participants at study visit according to the listed schedule before dosing and before clinical assessments.

x Prior to the start of IMP at Baseline visit. In participants who have consented to it, samples of serum will be collected and archived for future analysis.

y All ongoing or new medications from the end of the EFC15392 study should be reported in the LTS15823 study, even if reported prior to informed consent.

z All SAEs, AEs and AESIs will be collected starting from the end of the study visit in EFC15392 (including those prior to informed consent) and will continue until 30 days after the last dose of IMP or study end, whichever comes later. All AEs that occurred during treatment should be followed for at least 30 days following the last dose of IMP or until the event has resolved, the condition has stabilized, the etiology of the event is determined to be not related to IMP, or the participant is lost to follow-up. All participants will have a Follow-up visit 30 days after the last dose of IMP to collect safety information.

2 INTRODUCTION

2.1 STUDY RATIONALE

To evaluate the long-term efficacy and safety of venglustat in patients with autosomal dominant polycystic kidney disease (ADPKD) who have previously completed Stage 1 or Stage 2 of the EFC15392 study.

2.2 BACKGROUND

2.2.1 Venglustat

GZ402671, also referred to as venglustat, SAR402671 is a GCS inhibitor that decreases the synthesis of glucosylceramide (GL-1), a central building block for more complex glycosphingolipids (GSLs). Substrate reduction therapy (SRT) with GCS inhibitors is expected to have broad therapeutic applicability across a number of disorders, including lysosomal storage diseases, as well as other disorders associated with increased GL-1 or increased levels of GSLs that contain GL-1 at their core.

Sanofi is investigating venglustat as a potential SRT for treating patients with Fabry disease (FD), Gaucher disease Type 3 (GD3), Parkinson's disease patients with a confirmed acid-β-glucosidase (glucocerebrosidase gene [GBA]) mutation (GBA-PD), GM2 gangliosidosis and ADPKD. A novel GCS inhibitor, venglustat inhibits the enzymatic conversion of ceramide to GL-1, the first step in glycosphingolipid biosynthesis. By reducing the production of GL-1, the central building block for the synthesis of more complex GSLs (including globotriaosylceramide [GL-3], GM1, GM2, and monosialodihexosylganglioside [GM3]), SRT with venglustat offers a potential therapeutic strategy for FD, GD, GBA-PD, and ADPKD.

Venglustat is a potent and selective inhibitor of murine and human GCS in biochemical and cell-based in vitro assays. In vivo pharmacology studies in rodents and dogs showed reduction in plasma GL-1 concentrations as a pharmacodynamic (PD) marker of GCS inhibition. Reductions of GL-1 concentrations in plasma (rodents and dogs) and tissue (rodents only) were observed following oral venglustat administration. In both species, the effects of venglustat on plasma GL-1 were dose-dependent and correlated with plasma concentrations of the compound. Based on multiple preclinical studies following a single oral administration to rats, venglustat distributed extensively in kidney, liver, lung, spleen, intestine, and heart tissues and crossed the blood brain barrier.

In safety studies performed in adult mouse, rat and dog, the gastrointestinal tract, testes and lens of the eye have been identified as target organs of toxicity. A safety margin was established of approximately 4- to 15-fold based on the exposures at the no observed adverse effect level (NOAEL) in 26-week rat and 39-week dog safety studies. Also, there is approximately a 60-fold safety margin for human ether-a-go-go-related gene (hERG) ion channel in vitro activity and approximately a 35-fold safety margin for cardiac parameters evaluated in dogs compared with the exposure observed at the highest administered dose in Study TDR12768, a Phase 1, 14-day

repeat-dose study in humans with 20 mg malate salt capsule corresponding to 14.9 mg venglustat active moiety.

In a juvenile toxicology study (but not in 7 different adult toxicology studies), in rats given venglustat, unilateral/bilateral degeneration of germinal epithelium in the testes of males and lenticular (eye lenses) degeneration in both sexes was observed. The NOAEL for development endpoints was 45 mg/kg. The NOAEL for all anatomic findings was 15 mg/kg with the exception of findings in the lens. For this finding, the NOAEL was 5 mg/kg in females and 15 mg/kg in males.

2.2.2 Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening genetic disease caused by mutations in PKD1 and PKD2 genes characterized by the formation of multiple kidney cysts that enlarge with disease progression to result in end-stage renal disease and dialysis in ~50% of patients (1). Cysts may also develop in liver and other organs (eg, seminal vesicle, pancreas). At least 60% of ADPKD patients report pain (back pain and abdominal pain) and up to one third of patients report severe symptoms. The target population is those patients with ADPKD at high risk of progressing to end-stage renal disease (1C, 1D, and 1E of the Mayo Imaging Classification). Classes 1C, 1D, and 1E represent 30% to 40% of the diagnosed ADPKD population who can be identified by imaging measures of kidney size (2, 3). In the United States of America (USA), the diagnosed patient population is estimated to be between 1 in 2500 to 1 in 3000 or roughly 120 000 people which qualifies for an orphan designation (prevalence of less than 200 000). In the European Union (EU), the population is estimated to be approximately 170 000 people or 4.7 in 10 000 people. This is below the EU ceiling for orphan designation 5 in 10 000 (1).

Tolvaptan is approved in Japan, EU, USA, and Canada to slow the progression of cyst development and renal insufficiency. The liver toxicity led to the requirement in the EU for a risk management plan which includes 18 months of monthly monitoring of the liver function (4). Tolvaptan safety (risk of idiosyncratic liver toxicity) and tolerability (eg, thirst, polyuria, and nocturia in ~55%, 38%, and 29% of patients, respectively) make it a suboptimal chronic treatment. In clinical studies, treatment discontinuation rates were 23% for tolvaptan and 14% for placebo, primarily due to AEs.

[redacted]

2.2.3 Autosomal dominant polycystic kidney disease and venglustat

Human and murine ADPKD is associated with increased GCS activity, leading to a pathogenic accumulation of GSLs such as GL-1, lactosylceramide (GL-2), and GM3 (8, 9). Several structurally distinct GCS inhibitors have significantly reduced cyst growth and preserved renal function in 3 different preclinical ADPKD models: the orthologous model with conditionally inactivated PKD1 gene (aggressive course of ADPKD), the jck mouse model (moderately progressive phenocopy of human disease), and the pcy mouse model (slowly progressive disease) (10) (and unpublished data). Efficacy is consistently observed when kidney GL-1 lowering exceeds 70% (10). Kidney and serum GL-1 lowering is well-correlated in the mouse, suggesting that either can be used as a PD marker.

Efficacy of venglustat has been confirmed in the jck mouse model of ADPKD [redacted] Treatment with venglustat (and the related molecule, Genz-667161) significantly reduced cystogenesis, as demonstrated by the decreased kidney to body weight ratio and cyst volume. Reduced blood urea nitrogen measurements suggest preserved kidney function, since the experiment was not sufficiently powered to achieve statistical significance for this disease parameter. Kidney and serum GL-1 measurements show a strong correspondence between serum and kidney GL-1 lowering.

[redacted]

2.2.4 Clinical trials of venglustat in humans

The clinical program for venglustat includes 4 completed Phase 1 studies in adult healthy volunteer participants and 2 completed studies in participants with FD, 1 ongoing study in participants with GD3, 1 ongoing study in participants with GBA-PD, and 1 ongoing study in participants with late-onset GM2 gangliosidosis. Doses administered refer to the malate salt of the compound for the Phase 1 studies and to the active moiety for the Phase 2 study.

Completed studies of venglustat include the following:

- TDU12766 was a Phase 1, double-blind, randomized, placebo-controlled, sequential, ascending single oral dose study designed to assess the tolerability, safety, and pharmacokinetics (PK) of venglustat in healthy adult male participants.
- TDR12768 was a Phase 1, double-blind, randomized, placebo-controlled, sequential, ascending repeated oral dose study in healthy male and female participants. It was designed to assess the tolerability, safety, PK, and PD of 14-day ascending, repeated, oral doses of venglustat.
- FED12767 was a Phase 1, open-label, randomized, 2-sequence, 2-treatment crossover study designed to obtain information on the effect of a high fat meal on the PK of venglustat in healthy adult male participants. Additional objectives for Study FED12767 included assessing the tolerability and safety of venglustat after single oral doses in both fed and fasted conditions.
- ACT13739 was a Phase 2, multicenter, open-label, single-arm uncontrolled, once daily (QD), repeat-dose, 26-week clinical study. The study was designed to evaluate the safety, PD, PK, and exploratory efficacy of venglustat in enzyme replacement therapy treatment-naïve adult male participants with FD.
- LTS14116 was an open-label Phase 2 extension study that assessed the long-term safety, PD, and exploratory efficacy of venglustat in FD participants who completed the ACT13739 study.
- INT14339 was a Phase 1, single-center, open-label, 2-period single-sequence, non-randomized, drug-drug interaction study to assess the effect of multiple doses of the potent cytochrome P450 3A4 (CYP3A4) inhibitor itraconazole 100 mg capsule twice daily on the PK of single dose venglustat under fed conditions with washout duration of exactly 7 days between treatment periods.
- POP14499 was a Phase 1, single-center, open-label, single dose study in participants with mild, moderate and severe renal impairment, and in matched participants with normal renal function, to study the effect of renal impairment on venglustat PK and tolerability following a single dose of 15 mg venglustat given under fasted conditions on Day 1 of a 10-day PK sampling and observation period.
- ACC15856 was a palatability study in 12 healthy volunteers who tested the organoleptic characteristics of 5 different chewable tablet formulations of venglustat (different percentages of apricot flavor and sucralose as sweetener) compared with a reference formulation (without flavor or sweetener).

In completed clinical studies in healthy participants, venglustat was observed to be safe and well-tolerated. Overall, the AE profile of participants in the venglustat dosing groups was similar to that observed in the placebo groups.

PDY13949 is an ongoing 3-part study with: Part 1 evaluating biomarkers in GD1 and GD3, Part 2 for obtaining treatment efficacy first in an open-label setting followed by cohort expansion in a randomized, placebo-controlled manner in adult and pediatric participants with GD3 and finally Part 3 which is an open-label long-term treatment for Part 2 participants.

ACT14820 is an ongoing double-blind, randomized, placebo-controlled Phase 2 study to assess the efficacy, safety, PK, and PD of QD dosing of venglustat in participants with GBA-PD. Part 1 of the study will last up to 9 months, and Part 2 will last up to approximately 3 years.

EFC15299 is an ongoing multicenter, multinational, randomized, double-blind, placebo-controlled, 110 weeks Phase 3 study to assess the efficacy, PD, PK, safety, and tolerability of QD dosing of venglustat in late-onset GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease) together with a separate basket for juvenile/adolescent late-onset GM2 gangliosidosis and ultra‑rare diseases within the same and similar glucosylceramide-based sphingolipid pathway.

EFC15392 is a seamless Phase 2/3 multicenter, randomized, double-blind, placebo-controlled 2-stage study to characterize the efficacy, safety, tolerability and PK of venglustat in adult male and female participants at risk of rapidly progressive ADPKD. Two-stage study is as follows:

- Stage 1 (24 months of treatment): Randomized, double-blind, placebo-controlled, 3-arm study with primary objective to determine the effect of venglustat on the rate of TKV growth as compared to placebo in participants with eGFR between 45 and 89.9 mL/min/1.73 m^2 who are at risk of rapidly progressive ADPKD.
- Stage 2 (24 months of treatment): Randomized, double-blind, placebo-controlled, 2-arm study, with primary objective to determine the effect of venglustat on rate of renal function (eGFR) decline as compared to placebo in participants with eGFR between 30 and 89.9 mL/min/1.73 m^2 who are at risk of rapidly progressive ADPKD.

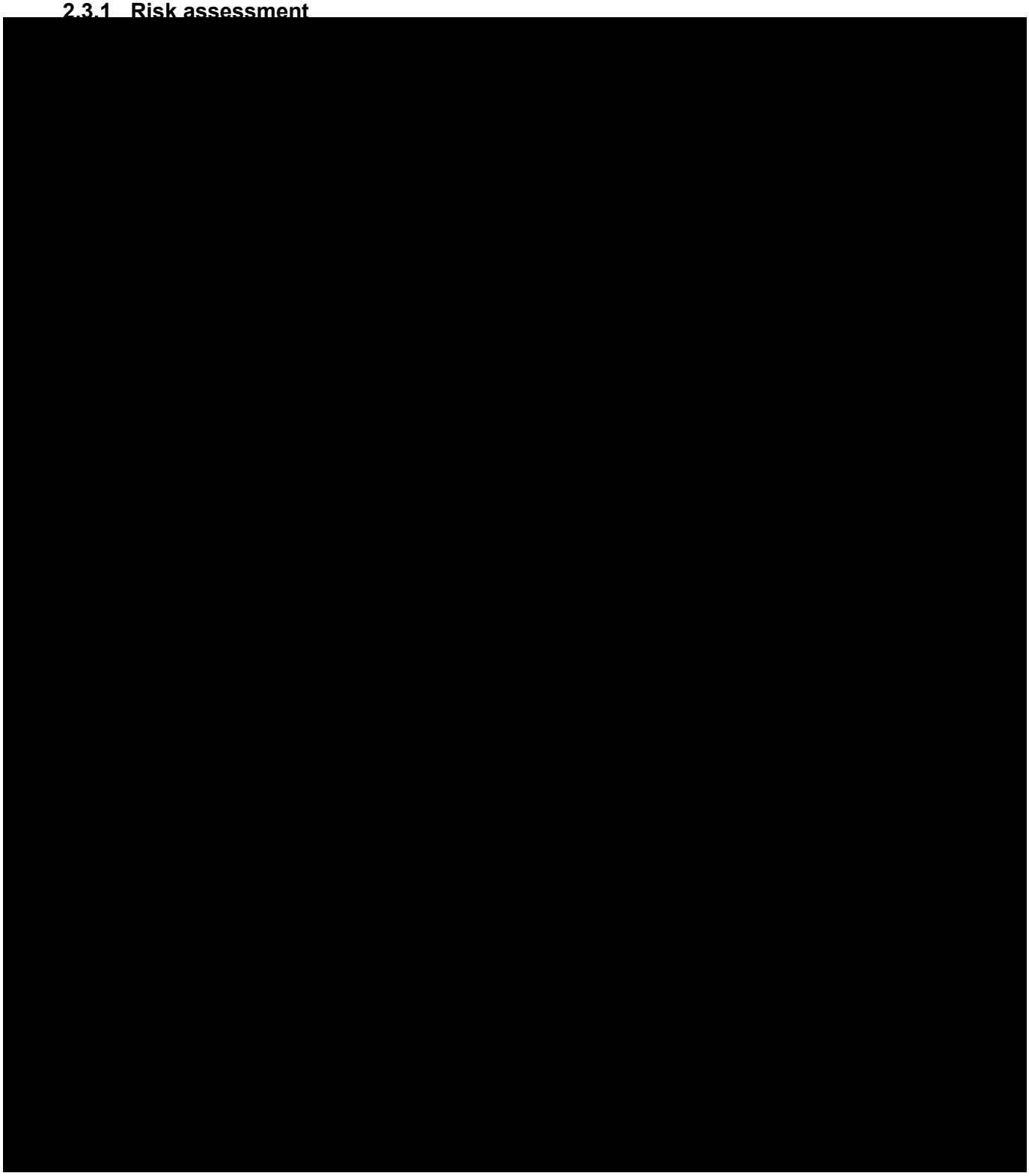
The seamless design of this 2-stage study is based on the similarities of the endpoints of the 2 stages and overlapping but not identical inclusion/exclusion criteria of the 2 stages.

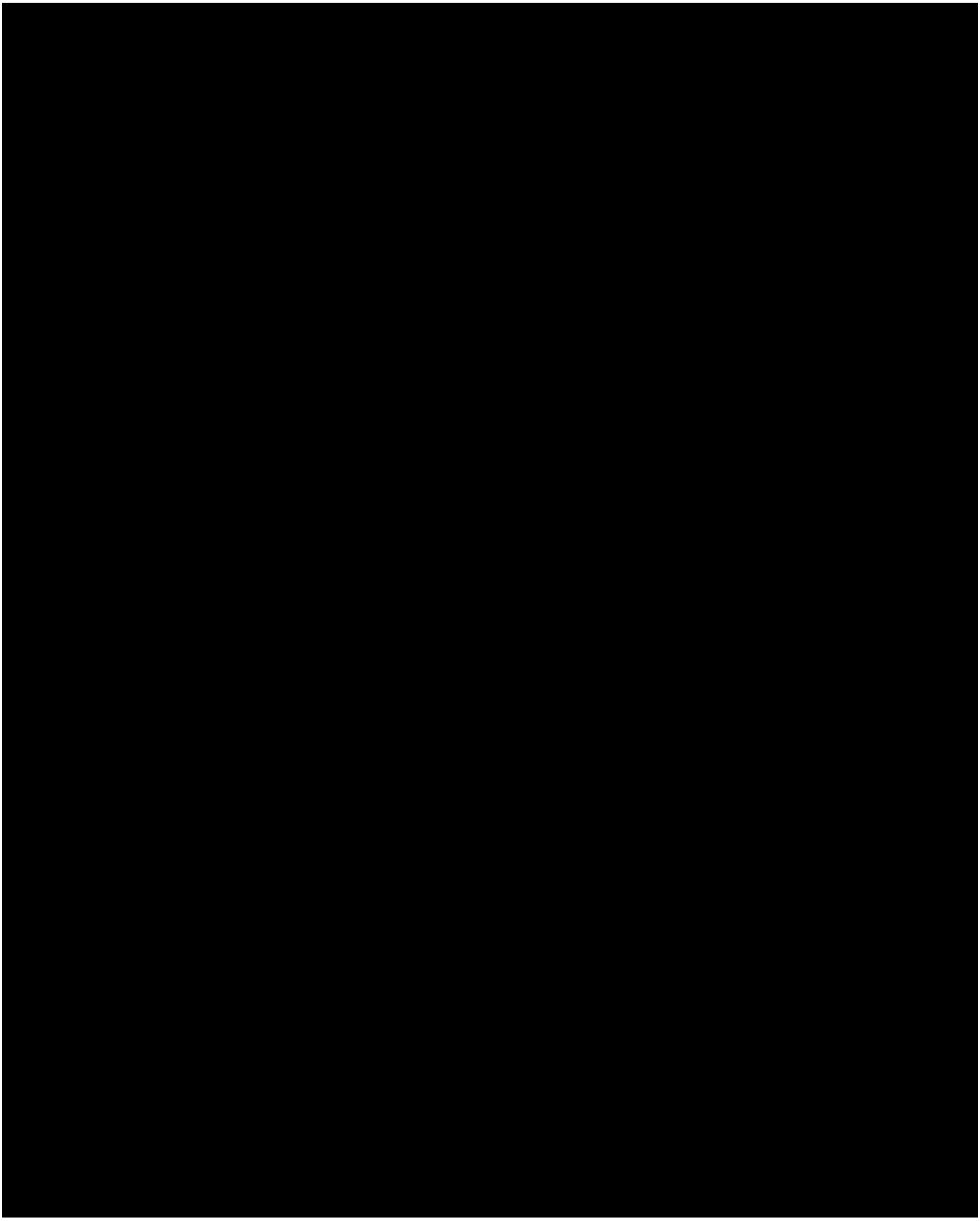
More information on the safety of venglustat and on the clinical program can be found in the Investigator's Brochure (IB).

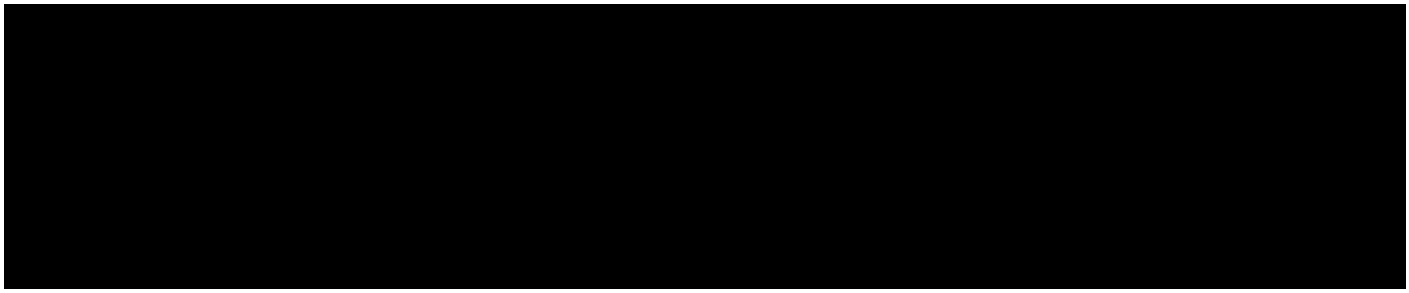
2.3 BENEFIT/RISK ASSESSMENT

[redacted]

2.3.1 Risk assessment







3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the effect of early versus delayed treatment with venglustat on the total kidney volume (TKV) in participants at risk of rapidly progressive ADPKD.	• Percent change in TKV based on magnetic resonance imaging (MRI) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.
Secondary	
• To determine the effect of early versus delayed treatment with venglustat on the renal function (estimated glomerular filtration rate [eGFR]).	• Change in eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.
• To characterize the safety profile of venglustat.	• Safety in terms of treatment-emergent adverse events (TEAEs), adverse events (AEs), serious adverse events (SAEs), laboratory parameters, vital signs, electrocardiogram and findings from physical examination will be assessed through the study and will be reported in the electronic case report form (eCRF).
• To evaluate the effect of venglustat on the lens by ophthalmological examination.	• Change from EFC15392 study baseline in the lens clarity by ophthalmological examination during the open-label extension treatment-emergent period.
• To evaluate the effect of venglustat on mood using Beck Depression Inventory-II (BDI-II).	• Change from EFC15392 study baseline in BDI-II score during the open-label extension treatment-emergent period.
Tertiary	
• To explore the impact of venglustat on total liver volume (TLV) (in participants with height-adjusted TLV [htTLV] >2 L/m).	• Change in TLV based on MRI (in participants with htTLV >2 L/m) from EFC15392 study baseline to 24 months of the open-label extension study.
• To explore the effect of venglustat on systolic blood pressure (SBP) and diastolic blood pressure (DBP).	• Change from EFC15392 study baseline during the open-label extension treatment-emergent period in: - SBP, - DBP.
• To explore the effect of venglustat on type, frequency and dosage of analgesic/over the counter (OTC) pain medication administration.	• Change from EFC15392 study baseline in type, frequency, and dosage of analgesic/OTC pain medication administration during the open-label extension study.

Objectives	Endpoints
• To explore the effect of venglustat on time to confirmed 30% and 40% reduction in eGFR.	• Time to confirmed 30% reduction in eGFR since randomization in the EFC15392 study, in early-treated compared to late-treated participants during the combined EFC15392 and LTS15823 period. • Time to confirmed 40% reduction in eGFR since randomization in the EFC15392 study, in early-treated compared to late-treated participants during the combined EFC15392 and LTS15823 period.
• To explore the effect of venglustat on biomarkers associated with ADPKD (eg, Fibroblast Growth Factor 23 [FGF23], asymmetric dimethylarginine [ADMA]) (not applicable for Chinese participants).	• Change in the levels of biomarkers associated with ADPKD (eg, FGF23, ADMA) from EFC15392 study baseline to 24 months of open-label extension study (not applicable for Chinese participants).
• To explore the pharmacodynamic (PD) effects of venglustat by measuring downstream metabolites of glucosylceramide synthase (GCS) in plasma (not applicable for Chinese participants).	• Change in the levels of downstream metabolites of GCS in plasma from EFC15392 study baseline to 24 months of open-label extension study (not applicable for Chinese participants).
• To explore the effect of venglustat on pain (brief pain inventory short form [BPI-SF]), fatigue (Brief Fatigue Inventory [BFI]), and the EuroQoL 5 dimension 5 level (EQ-5D-5L) score.	• Change from EFC15392 study baseline to 24 months of open-label extension study in: - BPI-SF, - BFI, - EQ-5D-5L.

3.1 APPROPRIATENESS OF MEASUREMENTS

For details please refer to Section 2.1, Section 2.2, and Section 4.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This will be an international, multicenter, open-label extension study rolling over adult participants at risk of rapidly progressive ADPKD who have previously completed Stage 1 or Stage 2 of Study EFC15392. All participants will be treated with venglustat 15 mg once daily for 24 months or until venglustat is commercially available for patients, whichever comes first. See Appendix 8 (Section 10.8) for definition applicable for patients participating in Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, and Spain (Section 10.8.2).

Duration of study: 25.5 months at the maximum. Screening period (when applicable): up to 2 weeks. Core treatment period: 24 months. Follow-up: 30 days after final dose of the IMP (venglustat).

Enrollment in the LTS15823 study must coincide with Visit 12 (Month 24; end-of-treatment visit) of the EFC15392 study. Patients who cannot be included in the extension study at the time of Visit 12 for administrative or logistical reasons, and provided they agree to participate in the LTS15823 study, will have a separate Screening visit (Visit 0) performed and must be enrolled in the LTS15823 study within 2 months of the last dose of IMP (Visit 12 [Month 24]) administered in the EFC15392 study. This 2-month window can be further extended up to 6 months following review and approval by the Sponsor.

Dose regimen: 15 mg orally once daily of venglustat.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is an international, multicenter, open-label extension study rolling over adult participants at risk of rapidly progressive ADPKD who have previously completed Stage 1 or Stage 2 of Study EFC15392. The purpose of the study is to obtain long-term efficacy and safety data, up to 4 years, with venglustat administration. Long-term efficacy will focus on patients treated early with venglustat (patients having received venglustat in Stage 1 or Stage 2 of the EFC15392 study) versus patients with delayed treatment (patients having received placebo in Stage 1 or Stage 2 of the EFC15392 study). The objective of the study is to demonstrate that patients treated early have a better long-term efficacy than patients treated with delay by evaluating the effect of early versus delayed treatment with venglustat on the TKV (primary objective) and on the rate of eGFR decline (secondary objective). In addition, patients previously treated with placebo will get the opportunity to benefit from venglustat treatment in this open label extension study.

4.2.1 Participant input into design

Not applicable.

4.3 JUSTIFICATION FOR DOSE

The 8 mg and 15 mg QD doses of venglustat resulted in about 70% and 75% reduction in plasma GL-1 from baseline, respectively, in the healthy volunteers (repeated dose study, TDR12768). This is in the similar range of plasma GL-1 reduction where efficacy was demonstrated in the nonclinical disease animal model of ADPKD by oral treatment of GCS inhibitors (Section 2.2.3). Therefore, 8 mg and 15 mg QD doses of venglustat in ADPKD patients anticipated to translate into ADPKD efficacy were selected for Stage 1 of the EFC15392 study.

All participants in the LTS15823 study will be treated with venglustat 15 mg once daily. The 15 mg dose was the highest dose determined to be safe and well-tolerated following review by the Data Monitoring Committee (DMC) of unblinded aggregate safety data from 150 participants who had completed at least 1 month of treatment (8 mg or 15 mg) in Stage 1 of the EFC15392 study. The 15 mg dose was the dose selected for Stage 2 of Study EFC15392. This dose selection process was specified in the EFC15392 protocol.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the trial globally.

A participant is considered to have completed the study if he/she has completed 24 months of the treatment in the study including the Month 25 visit.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of participant and disease characteristics

I 01. Male or female adult with ADPKD who has completed the treatment period in Stage 1 or Stage 2 of Study EFC15392*.

* Eligible patients who agreed to participate in the long-term extension study must be enrolled in the LTS15823 study at the time of Visit 12 (Month 24; end-of treatment visit) of the EFC15392 study. Patients who cannot be included in the extension study at the time of the end-of-treatment visit of the EFC15392 study for administrative or logistical reasons will have a separate Screening visit (Visit 0) of LTS15823 study performed and must be enrolled in the LTS15823 study within 2 months of the last dose of IMP (Visit 12 [Month 24]) in the EFC15392 study. This 2-month window can be further extended up to 6 months following review and approval by the Sponsor.

I 02. The patient has an eGFR >30 mL/min/1.73 m^2:

- That was measured at Visit 11 of the EFC15392 study for participant enrolled in the LTS15823 study at the time of Visit 12 (Month 24; end-of treatment visit) of the EFC15392 study.
- At Screening visit ** for participant enrolled in the LTS15823 study not concomitantly to the Visit 12 (Month 24; end-of treatment visit) of the EFC15392 study.

  **If necessary, a second pretreatment eGFR value can be obtained for confirmation of eligibility to account for potential eGFR variability.

Sex, contraceptive/barrier method and pregnancy testing requirements

I 03. All

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

- Male participants must agree to practice true abstinence in line with their preferred and usual lifestyle or to use double-contraceptive methods (see contraceptive guidance in Appendix 4 [Section 10.4.2]) for the entire duration of the study and for at least 90 days following their last dose of IMP.

b) Female participants

- The participant, if female of childbearing potential, must have a negative urine pregnancy test at the Baseline visit.
- Female participants of childbearing potential must agree to practice true abstinence in line with their preferred and usual lifestyle or to use double-contraceptive methods (including a highly effective method of contraception) for the entire duration of the study and for at least 6 weeks following their last dose of IMP (see contraceptive guidance in Appendix 4 [Section 10.4.2]).

Informed Consent

I 04. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1) of the protocol before performance of any study related procedures not part of standard medical care which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other inclusions

I 05. Able to read, comprehend, and respond to the study questionnaires.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

For participants who have lag phase between the end of the EFC15392 study and Screening visit (Visit 0) in the LTS15823 study:

Medical conditions

E 01. The patient has a new clinically significant, uncontrolled medical condition that, in the opinion of the Investigator, would put the safety of the patient at risk through participation, or which would affect the efficacy or safety analysis if the condition exacerbated during the study, or that may significantly interfere with study compliance, including all prescribed evaluations and follow-up activities. The list of medical conditions that should be taken into account includes, but is not limited to the following:

Congestive heart failure New York Heart Association (NYHA) Grade III/IV	Clinically significant cardiac arrhythmia
Severe unstable angina pectoris within 6 months of Visit 0	Hypertensive emergency[a] within 6 months of Visit 0
Stroke or transient ischemic attack within 3 months of Visit 0	Current malignancy[b]
Myocardial infarction within 3 months of Visit 0	Current tuberculosis
Cushing's disease	Uncontrolled diabetes mellitus
Addison's disease	Uncontrolled thyroid disorder

a Systolic blood pressure (SBP) >180 mm Hg or diastolic blood pressure (DBP) >120 mm Hg, and acute target organ damage (11).
b Localized basal cell or squamous cell carcinoma of the skin that has been resected is not exclusionary.

E 02. A history of drug abuse and/or alcohol abuse or alcohol dependence during the lag phase between the end of the EFC15392 study and Screening visit (Visit 0) in the LTS15823 study when applicable.

Prior/concomitant therapy

E 03. Administration of tolvaptan or other polycystic kidney disease-modifying agents (somatostatin analogues) within 3 months prior to the Screening visit (Visit 0) in the LTS15823 study when applicable.

E 04. The patient is currently receiving potentially cataractogenic medications, including a chronic regimen (more frequently than every 2 weeks) of any route of corticosteroids (including medium and high potency topical steroids), or any medication that may cause cataract, according to the Prescribing Information.

E 05. The patient has received strong or moderate inducers or inhibitors of CYP3A4 within 14 days or 5 half-lives, whichever is longer, prior to the Baseline visit. This also includes the consumption of grapefruit, grapefruit juice, or grapefruit-containing products within 72 hours of starting venglustat administration.

Prior/concurrent clinical study experience

E 06. Participation in another investigational interventional study or use of IMP, within 3 months or 5 half-lives, whichever is longer, before the Baseline visit (Visit 1) except participation in the EFC15392 study when applicable.

Diagnostic assessments

E 07. Liver enzymes (alanine aminotransferase /aspartate aminotransferase) or total bilirubin >2 times the upper limit of normal (ULN) unless the patient has the diagnosis of Gilbert syndrome. Patients with the Gilbert syndrome should have no additional symptoms or signs which suggest hepatobiliary disease and serum total bilirubin level no more than 3 mg/dL (51 µmol/L) with conjugated bilirubin less than 20% of the total bilirubin fraction.

Other exclusions

E 08. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized. See Appendix 8 (Section 10.8) for any country-related specific regulation that would prevent the patient from entering the study.

E 09. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

For participants with or without lag phase between the end of EFC15392 study and entry into LTS15823 study:

Medical conditions

E 10. The patient is pregnant or lactating.

E 11. Presence of severe depression as measured by Beck Depression Inventory II (BDI-II) >28 at Visit 1 (for participants enrolled in the LTS15823 study at the time of the end-of-treatment visit of the EFC15392 study) or at Visit 0 (for participants enrolled in the LTS15823 study after the end-of-treatment visit of the EFC15392 study).

Other exclusions

E 12. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the International Council for Harmonisation Good Clinical Practice (ICH-GCP) Ordinance E6).

E 13. Any specific situation during study implementation/course that may raise ethics considerations.

E 14. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

1. Refrain from consumption of grapefruit, grapefruit juice or grapefruit-containing products from 3 days before the start of study intervention until after the final dose.
2. Blood samples (biochemistry, blood glucose, biomarkers, etc) will be collected at the beginning of the visit in fasted conditions (fast overnight [eat nothing and drink only water] for at least 8 hours before blood samples are taken).
3. Over-the-counter dietary supplements (eg, herbal remedies) or prescriptions, are permitted during the study period. The Investigator should consider substituting medications that have cataractogenic potential according to their Prescribing Information for noncataractogenic treatments, as appropriate.

5.3.2 Caffeine, alcohol, and tobacco

No specific restrictions are required.

5.3.3 Activity

No specific restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Participant number will remain the same for rescreened participants for every screening/rescreening event.

Rescreening is possible for participants who have lag phase between the end of the EFC15392 study and the Screening visit (Visit 0) in the LTS15823 study, in cases where the original screening failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment. The patient may be rescreened once, after consultation with the Sponsor, while the screening period is still open if a participant failed for reasons of a nonpermanent medical condition, such as an acute disease or an event that could be corrected or resolved in an acceptable timeframe.

If a patient had screen-failed during a regional or national emergency for reasons not related to eligibility, rescreening shall be permitted when the situation normalizes (provided the rescreening will be still within 6 months of the last dose of IMP (Visit 12 [Month 24]) administered in the EFC15392 study and after consultation with the Sponsor).

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT OR ADMINISTRATION OF STUDY INTERVENTION ADMINISTRATION

During a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, if the site is unable to adequately follow protocol mandated procedures, contingency measures should be considered for enrollment or administration of study treatment. Contingency measures proposed in Appendix 9 (Section 10.9) should be considered for enrollment or administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Study intervention(s)

Investigational medicinal product(s)

- Formulation: venglustat is provided in capsule formulation containing 15 mg of venglustat (active moiety). Venglustat is not approved in any territory.
- Route(s) of administration: oral.
- Dose regimen: 15 mg once daily.

Table 3 - Overview of study interventions administered

Intervention label	GZ402671 or SAR402671
Intervention name	Venglustat
Type	Drug
Dose formulation	Capsule
Unit dose strength(s)	15 mg
Dosage level(s)	15 mg once daily
Route of administration	Oral
Use	Experimental
IMP or NIMP	IMP
Packaging and labeling	Venglustat will be packaged in blister packs. Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with Good Manufacturing Practices (GMP) requirements and the local regulatory specifications and requirements.
Current/Former name(s) or alias(es)	Not applicable

Table 4 - Arms and associated interventions

Arm name	Venglustat
Associated interventions (intervention label)	Venglustat

Venglustat may be supplied at the site or from the Principal Investigator (PI)/site to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9).

6.1.1 Devices

Not applicable.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.9).

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 the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to participant (DTP) shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a single-arm open-label study; therefore this section is not applicable.

6.4 STUDY INTERVENTION COMPLIANCE

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules, etc during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of venglustat capsules dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5 DOSE MODIFICATION

Not applicable.

6.5.1 Retreatment criteria

Temporary treatment discontinuation because of suspected AEs may be considered by the Investigator. 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 participant is not affected, and if the selection criteria for the study are still met (refer to Section 5), treatment with the IMP may be re-initiated. For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the electronic case report form (eCRF).

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Continued access to the study intervention after the end of the study will be handled according to the local regulations.

6.7 TREATMENT OF OVERDOSE

For this study, any dose of venglustat greater than 15 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should do the following:

1. Contact the Sponsor immediately.
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities until venglustat can no longer be detected systemically (at least 6 days).
4. Document appropriately in the eCRF.

6.8 CONCOMITANT THERAPY

A concomitant medication is any treatment received by the participant concomitantly to the IMP.

Concomitant medications should be kept to a minimum during the study. Furthermore, changes in concomitant medications should be kept to a minimum and only occur if considered to be absolutely necessary in the medical judgment of the Investigator. However, if these are considered necessary for the participant's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator and must be recorded in the eCRF.

Concomitant medications, including over-the-counter dietary supplements (eg, herbal remedies) or prescriptions, are permitted during the study period, except for tolvaptan use which is forbidden throughout the study and the medications listed in the following section.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1 List of forbidden concomitant medication

During the study treatment periods, the following medications are prohibited:

- Use of investigational medication in any other clinical study.
- Chronic use of strong or moderate CYP3A inducers or inhibitors.
- Tolvaptan.
- Polycystic Kidney Disease-modifying agents (eg, somatostatin analogues).
- Alpha-adrenergic receptor agonist glaucoma medications because they can worsen the vision of participants with cataracts.

Venglustat interruptions are permitted for those participants who require temporary use (≤2 weeks) of strong or moderate inhibitors or inducers of CYP3A (per the United States Food and Drug Administration [FDA] classification) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling**)** for the treatment of acute illness. Such medications must not be used on more than a total of 2 occasions (ie, up to 2 weeks per occasion for a maximum of 30 days of venglustat interruptions) during the study treatment periods.

Given nonclinical lens findings (see IB), a chronic regimen (ie, more frequent than once every 2 weeks) of the following medications is forbidden during the clinical trial:

- Corticosteroids:
  - May be used on a restricted basis in participants who require temporary use (≤1 week) for the treatment of any acute condition for which no appropriate substitute is found. Such medications must not be used on more than a total of 4 occasions (ie, up to 1 week per occasion) during the study treatment periods.
  - Participants with chronic skin diseases can use low and least potent (Class VI to VII) topical steroids. Application to eyelids and periorbital region should be avoided.
- Psoralens used in dermatology with ultraviolet light therapy.

- Typical antipsychotics.
- Amiodarone.
- Allopurinol.

The Investigator should consider substituting medications listed in the previous paragraphs and medications that have cataractogenic potential according to their Prescribing Information for noncataractogenic treatments, as appropriate.

Atypical antipsychotics are allowed.

Other medications which are unlikely to interfere with the PK or PD of the IMP or confound interpretation of the study endpoints are allowed as needed and discussed with the Investigator. However, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

6.8.2 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention.

Definitive (permanent) intervention discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP, whatever the reason.

The participants who develop loss of 3 or more lines of BCVA in either eye due to posterior subcapsular cataract could be discontinued from study treatment if recommended by the DMC (if DMC will decide that benefit/risk ratio is not favorable for this participant).

If a participant experiences a 50% reduction in eGFR compared to the screening value on at least 2 occasions separated by a period of at least 30 days during the course of this trial, the participant will stop the treatment and alternative therapy will have to be discussed by the Investigator.

If a participant experiences a reduction in eGFR below 30 mL/min/1.73 m^2 at on 2 occasions separated by a period of 3 months during the course of this study, the participant will be discontinued from the study.

If a participant experiences a reduction in eGFR below 25 mL/min/1.73 m^2, a repeated test must be performed in 30 days. If eGFR result repeated in 30 days is below 30 mL/min/1.73 m^2, the participant will be discontinued from the study.

The following may be justifiable reasons for the Investigator or Sponsor to discontinue a participant from treatment.

Participant specific:

- The participant experiences 2 similar SAEs or 1 life-threatening SAE (assessed as related by the Investigator and/or the Sponsor).
- The participant meets criteria for Hy's law (confirmed alanine aminotransferase ALT >5 × ULN range or confirmed ALT >3 × ULN and bilirubin >2 × ULN).
- The participant becomes pregnant (see Appendix 4 [Section 10.4] and Section 8.3.5).

Trial specific:

- Any AEs, per Investigator judgment, that may jeopardize the participant's safety.
- Any use of prohibited concomitant treatment (see Section 6.8.1).
- At participant’s request, ie, withdrawal of the consent for intervention.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (after 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned participant.

See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Handling of participants after permanent intervention discontinuation

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

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

Participants who prematurely and permanently discontinue IMP should complete rapidly (within 7 days) an end-of-treatment (EOT) assessment visit without MRI.

Investigator should ask participant who prematurely and permanently discontinued IMP to continue study visits for safety and efficacy assessments up to and including the last scheduled visit, if possible.

If the participant refuses to attend all scheduled visits, the Investigator should ask the participant to return to the site at 24 months (to have at least an MRI and blood sample for eGFR evaluation, as well as safety assessments performed).

Participants who withdraw from the study due to pregnancy should be followed-up throughout the pregnancy up to approximately 6 to 8 weeks beyond the estimated delivery date so that the outcome of the pregnancy is determined. Additional follow-up information may be requested about the baby until at least 1 year after the birth of the baby, due to potential risk of abnormalities not present at birth. See Appendix 4 for guidance.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm in Appendix 6 (Section 10.6) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the participant.

7.1.5 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned AE was unlikely and if the selection criteria for the study are still met (refer to Section 5).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

7.1.5.1 Study intervention restart or rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit (with procedures identical to EOT visit without MRI) should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost-to-follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost-to-follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All eligibility evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- For participants enrolled in the LTS15823 study at Visit 12 (Month 24; end-of-treatment visit) of the EFC15392 study, the maximum amount of blood collected from each participant at scheduled visits over the duration of the study will not exceed 76 mL (samples collected at Baseline visit/Visit 1 of the LTS15823 study will be collected as part of the Visit 12 [Month 24] of the EFC15392 study as described in Section 1.3.1.
- For participants with the lag phase between end-of-treatment in the EFC15392 study and the start of the LTS15823 study (when patient will have a separate Screening visit (Visit 0) as described in Section 1.3.2), the maximum amount of blood collected from each participant at scheduled visits over the duration of the study will not exceed 109 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

8.1 EFFICACY ASSESSMENTS

Planned time points for all efficacy assessments are provided in the SoA.

8.1.1 Magnetic resonance imaging

Magnetic resonance imaging will be performed at certified facilities and liver and kidney volumes calculated according to a separate protocol. Images will be reviewed/assessed by a central reader.

8.1.2 Estimated glomerular filtration rate

Estimated glomerular filtration rate will be calculated from the creatinine result from the general chemistry laboratory assessments according to the SoA (Section 1.3). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will be used:

$$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if Black)}$$

Where:

- SCr is serum creatinine in mg/dL.
- κ is 0.7 for females and 0.9 for males.
- α is -0.329 for females and -0.411 for males.
- Min indicates the minimum of SCr/κ or 1, and
- Max indicates the maximum of SCr/κ or 1.
- For calculation of eGFR in Asian population of participants (except Japanese participants), the Asian-modified CKD-EPI (aCKD-EPI) equation will be used (12):

$$\text{Female and SCr} \leq 0.7\text{: } 151 \times (SCr / 0.7)^{-0.328} \times (0.993)^{age}$$
$$\text{Female and SCr} > 0.7\text{: } 151 \times (SCr / 0.7)^{-1.210} \times (0.993)^{age}$$
$$\text{Male and SCr} \leq 0.9\text{: } 149 \times (SCr / 0.9)^{-0.412} \times (0.993)^{age}$$
$$\text{Male and SCr} > 0.9\text{: } 149 \times (SCr / 0.9)^{-1.210} \times (0.993)^{age}$$

- For calculation of eGFR in Japanese participants, CKD-EPI Study equation multiplied by a Japanese coefficient of 0.813 will be used (13).

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

Whenever possible, the same physician or appropriately trained member of the site study team (in countries/states which permit nurse practitioners or physician assistants to perform physical examinations under the supervision of a physician) should perform the physical examination at all study visits. The findings of each examination will be recorded.

- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, musculo/skeletal, and neurological systems. Height and weight will also be measured and recorded.
- A full standard basic neurological examination will be performed as part of the complete physical examination. Results will be documented in the eCRF pages dedicated to neurological examination. For details, please refer to the Study Reference Manual.
- A mental status evaluation will be performed as part of the complete physical examination and should include a Mini Mental State Examination (MMSE) or an equivalent local

standard method for assessment of the cognitive state of a participant, provided the method covers all the areas assessed by MMSE.

- Height measured in the EFC15392 study will be recorded only at first visit (Visit 1/Visit 0). Weight will be measured and recorded at time points provided in the SoA.
- Abbreviated physical examinations will focus on areas important for assessment of AEs if necessary.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

- Oral or tympanic temperature [°C], pulse rate, respiratory rate, and blood pressure will be assessed.
- Heart rate, SBP and DBP will be recorded after 10 minutes in the sitting position. The arm with the higher pressure at the initial Screening visit should be used for all subsequent BP measurements (14). Blood pressure will be measured under standardized conditions using the same method for a given participant. It will be determined at each study visit using a well calibrated apparatus.
- For all seated BP measurements, 3 separate measurements should be taken with at least 1 minute between readings, following at least 10-minute rest period and prior to phlebotomy.
- If there is a difference of more than 10 mm Hg (systolic) between the second and third readings in one sitting, a fourth and fifth reading will be recorded for that sitting.

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.3 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- ECG recordings should be performed before blood samplings. The ECG will be evaluated as “normal” or “abnormal”.
- All ECG recordings will be centrally read by independent experts. Refer to central ECG reading manual for more details.

8.2.4 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 half-lives after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Pregnancy testing

- Refer to Section 5.1 for pregnancy testing entry criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the intervals specified in the SoA.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.2.6 Suicidal ideation and behavior risk monitoring

Venglustat is considered to be CNS-active. In addition, there has been an isolated report of suicidal ideation/behavior as reported in the IB in participant with FD with depressed mood receiving venglustat. The Sponsor considers important to monitor for such events before and during this clinical study.

Participants being treated with venglustat should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should

be given to discontinuing venglustat in participants who experience signs of suicidal ideation or behavior.

Families and caregivers of participants being treated with venglustat should be instructed to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the study Investigator.

Participants will be screened during planned interactive visits utilizing the Beck Depression Inventory-II (BDI-II) to assess for evidence of evolved depression.

8.2.6.1 Beck Depression Inventory, second edition

Depression will be monitored during the study by using the BDI-II according to the SoA (see Section 1.3). Beck Depression Inventory-II (Appendix 10 [Section 10.10]) is a 21-question, multiple choice, self-report inventory. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and disinterest in sex.

The wording of the BDI-II is clear and concise. The test contains 21 items, most of which assess depressive symptoms on a Likert scale of 0 to 3. The 2 exceptions to this are Questions 16 and 18. Question 16 addresses changes in sleeping pattern, while Question 18 addresses changes in appetite. Participants will be asked to report their own feelings over the past 2 weeks instead of 1 week, as in the BDI and BDI-IA. The reason for this is to be consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for depression. There were also 2 items added to indicate any directional changes in eating and sleeping patterns. Finally, all forms of the inventory are written at the 5th grade reading level.

Clinical interpretation of scores is accomplished through criterion-referenced procedures utilizing the following interpretive ranges: total BDI-II scores of 0 to 13 indicate minimal depression, scores of 14 to 19 indicate mild depression, scores of 20 to 28 indicate moderate depression, and scores of 29 to 63 indicate severe depression.

Whenever possible, the BDI-II should be done prior to clinical interaction with the Investigator. At Visit 1 (Section 1.3.1) or Visit 0 (Section 1.3.2), participants with BDI-II of 20 to 28, inclusive, should be evaluated by a mental health specialist before the Investigator can determine if the participant would be able to fully participate in the trial. Participants with a BDI-II of >28 (severe depression) at Visit 1 (Section 1.3.1) or Visit 0 (Section 1.3.2) will be excluded.

If a participant has a score of ≥20 during the study, the participant must be referred to his or her health care professional for psychiatric evaluation. If the participant has any score but picks out Statement 2 or 3 for Question 9, the local suicide assessment and management protocol must be followed, and participant must be supervised until appropriate mental health personnel is available. This will be captured as an AE. The participant may continue on the study, but this is dependent on the outcome of psychiatric evaluation and judgment of the PI.

8.2.7 Ophthalmological examination

The effect of venglustat on the lens will be closely monitored throughout the study. The full ophthalmological examination will include BCVA using Snellen chart, and examination of the cornea, lens, and retina with slit-lamp. The examination should include pupil dilation and evaluation of the lens according to the WHO simplified cataract grading system. If a new or worsening lens abnormality is found, documentation of finding with lens photography using standard local photographic methods is recommended. For opacities present at baseline/previous visit, changes in WHO Grade ≥1.0 for nuclear, cortical, or posterior subcapsular opacification compared with baseline or previous assessment will be considered as a worsening.

In countries where the Latin alphabet is not used, the Snellen chart could be substituted with the Tumbling E distance chart based on the Snellen fraction.

For participants enrolled in LTS15823 study at Visit 12 (Month 24) of the EFC15392 study, a full ophthalmological examination will be performed prior to start of treatment (at Month 24 Visit of the EFC15392 study), at Month 12 (Visit 6), and at Month 24 (Visit 10) (or upon withdrawal or discontinuation) with pupil dilation and WHO simplified cataract grading system evaluation of lens opacities.

For participants enrolled in the LTS15823 study after the end-of-treatment visit of the EFC15392 study, a full ophthalmological examination will be performed prior to start of treatment (at Visit 0 or at Visit 1), at Month 12 (Visit 6), and at Month 24 (Visit 10) (or upon withdrawal or discontinuation) with pupil dilation and WHO simplified cataract grading system evaluation of lens opacities.

For all participants, at the visits at Month 6 (Visit 4) and Month 18 (Visit 8), only BCVA examination will be required.

If at any time during study participation the participant experiences a decrease ≥2 lines in BCVA compared to baseline or previous assessment, full ophthalmological examination with pupil dilation and WHO simplified cataract grading system evaluation should be performed. If a new or worsening lens abnormality is found, documentation of the finding with lens photography is recommended.

If participant had change in WHO Grade ≥1.0 in any of the 3 features (nuclear, cortical and posterior subcapsular opacification) of the lens, all subsequent scheduled (every 3 month) ophthalmic assessments in this participant should include pupil dilation with WHO simplified cataract grading system evaluation.

Pupil dilation and full eye examination can be performed at any time if deemed medically necessary; WHO simplified cataract grading system evaluation should be performed if a change from baseline is observed during slit-lamp examination.

The examination should be performed by the same ophthalmologist (optometrist if allowed according to local regulations) throughout the study, if possible. Abnormal findings reported by the clinical sites will be reviewed by the DMC and/or the clinical site to adjudicate these findings as AE of special interest (AESI) and assess their seriousness/severity.

8.2.8 Participant reported outcomes

Table 5 shows the concepts of measurement and their related PRO questionnaires to be used in the trial. Participant reported outcomes performed on site will be completed prior to any procedures or discussions about the treatment and disease.

Table 5 - Participant reported outcome (PRO) concepts and questionnaires

Concept	PRO questionnaire
Overall pain	BPI-SF (Appendix 11 [Section 10.11])
Overall fatigue	BFI (Appendix 12 [Section 10.12])
Health status	EQ-5D-5L (Appendix 13 [Section 10.13])

BFI = Brief Fatigue Inventory: BPI-SF = Brief Pain Inventory short-form; EQ-5D-5L = EuroQoL 5-dimension 5-level; PRO = Participant reported outcome.

Overall pain

Overall pain will be measured using the Brief Pain Inventory Short Form (BPI-SF) (15); one of the most widely used instruments for measuring pain in clinical trials (Appendix 11 [Section 10.11]). The BPI-SF comprises 15 questions related to pain severity, location, treatment and pain interference in the previous 24 hours; and 1 item asks about pain “right now”. Most items provide an 11-point numeric rating scale (NRS) to indicate severity of pain (n=4), pain interference (n=7) and treatment relief (n=1). A binary categorical response is given to a single item about pain incidence, and a body diagram is completed to indicate pain location. Scores are by items and by dimensions; the global score ranges from 0 to 10. Lower scores indicate lower pain. The BPI-SF will be administered at the Baseline and Months 1, 6, 12, 18, and 24 visits.

Overall fatigue

The Brief Fatigue Inventory (BFI) (16) has been used widely in clinical research in both drug development and observational studies (Appendix 12 [Section 10.12]). It will be used in the current study to measure overall fatigue. The BFI comprises 10 questions related to fatigue incidence in the past week (1 item; yes/no), fatigue severity (3 items; 2 recalling the past 24 hours, 1 “right now”, all on an 11-point NRS) and fatigue impact in the past 24 hours (6 items on 11-point NRS). Scores are by dimension, 1-item and the global score ranging from 0 to 10. Lower scores indicate lower fatigue. The BFI will be administered at the Baseline and Months 1, 6, 12, 18, and 24 visits.

Quality of life/health status

The EuroQoL 5-dimension 5-level (EQ-5D-5L) is used widely in clinical trials to assess 5 dimensions of health outcome (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) from a wide variety of interventions on a common scale, for purposes of evaluation, allocation, and monitoring. The EQ-5D-5L will be measured at Baseline and Months 1, 3, 6, 12, 18, and 24 visits (Appendix 13 [Section 10.13]).

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of AEs and SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.8.

The definitions of unsolicited and solicited AEs can be found in Appendix 3 (Section 10.3).

The device-related safety events and device deficiencies are not applicable for this study.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the end–of-study visit in the EFC15392 study (including AEs prior to signing the ICF) until end of the study at the time points specified in the SoA (Section 1.3).

All SAEs and AESIs (collected from the signing the ICF) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs, and AESIs (as defined in Section 8.3.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information in the IB.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the follow-up visit (30 days after the last dose of IMP).
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed-up to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be withdrawn from the study.

8.3.6 Cardiovascular and death events

Not applicable.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.8 Adverse event of special interest

Adverse event of special interest

An AESI is an AE (serious or nonserious) 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. An AESI may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP:
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
- Increase in ALT >3 ULN (see Appendix 6 [Section 10.6]).
- Other project specific AESI(s):
  - New or worsening lenticular opacities and cataracts.

For opacities present at baseline/previous visit, increase in WHO Grade ≥1.0 for nuclear, cortical, or posterior subcapsular opacification compared with baseline or previous assessment will be considered as a worsening.

8.3.9 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.3.9.1 Medical device deficiencies

Not applicable.

8.4 PHARMACOKINETICS

- PK parameters are not evaluated in this study.

8.5 GENETICS AND/OR PHARMACOGENOMICS

Genetics are not evaluated in this study.

8.6 BIOMARKERS

- Collection of biological samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:
  - Serum (fibroblast growth factor 23 [FGF23]),
  - Plasma (GL-1, GM3, asymmetric dimethylarginine [ADMA]),
  - Urine (monocyte chemoattractant protein 1 [MCP1] detection).

Samples will be tested for PD biomarkers associated with ADPKD such as FGF23 and ADMA in plasma to evaluate their association with the observed clinical responses. Urine samples (24-hour urine collections) will be analyzed for markers of kidney injury such as MCP1.

The final list of biomarkers that will be analyzed in samples collected in the LTS15823 study may change based on the results of the analysis of biomarkers performed in the EFC15392 study.

Special procedures for collection, storage, and shipment of serum, plasma, and urine samples will be described in a separate laboratory manual provided by the central laboratory. Approximately 6 mL of whole blood will be collected at each time point.

Additional exploratory biomarkers may be evaluated from remnant samples if available data during the sample retention period suggests a relationship to disease course and/or treatment response. These assessments may include analysis of protein and/or sphingolipid biomarkers using targeted or proteomic/metabolomic approaches.

In addition, remnant samples may be used for research to develop methods, assays, prognostics and/or companion diagnostics related to the disease process, pathways associated with the disease state, and/or mechanism of action of venglustat.

Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to venglustat. Participation is optional and participants will have to provide consent to participate in this future use of nongenomic samples analysis.

Collection of samples for biomarker research is not applicable for Chinese participants.

8.7 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.8 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

8.9 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (biobanking) (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining and/or extra clinical samples, data and samples may be used after the study ends for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects.

Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research).

All study participant data and samples will be coded such that no participant direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The samples will be stored for a maximum of 15 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

All samples from Chinese participants will be disposed following completion of the clinical study report.

9 STATISTICAL CONSIDERATIONS

The study is designed to test the following hypotheses for the primary efficacy endpoint: percent change in TKV based on MRI from the EFC15392 study baseline to 24 months of open-label extension study, in early treated and delayed-treated participants:

- Null hypothesis: No difference between early-treated participants and delayed-treated participants with regards to the mean percent change in TKV from the EFC15392 study baseline to 24 months of open-label extension study.
- Alternative hypothesis: Early-treated participants have lower mean percent change in TKV from the EFC15392 study baseline to 24 months of open-label extension study, compared to delayed-treated participants.

9.1 SAMPLE SIZE DETERMINATION

Since this study is the extension of the EFC15392 study, no formal sample size calculation was performed. A maximum of 640 participants who completed the EFC15392 study will be enrolled, including:

- Early venglustat: A maximum of 280 participants who were randomized to venglustat 15 mg in the EFC15392 study.
- Early venglustat: A maximum of 80 participants who were randomized to venglustat 8 mg in the EFC15392 study.
- Delayed venglustat: A maximum of 280 participants who were randomized to placebo in the EFC15392 study.

9.2 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 6 - Populations for analyses

Population	Description
Screened	All participants who sign the LTS15823 study ICF.
Enrolled	All participants from screened population who have been allocated to an LTS15823 intervention kit by interactive response technology (IRT) regardless of whether the intervention was received or not.
Primary Efficacy	All participants who completed Stage 1 or Stage 2 treatment in the EFC15392 study within 3 months prior to inclusion in the LTS15823 study. Participants will be analyzed according to the intervention assigned by randomization in the EFC15392 study (early venglustat or delayed venglustat). Participants randomized to venglustat 8 mg in Stage 1 of the EFC15392 study will be included in the primary efficacy population (in the early venglustat group), only if venglustat 8 mg shows similar effect compared to venglustat 15 mg in Stage 1 of the EFC15392 study, with regards to TKV slope (see Section 9.3.1 for details).
Safety	All participants who take at least 1 dose of study intervention in the LTS15823 study. Participants will be analyzed according to the intervention they actually received (early venglustat or delayed venglustat).

Enrolled participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant enrolled more than once, only the data associated with the first enrollment will be used in any analysis population. The safety experience associated with any later enrollment will be reported separately.

9.3 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.3.1 General considerations

Statistical tests and confidence intervals will be based on 2-sided tests with nominal significance level of 0.05.

For efficacy analyses, the 2 following groups will be compared:

- Delayed venglustat: participants who were randomized to placebo in Stage 1 or Stage 2 of the EFC15392 study.
- Early venglustat: participants who were randomized to venglustat (8 mg or 15 mg) in Stage 1 or Stage 2 of the EFC15392 study.

Participants randomized to venglustat 8 mg in Stage 1 of the EFC15392 study will be included in the primary efficacy population (in the "Early venglustat" group) only if venglustat 8 mg and 15 mg show similar effect with regards to the primary efficacy endpoint in the EFC15392 Stage 1 study. RR_8 and RR_{15} denote the relative reduction versus placebo with regards to the annualized rate of change in TKV, for the venglustat 8 mg and venglustat 15 mg, respectively. The following rule will apply:

- If $RR_8 \geq 2/3\ RR_{15}$ then participants randomized to venglustat 8 mg in Stage 1 of the EFC15392 study will be included in the primary efficacy population and part of the "Early venglustat" group.
- If $RR_8 < 2/3\ RR_{15}$ then participants randomized to venglustat 8 mg in Stage 1 of the EFC15392 study will be not be included in the primary efficacy population.

In addition, participants included in the LTS15823 study more than 3 months (91 days) after having completed the EFC15392 study treatment will be excluded from the primary efficacy population.

While the primary comparison of interest is at 24 months of the LTS15823 study, efficacy analyses will present each scheduled assessment from the EFC15392 and LTS15823 studies.

For safety analyses, the 2 following groups will be presented:

- Delayed venglustat: participants having received placebo in Stage 1 or Stage 2 of the EFC15392 study.
- Early venglustat: participants having received venglustat (8 mg or 15 mg) in Stage 1 or Stage 2 of the EFC15392 study.

All participants having received venglustat in the LTS15823 study (whether included less or more than 3 months after having completed the EFC15392 study treatment) will be included in the safety population.

Baseline value is generally defined as the last available value before first IMP administration in the EFC15392 study. For eGFR, baseline is defined as the average of eGFR values assessed prior to first IMP administration in the EFC15392 study.

In addition, the baseline value in the LTS15823 study is defined as the last available value before first IMP administration in the LTS15823 study. For TKV and total liver volume (TLV), due to the possibility to perform the LTS15823 first visit remotely and then to have potential late MRI examination, baseline in the LTS15823 study is defined as the first available value up to first IMP administration in the LTS15823 study + 30 days. For eGFR, baseline in the LTS15823 study is defined as the average of eGFR values assessed prior to first IMP administration in the LTS15823 study.

Observation period

The observation period will be divided into 4 segments:

- The **pretreatment period** is defined as the period up to first IMP administration in the LTS15823 study.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration in the LTS15823 study to the last IMP administration in the LTS15823 study + 30 days. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP + 1 day.
  - The **residual treatment** period is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

9.3.2 Primary endpoint

The primary endpoint is percent change in TKV based on MRI from the EFC15392 study baseline to 24 months of open-label extension study, in early treated and delayed-treated participants.

The primary estimand will be the difference (early venglustat versus delayed venglustat) in mean percent change in TKV from the EFC15392 study baseline to 24 months in the LTS15823 study, in all participants from the primary efficacy population, regardless of whether or not participants completed the LTS15823 treatment period (treatment policy strategy).

Percent change from the EFC15392 study baseline in TKV will be analyzed using a mixed effect model with repeated measures (MMRM). The MMRM will include percent change in TKV at the following time points:

- Month 18 in the EFC15392 study.
- Baseline in the LTS15823 study.
- Month 24 in the LTS15823 study.

Percent change in TKV at Month 1 and Month 9 in the EFC15392 study will not be included in the MMRM since TKV at these time points was only assessed in participants from Stage 1.

The MMRM will include fix effect of treatment group (early venglustat versus delayed venglustat), Mayo Imaging Classification (as per randomization stratification factor in the EFC15392 study: Class 1C versus 1D versus 1E), time point (as a categorical variable), treatment*time point interaction, Mayo Imaging Classification*time point interaction as well as the continuous fixed covariates of baseline TKV and the baseline-by-time point interaction.

This model will include an unstructured covariance matrix to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method. Denominator degrees of freedom will be estimated using Kenward-Roger approximation.

Within group mean percent change in TKV will be obtained from MMRM, using weights for each stratum (Mayo Class 1C, 1D, and 1E) equal to the observed proportion of participants in each stratum in the primary efficacy population (ie, “population weight”). The difference in baseline adjusted least-squares means will be used to compare the early venglustat group to the delayed venglustat group, at the 2-sided 0.05 level.

The primary analysis will include all observed TKV data in participants from the primary efficacy population, regardless of whether or not participants completed the treatment period. Participants who prematurely and permanently discontinue IMP in the LTS15823 study will be requested to obtain an MRI scan at 24-month visit and their data collected after treatment discontinuation will be included in the primary analysis. All efforts will be made to minimize the amount of missing data.

In order to evaluate the robustness of the primary analysis, sensibility analyses will be performed and described in the SAP.

Secondary analysis

A secondary analysis will estimate the difference in mean percent change in TKV from baseline during the on-treatment period (while on treatment strategy). In this secondary analysis, TKV assessed more than 30 days after the last LTS15823 study IMP administration will be excluded from the analysis. The TKV assessed in enrolled but not treated participants will also be excluded from the analysis. Any missing data during the on-treatment period will be considered "at random" in this secondary analysis; therefore, no imputation will be required since the MMRM provides valid inference under missing at random assumption.

9.3.3 Secondary endpoints

Change in eGFR from the EFC15392 study baseline to 24 months of open-label extension study will be analyzed using a MMRM similar to those used to analyze percent change in TKV. The MMRM will include change in eGFR at all time points in the EFC15392 and LTS15823 studies (change at Months 1, 3, 6, 9, 12, 15, 18, 21, and 24 in the EFC15392 study and at Baseline, Months 1, 6, 12, 18, and 24 in the LTS15823 study).

If the model does not converge with an unstructured covariance matrix (due to the high number of time points), the following covariance matrix structures will be used in the order:

- Heterogeneous Toeplitz (TOEPH).
- First-order heterogeneous autoregressive (ARH[1]).
- Heterogeneous Compound Symmetry (CSH).
- Toeplitz (TOEP).
- First-order autoregressive (AR[1]).
- Compound Symmetry (CS).

The first covariance structure yielding convergence will be used as the primary analysis.

Missing data will be handled using a multiple imputation method similar to those of the primary endpoint.

Secondary analysis

The difference in mean percent change in eGFR from baseline during the on-treatment period (while on treatment strategy) will be estimated using method similar to the primary endpoint.

Supplemental analysis

In addition, a supplemental analysis will be performed using the same method as the primary analysis but excluding all participants with an eGFR at screening in the EFC15392 study of 30 to 44.9 mL/min/1.73 m^2.

Multiplicity considerations

A fixed-sequence testing procedure will be used in order to control the Type I error rate for primary and secondary endpoints. The primary endpoint will be tested at the 0.05 level, then only if significant (p-value <0.05), then the secondary endpoint will be tested at the same 0.05 level.

9.3.4 Tertiary/exploratory endpoint(s)

Tertiary and exploratory endpoints analysis will be described in the SAP.

9.3.5 Safety analysis

Safety data will be presented separately for the 2 following periods:

- Safety analysis of the open-label extension study. This analysis will present safety data during the open-label extension treatment-emergent period, on the LTS15823 safety population (see Section 9.3.1). Safety analyses will present safety data from the following groups:
  - Delayed venglustat,
  - Early venglustat.
- Safety analysis of the overall venglustat treatment period. This analysis will present all safety data collected from the first intake of venglustat (either during the EFC15392 study or during the long-term extension LTS15823 study) to the last intake of venglustat +30 days. All participants having received venglustat will be included in this analysis. Safety analyses will present safety data from the following group:
  - Overall venglustat: participants having received venglustat during the EFC15392 study and/or during the long-term extension LTS15823 study.

9.3.5.1 Adverse events

General common rules for adverse events

The AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and analyzed in the following 3 categories:

- Pretreatment AEs: AEs that developed, worsened, or became serious during the pretreatment period.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened, or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Similarly, deaths will be analyzed in the pretreatment, treatment-emergent, and post-treatment periods.

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent AESIs (defined with a preferred term or a prespecified grouping), all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

Deaths will also be analyzed.

9.3.5.2 Laboratory variables, vital signs, and electrocardiograms (ECGs)

Quantitative analyses

For laboratory variables, vital signs, and ECG variables, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period. These analyses will be performed using central measurements (when available) for laboratory variables and ECG variables.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled, or repeated).

For laboratory variables, vital signs, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing.
- Abnormal.

9.3.6 Other analysis

Not applicable

9.4 INTERIM ANALYSES

No interim analysis is planned.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines,
  - Applicable ICH Good Clinical Practice (GCP) Guidelines,
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR).
- The protocol, protocol amendments, ICF, IB, IDFU and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted. And

- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participants, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that address the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy and Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

"Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American

population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or precontractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study,
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an

adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:

- The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
- Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to 30 years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: [redacted] (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Data Monitoring Committee

- Participant safety will be continuously monitored by the DMC, operating independently from the Sponsor and Clinical Investigators, which includes safety signal detection at any time during the study. The DMC will be reviewing safety data in an unblinded fashion, aggregated by treatment group (ie, groups labelled delayed venglustat or early venglustat).
- The specific responsibilities of the DMC and the frequency of data review will be described in the DMC charter.

10.1.5.2 Steering committee

- The Steering Committee (SC) is composed of field experts and Sponsor-based scientists with clinical and methodological expertise. This Committee, led by a Chairperson, selected by the Sponsor, will provide advice to the Sponsor regarding scientific issues and operational conduct of the study. The SC will also review any amendments, and provide input regarding interpretation of study results. The members will remain blinded to treatment group (ie, groups labelled delayed venglustat or early venglustat) until completion and unblinding of the EFC15392 study. Detailed activities and responsibilities of the SC will be provided in the SC charter.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "European Federation of Pharmaceutical Industries and Associations (EFPIA) Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in eCRF Completion Instructions.

- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio,
  - Discontinuation of further study intervention development.
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines,
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator,
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation, or as a part of contingency measures included in Appendix 9 (Section 10.9). Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 7 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	
	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	MCV
	MCH
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
	Prothrombin time (PT)
	Partial thromboplastin time (PTT)
	International normalized ratio (INR)
Clinical chemistry[a]	
	Blood urea nitrogen (BUN)
	Serum cystatin C
	Urea
	Creatinine
	Glucose [fasting]
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)
	ALT/ Serum glutamic-pyruvic transaminase (SGPT)

Laboratory tests	Parameters
	Alkaline phosphatase[b]
	Total and direct bilirubin
	Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) (if applicable)[d] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) (if applicable)[d] • All study-required laboratory tests will be performed by a central laboratory, with the exception of urine dipstick

NOTES :
a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 and Appendix 6 (Section 10.6). All events which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner.
b If alkaline phosphatase is elevated, consider fractionating.
c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.
d According to SoA.

Investigators must document their review of each laboratory safety report. All samples from Chinese participants will be analyzed in a qualified bioanalytical laboratory in China.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.

- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by participant will be collected during interview with the participants and by review of available medical records at the next visit.
- Solicited AEs are predefined systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements, ophthalmic examination abnormalities), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - 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,
  - Leading to unscheduled full ophthalmological examination with or without WHO simplified cataract grading system evaluation.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

A) Results in death

B) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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.

C) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

E) Is a congenital anomaly/birth defect

F) Is a suspected transmission of any infectious agent via an authorized medicinal product

G) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  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, etc).
  - Development of drug dependence or drug abuse,
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × 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.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. “Severe” is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor representative.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor representative with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator Study File.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:

   NOTE: Documentation can come from the review of participant's medical records, medical examination, or medical history interview.

   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.

2. Postmenopausal
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH/estradiol level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, a single FSH/estradiol measurement is insufficient.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male participants

- Male participants with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following for the duration of the study and for 90 days following their last dose of IMP:
    - Refrain from donating sperm,

      and
    - At least 1 of the following conditions applies:
        - Are and agree to remain abstinent from penile-vaginal intercourse on a long-term and persistent basis, when this is their preferred and usual lifestyle,

          or
        - Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see Table 8 for female participants).
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

Female participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly for the duration of the study and for at least 6 weeks following their last dose of IMP as described in Table 8.

Table 8 - Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: - Oral, - Intravaginal, - Transdermal. • Progestogen-only hormone contraception associated with inhibition of ovulation: - Oral, - Injectable.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b] - Intrauterine device, - Intrauterine hormone-releasing system. • Bilateral tubal occlusion.
Vasectomized partner. *A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

Note:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case 2 highly effective methods of contraception should be utilized during the treatment period and for at least 6 weeks for females and 90 days for males following their last dose of IMP.

Male participants with partners of reproductive potential who become pregnant:

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

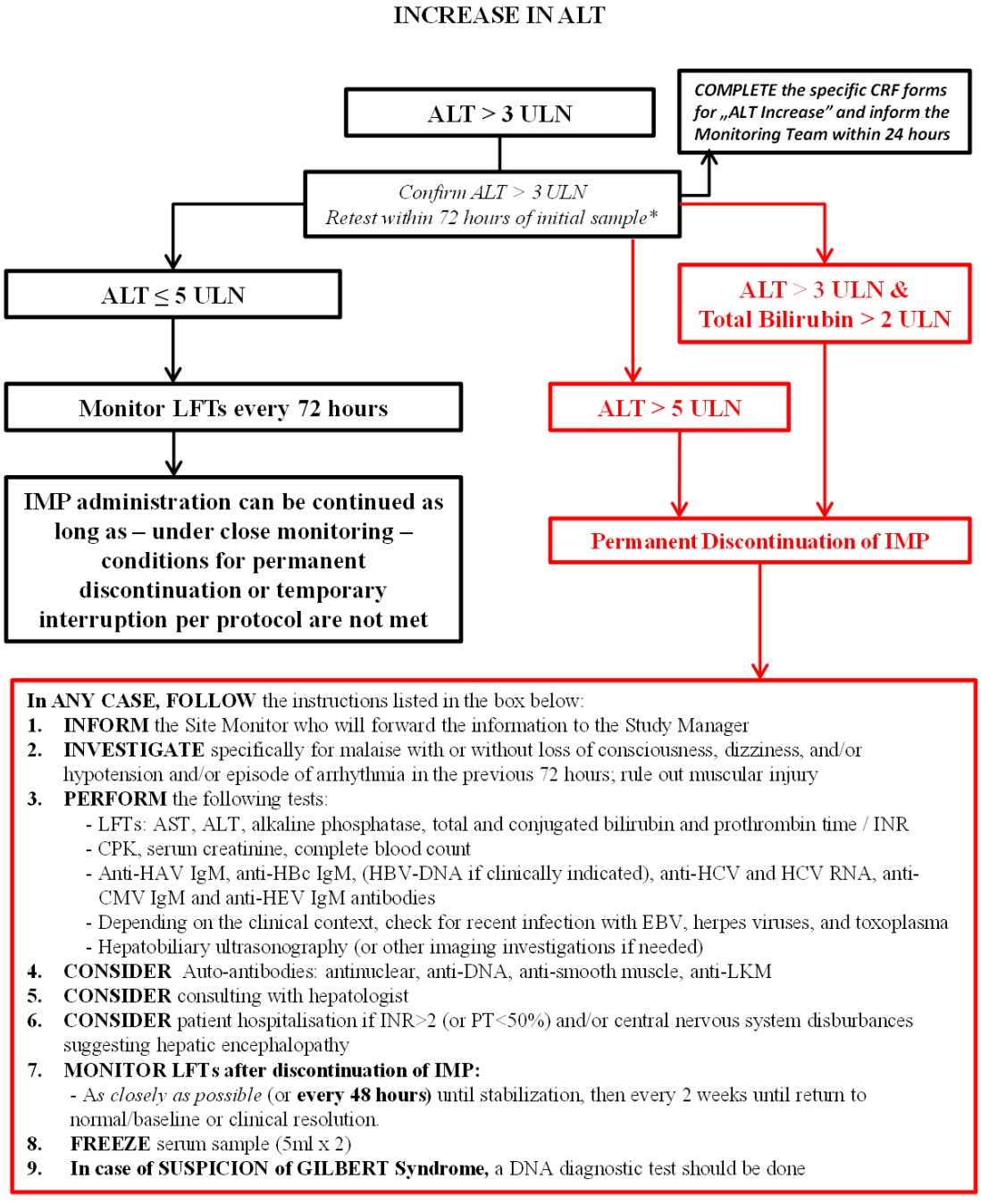
Female participants who become pregnant:

- The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Additional follow-up information may be requested about the baby until at least 1 year after the birth of the baby, due to potential risk of abnormalities not present at birth.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 10.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment and will be withdrawn from the study.

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS



*If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.

Note:

"Baseline" refers to ALT sampled at Baseline visit; or if baseline value unavailable, to the latest ALT sampled before the Baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.

See Section 10.3 for guidance on safety reporting.

Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Germany

- Exclusion criterion E08

The participant will not be eligible to participate in the trial if the participant has been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities, or if the participant is an employee of the Sponsor or Investigator or otherwise dependent on them.

10.8.2 Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, Spain

In order to comply with the request received during the European VHP review phase, patients participating in the countries listed above will be treated with venglustat 15 mg once daily (QD) for 24 months.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in sections (Section 5.2, Section 5.5, Section 1, Section 7.1.4, Section 7.1.5, Section 8, and Section 10.1.3) for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening, enrollment, and/or administration of study treatment may be temporarily delayed/halted.

The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local laboratories).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained) to make clinical supplies available to the participant for the duration of the emergency: the DTP supply of venglustat from the site where allowed by local regulations and agreed upon by the participant. The DTP supply of IMP is not contingent on availability of contemporaneous laboratory results or other study specific assessments.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency (where allowed by local regulations) if onsite visits are not possible:

- Telephone contacts are to be performed in place of an onsite study visits and per study protocol schedule. Essential data (that can be checked via interview to evaluate participant safety) to be captured via telephone contact and documented in the source records include, but is not limited to, AEs, SAEs, change in or new concomitant medications, urine pregnancy test results, IMP compliance, potential signs of depressed mood, complaints about changes in vision, vital signs (if participants can measure temperature and BP at home).
- Visit ePROs (questionnaires) should be completed by the participant in the eDiary as usual. eDiary data can still be checked online by the Investigator/site team prior to calling the participant to ensure any follow-up questions or findings can be discussed.
- If it is feasible and there is no additional risk for a participant from the hazard the led to declaration of national emergency, consider performing blood tests in local laboratories:
  - Blood chemistry: at the minimum blood creatinine, AST, ALT, eGFR calculated with CKD-EPI equation,
  - Complete blood count.
- Participants with a recent eGFR **>45 mL/min/1.73 m^2**, may continue IMP up to 6 months, without having an onsite visit.
- Participants with a recent eGFR **≤45 and >30 mL/min/1.73 m^2**, may continue IMP up to 3 months, without having an onsite visit. Participant who are not be able to repeat eGFR in 3 months will have to interrupt the treatment. Temporary IMP discontinuation will need to be registered in IRT.
- Participants with a recent eGFR **≤30 and >25 mL/min/1.73 m^2**, who are not be able to repeat creatinine in 30 days will have to interrupt the treatment. If eGFR result repeated in 30 days is below 30 mL/min/1.73 m^2, the participant will have to stop the treatment permanently.
- When telephone contact is performed in place of an onsite study visits, assessments of efficacy and safety data that cannot be obtained remotely (eg, MRI, ECG, ophthalmological and neurological examination) will be performed when participants are able to resume normal site visits. Safety assessment that cannot be obtained remotely

may be performed prior to next regular onsite visit if Investigator considers that this is clinically indicated and feasible, and that this will not involve an additional risk for a participant from the hazard that led to declaration of national emergency.

If eligible participants who agreed to enter in the long-term extension study at Visit 12 (end-of treatment) of the EFC15392 study cannot attend site to perform this visit because of a regional or national emergency declared by a governmental agency, a remote LTS15823 Visit 1 can be performed where allowed by local regulations if the following conditions are fulfilled:

- Site must receive from the participant signed and dated written informed consent for participation in the LTS15823 study. This consent must be signed and dated prior to the visit of home health vendor to collect assessments for a remote LTS15823 Visit 1.
- A home health vendor must visit the participant on the day of the remote Visit 1 to collect laboratory samples planned for Visit 12 (end-of treatment) of the EFC15392 study and to perform urine pregnancy test (for WOCBP).
- The DTP supply of venglustat from the site is allowed by local regulations and agreed upon by the participant.
- A home health vendor service is in place to visit participant in 1 month (for Visit 2 of the LTS15823 study) to collect laboratory samples and assess AEs after 1 month on venglustat treatment in the LTS15823 study.

On the day of the remote Visit 1, the Investigator will have a call with the patient and inquire about BP measurements, AEs, concomitant medications and results of performed urine pregnancy test (if applicable), will evaluate BDI-II score completed by the patient, and will enroll patient if eligibility is confirmed. If patient is enrolled, IMP will be sent to participant via DTP process. Site will need to follow up via telephone with the participant once IMP is delivered.

Missing assessments of Visit 12 of the EFC15392 and LTS15823 Visit 1(including body weight measurement and MRI examination) will be performed as soon as onsite visit is possible.

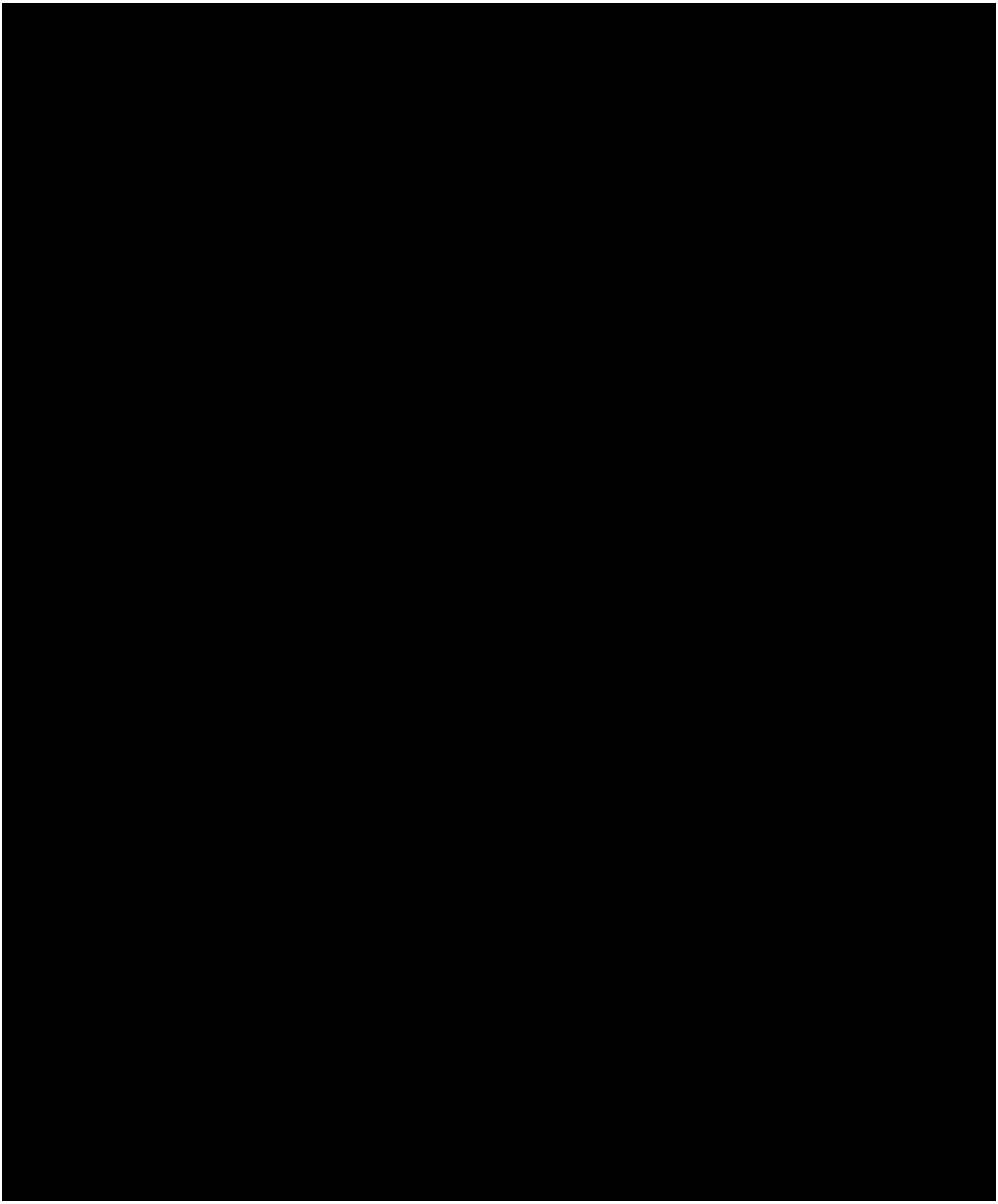
For participants who had lag phase between the end of the EFC15392 study and Screening visit in the LTS15823 study:

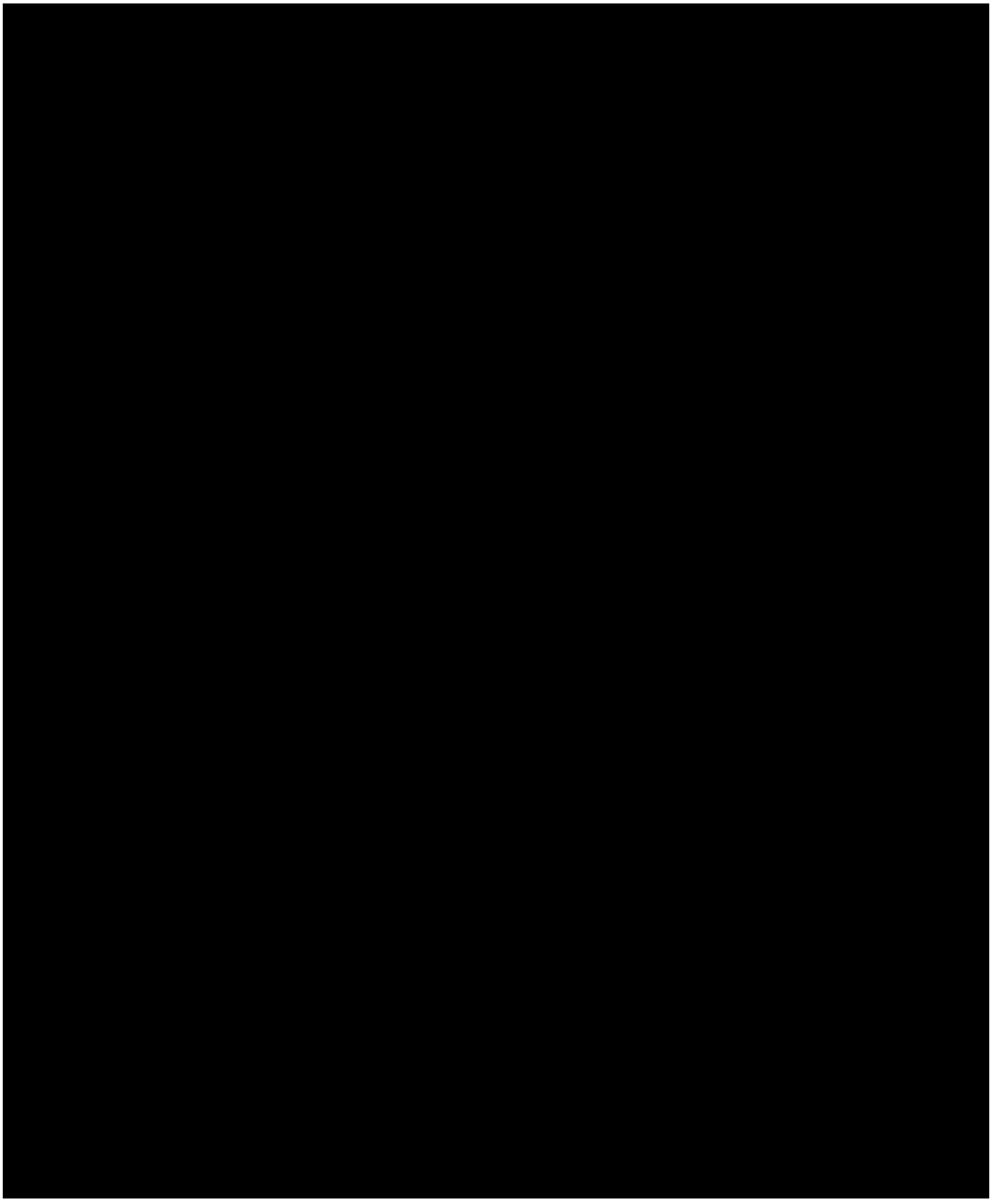
- Screening in the LTS15823 study during a regional or national emergency declared by a governmental agency can be performed only if allowed by local competent authorities and after Sponsor`s agreement is obtained.
- If a participant who completed the treatment period in Stage 1 or Stage 2 of the EFC15392 study was screen-failed during a regional or national emergency for reasons not related to eligibility, rescreening shall be permitted when the situation normalizes and after Sponsor`s agreement is obtained.
- If eligibility assessment cannot be performed due to department/service shutdowns (MRI, ophthalmology, etc) during the screening period, the participant cannot be randomized, and screening period can be extended with randomization after site will be able to reopen. In such scenario, certain screening assessment will have to be repeated before Visit 1:
  - Blood chemistry (if >2 weeks after Visit 0),

- Complete blood count (if >4 weeks after Visit 0),
- BCVA and lens assessment according to WHO simplified cataract grading system (if >3 months from initial assessment in the LTS15823 study),
- ECG (if >3 months from Visit 0 ECG test),
- BDI-II (if >2 weeks after Visit 0),
- MRI (decision on case by case basis: if >1 to 3 months before Visit 1).

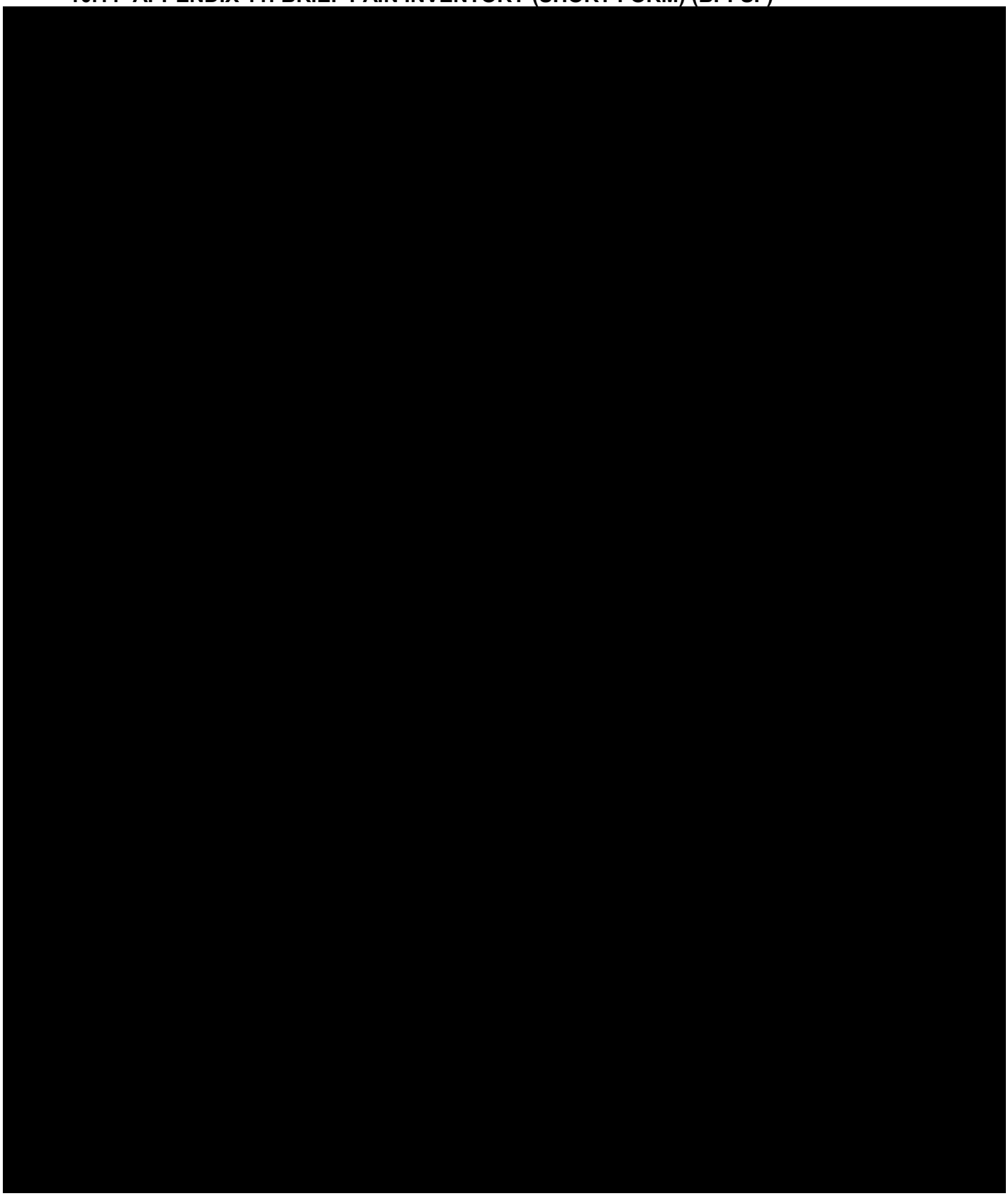
Contingencies implemented due to emergency will be documented.

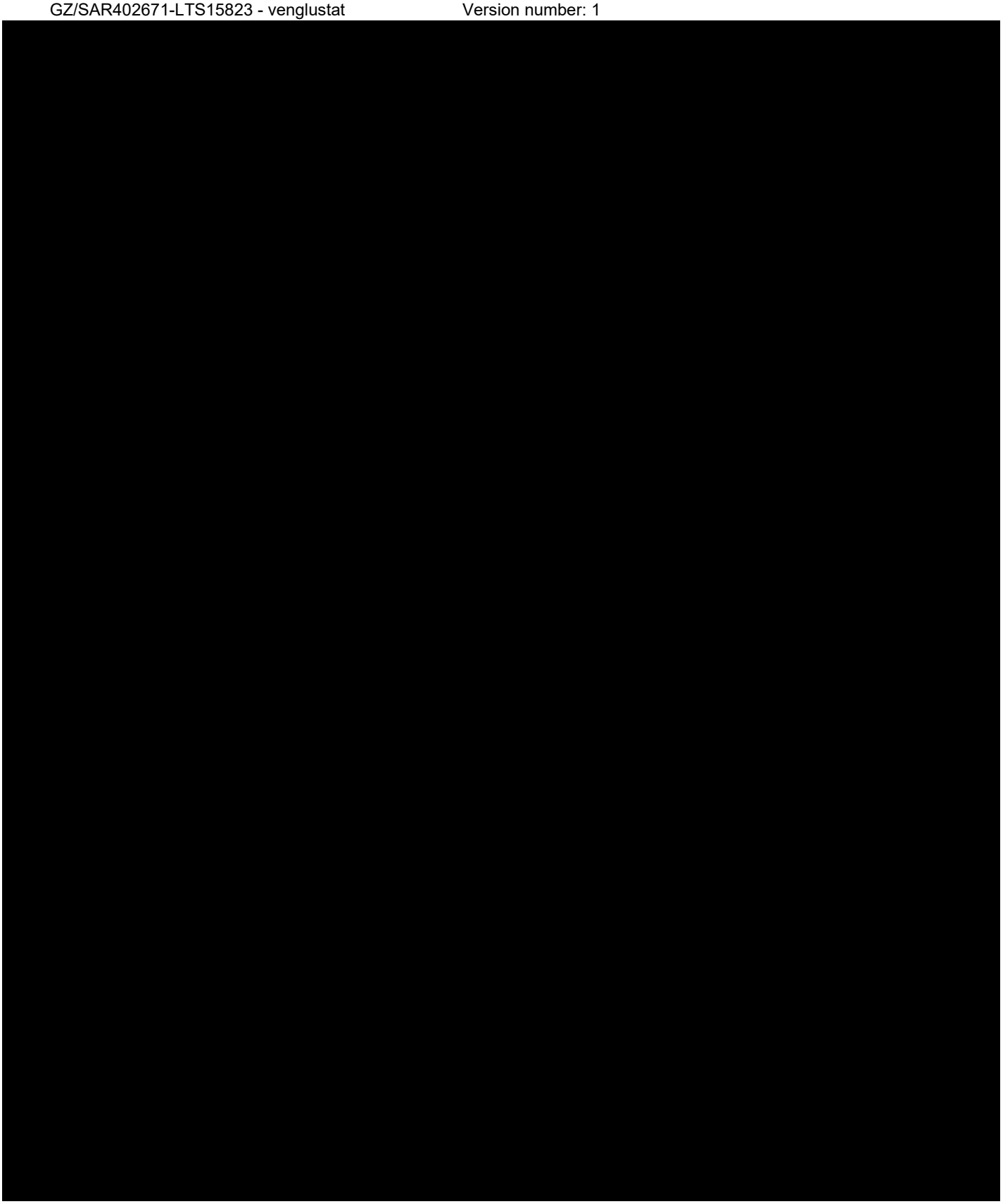
10.10 APPENDIX 10: BECK DEPRESSION INVENTORY II



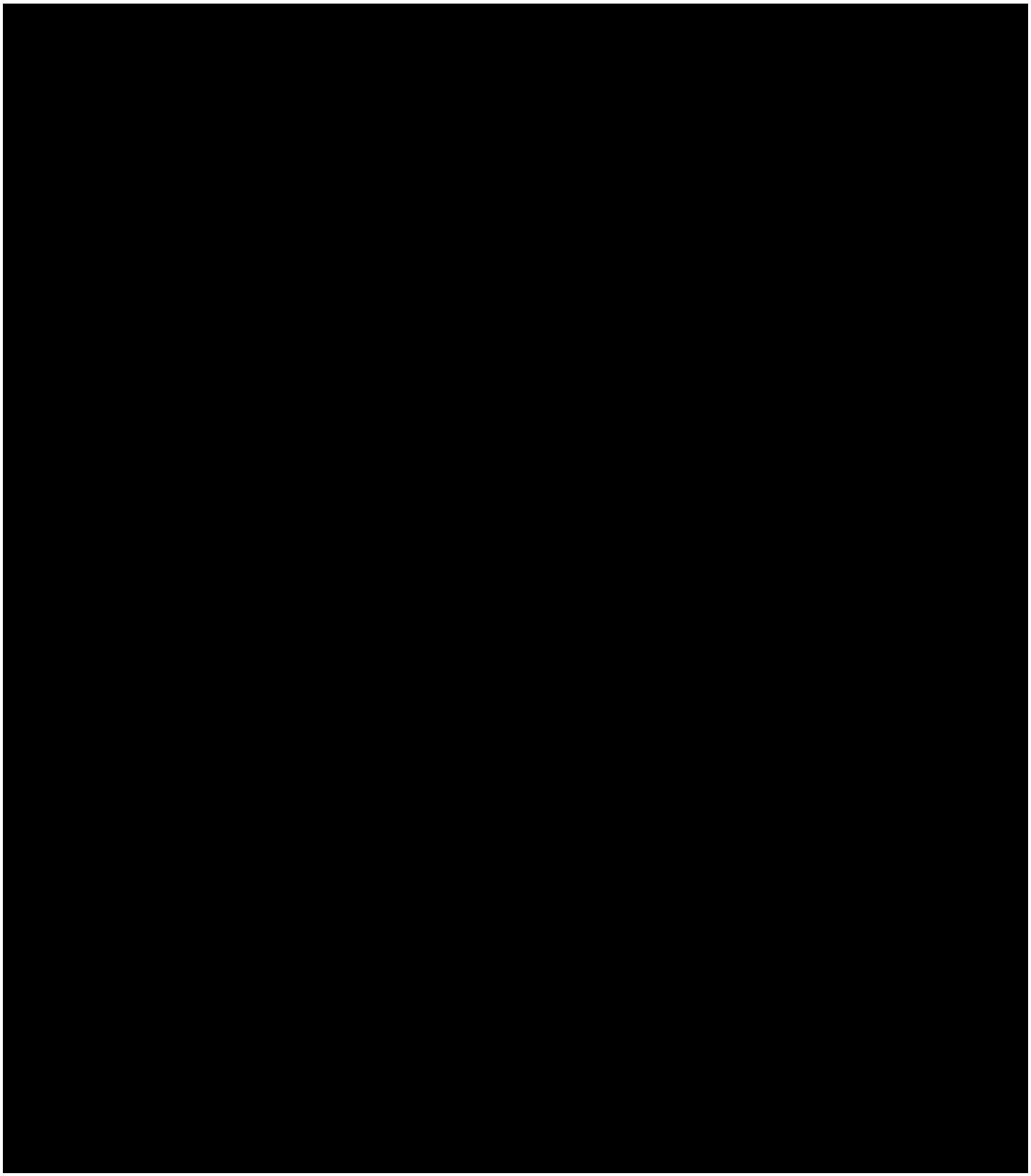


10.11 APPENDIX 11: BRIEF PAIN INVENTORY (SHORT FORM) (BPI-SF)

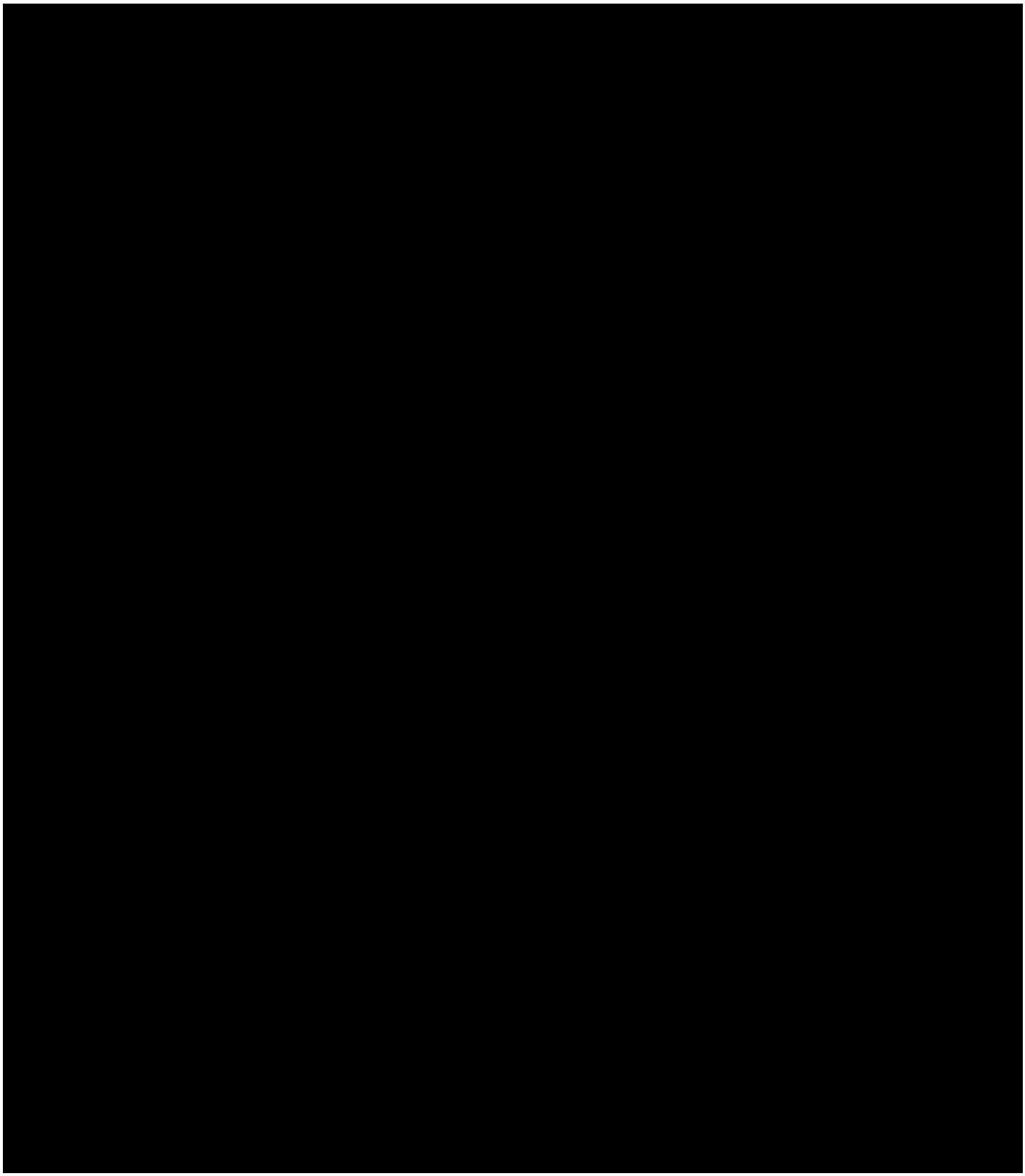




10.12 APPENDIX 12: BRIEF FATIGUE INVENTORY (BFI)



10.13 APPENDIX 13: EUROQOL (EQ-5D-5L)



10.14 APPENDIX 14: ABBREVIATIONS

ADMA:	asymmetric dimethylarginine
ADPKD:	autosomal dominant polycystic kidney disease
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
BCVA:	best corrected visual acuity
BDI-II:	Beck depression inventory II
BFI:	brief fatigue inventory
BP:	blood pressure
BPI-SF:	brief pain inventory short form
CKD:	chronic kidney disease
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
CNS:	central nervous system
CSF:	cerebral spinal fluid
CYP3A4:	cytochrome P450 3A4
DBP:	diastolic blood pressure
DMC:	data monitoring committee
DTP:	direct-to participant
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EOT:	end-of-treatment
EQ-5D-5L:	EuroQol 5 dimension 5 level
EU:	European Union
FD:	Fabry disease
FDA:	United States Food and Drug Administration
FGF23:	fibroblast growth factor 23
FSH:	follicle-stimulating hormone
GBA:	glucocerebrosidase
GBA-PD:	Parkinson's disease with a confirmed acid-β-glucosidase gene mutation
GCS:	glucosylceramide synthase
GD:	Gaucher disease
GD3:	Gaucher disease Type 3
GL-1:	glucosylceramide
GM3:	monosialodihexosylganglioside
GSL:	glycosphingolipid
HRT:	hormone replacement therapy
IB:	investigator's brochure
ICF:	informed consent form
IMP:	investigational medicinal product
IRT:	interactive response technology
MCP1:	monocyte chemoattractant protein 1
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	mixed effect model with repeated measures

MMSE:	mini mental state examination
MRI:	magnetic resonance imaging
NMPA:	National Medical Products Administration
NRS:	numeric rating scale
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamics(s)
PI:	principal investigator
PK:	pharmacokinetic(s)
QD:	once daily
SAE:	serious adverse event
SBP:	systolic blood pressure
SRT:	substrate reduction therapy
SUSAR:	suspected unexpected serious adverse reaction
TE:	treatment emergent
TEAE:	treatment-emergent adverse event
TKV:	total kidney volume
TLV:	total liver volume
ULN:	upper limit of normal
VHP:	Voluntary Harmonization Procedure
WHO:	World Health Organization
WOCBP:	women of childbearing potential

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

The summary of changes for the current protocol amendment (amended protocol 01) is included after the title page.

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